Total Synthesis of (+)-Sinefungin

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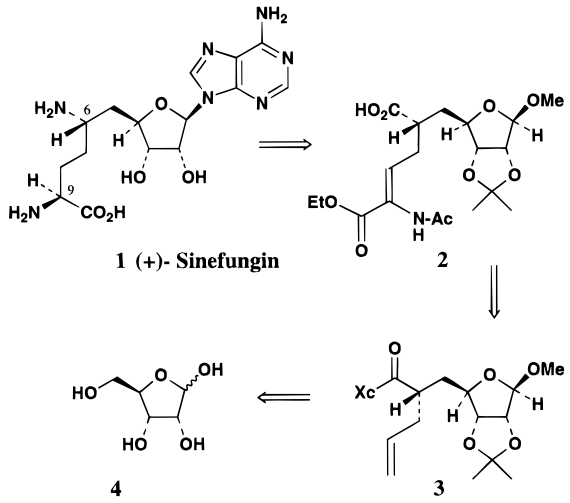
Sinefungin (**1**) a nucleoside antibiotic isolated from *Streptomyces* has been synthesized from D-ribose. Both the C-6 and C-9 stereogenic centers were constructed by efficient asymmetric syntheses. The C-6 amine stereochemistry was set by a highly diastereoselective allylation (>99% de) of a (1*S*,2*R*)-1-amino-2-indanol-derived oxazolidinone **9** followed by a Curtius rearrangement of **11** to **12**. The C-9 amino acid stereochemistry of sinefungin **(1)** was established by a rhodium chiral bisphosphine-catalyzed asymmetric hydrogenation of an α-(acylamino)acrylate derivative. The anomeric adenosylation of the mixture of anomeric acetates **20** in the presence of C-6 urethane NH was found to be extremely difficult. Conversion of the C-6 urethane NH as its *N*-benzyl derivative **21** was necessary prior to the adenosylation reaction. Successful adenosylation was effectively carried out by Vorbrüggen's protocol utilizing persilylated N^6-benzoyladenine and trimethylsilyl triflate.

Introduction

The "small molecule" biological methylations are involved in numerous crucial biochemical processes with well-defined physiological function. *S*-Adenosylmethionine (SAM) serves as a methyl donor, and various methyl transferase enzymes catalyze these transmethylation reactions.[1] For example, catechol-*O*-methyltransferase catalyzes the transfer of a methyl group from SAM to a catechol substrate which represents the major extraneuronal inactivation pathway of endogenous catecholamines.[2] Since the discovery of SAM by Cantoni[3] in 1952, many SAM-dependendent methyl transferases have been recognized. As a consequence, various methyltransferase enzymes have become potential targets for the design of chemotherapeutic agents.[4] Sinefungin, a novel antifungal nucleoside isolated[5] from the cultures of *Streptomyces griseolus*, has been shown to inhibit many methyltransferase enzymes.[6] Sinefungin, which is structurally related to SAM, has also exhibited many other significant biological properties including antifungal, antitumor, antiparasitic, and antiviral activities.[7] However, clinical use of sinefungin is severely limited because of its known in vivo toxicity.[8] Many of the biological activities of sinefungin are believed to be related to inhibition of the SAM-dependent methyl transferase enzymes. The significant biological properties of sinefungin continue to foster immense interest in its chemistry and total synthesis.[9,10] In connection with our interest in sinefungin-based design of antiviral agents, we required an efficient, flexible, and enantioselective synthesis of sinefungin. We describe here a stereocontrolled synthesis of sinefungin in which both the C-6 and C-9 remote chiral centers were constructed through efficient asymmetric synthesis in a stereopredictable fashion.

Scheme 1



Results and Discussion

Our retrosynthetic analysis of sinefungin is outlined in Scheme 1. The key elements of our synthesis involved a Curtius rearrangement to incorporate the C-6 amino functionality and an asymmetric hydrogenation of the α-(acylamino)acrylate derivative to establish the C-9 asymmetric center. To set the stereochemistry at C-6, our desired intermediate was the allyl derivative **3**, which would be obtained by a diastereoselective alkylation of

[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1996.

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(8) Zweygerth, E.; Schillinger, D.; Kaufmann, W.; Roettcher, D. *Trop. Med. Parasitol.* **1986**, *37*, 255.

(9) For total synthesis, see; (a) Maguire, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 948. (b) Buchanan, J. G.; Flinn, A.; Mundill, P. H.; Wightman, R. H. *Nucleosides Nucleotides* **1986**, *5*, 313. (c) Geze, M.; Blanchard, P.; Fourrey, J. L.; Robert-Gero, M. *J. Am. Chem. Soc.* **1983,** *103*, 7638. (d) Mock, G. A.; Moffat, J. G. *Nucleic Acids Res.* **1982**, *10*, 6223. For synthesis of 6-deaminosinefungin derivatives, see; Peterli-Roth, P.; Maguire, M. P.; Leon, E.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 4186.

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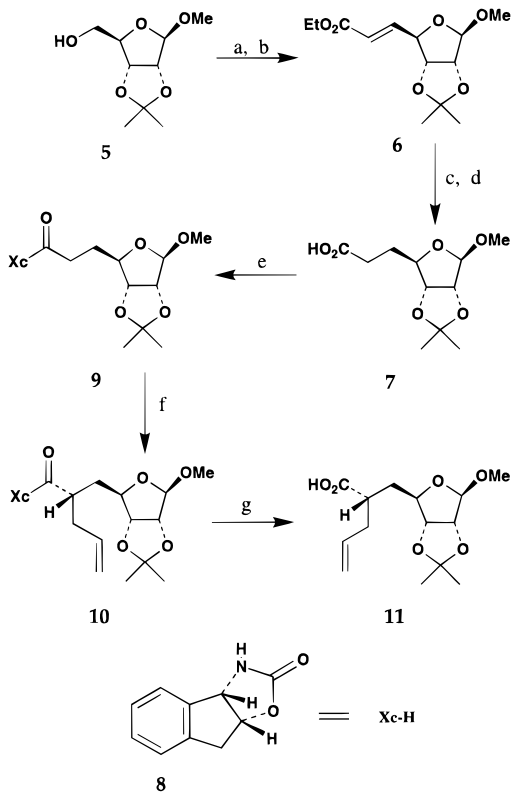
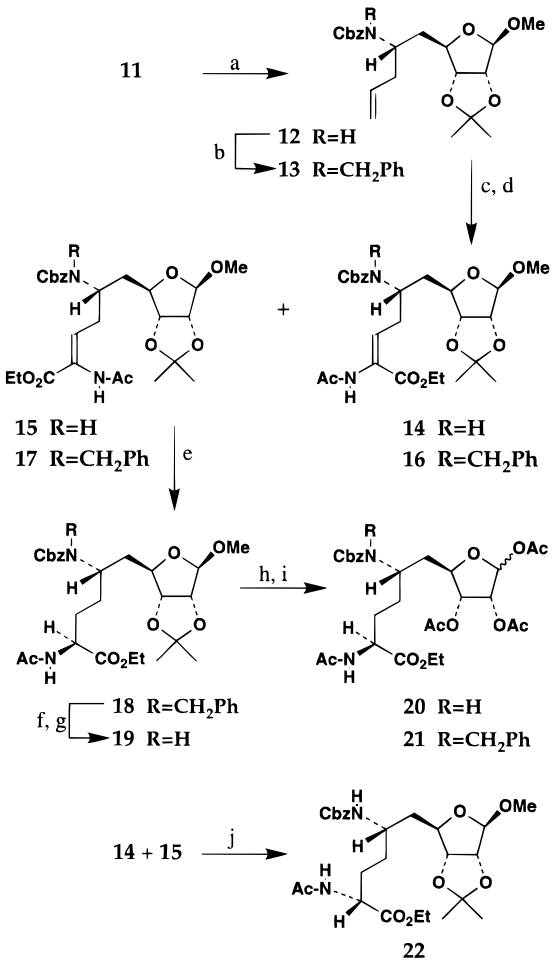
Scheme 2[a]



[a] Key: (a) DMSO, $(COCl)_2$, CH_2Cl_2, −60 °C to −50 °C, 2 h and then Et_3N; (b) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, 0 °C to 23 °C; (c) H_2, 10% Pd−C, EtOAc; (d) LiOH, THF−H_2O, 23 °C; (e) Me_3CCOCl, Et_3N, THF, −15 °C to 0 °C then −78 °C and then *N*-lithiooxazolidinone **8**; (f) $(TMS)_2NLi$, THF, −78 °C, 1 h and then $CH_2{=}CHCH_2I$, −78 °C to −40 °C, 6 h; (g) LiOOH, THF−H_2O, 0 −23 °C.

Scheme 3[a]



[a] Key: (a) $(PhO)_2P(O)N_3$, Et_3N, PhMe, 114 °C, 2 h and then $PhCH_2OH$, 114 °C, 12 h; (b) NaH, $PhCH_2Br$, $nBu_4N^+I^-$ (cat), THF−DMF (10:1); (c) O_3, CH_2Cl_2−MeOH (1:1), −78 °C then Me_2S, −78 °C to 23 °C; (d) KO*t*Bu, $(PhO)_2P(O)CH(NHAc)CO_2Et$, CH_2Cl_2, −78 °C, 1 h and then above aldehyde, −78 °C to 23 °C, 4 h; (e) H_2, $[Rh(COD)(R,R\text{-DIPAMP})_2]^+BF_4^-$, 50 psi, MeOH, 23 °C, 10 h; (f) H_2, 20% $Pd(OH)_2$−C, MeOH; (g) $PhCH_2OCOCl$, Et_3N, DMAP, CH_2Cl_2; (h) aqueous HCl, dioxane, 23 °C; (i) Ac_2O, pyridine, 0 °C to 23 °C, 10 h; (j) H_2, [Rh(norbornadiene)(*S*,*S*-Chiraphos)]$^+ClO_4^-$, MeOH, 50 psi, 23 °C, 10 h.

the corresponding chiral imide. The required chiral imide would be derived from D-ribose, and the adenine was planned to be introduced toward the end of the synthesis. Thus, the protected methyl glycoside **5**[11] was readily converted to α,β-unsaturated ester **6** by Swern oxidation of **5** followed by immediate exposure of the resulting aldehyde to a Horner−Emmons olefination reaction with triethyl phosphonoacetate and sodium hydride in THF at 23 °C for 30 min. Only the trans α,β-unsaturated ester **6** was isolated in 72% yield after silica gel chromatography. Hydrogenation of **6** with 10% Pd−C in ethyl acetate and saponification of the resulting saturated ester with 1 M aqueous LiOH at 23 °C for 12 h afforded the glycosidic acid **7**. To establish the stereochemistry of the C-6 amine, the acid **7** was subjected to a diastereoselective asymmetric alkylation process. The acid **7** was first converted to carboximide **9** utilizing Evans's protocol[12] as follows: the chiral oxazolidinone **8**[13] was deprotonated with n-BuLi at −60 °C in THF; the resulting lithio derivative was reacted with the mixed anhydride derived from acid **7**, pivaloyl chloride, and triethylamine at −78 °C to furnish the carboximide **9** in 70% yield after silica gel chromatography. Treatment of this carboximide with lithum hexamethyldisilazide in THF at −78 °C for 1 h provided the lithium enolate which was reacted with allyl iodide at −78 °C to −40 °C for 6 h to afford the allylation product **10** in 78% yield after chromatography over silica gel. The ^{1}H-NMR (400 MHz) and HPLC analysis before and after chromatography reveal the presence of a single diastereomer. The removal of the chiral auxiliary was effected by exposure to lithium hydroperoxide in aqueous THF under standard reaction conditions to provide the acid **11**.[14] The stereochemistry of the asymmetric alkylation process was assigned based upon the comparison of an authentic sample **11**, prepared utilizing (*S*)-(−)benzyl-2-oxazolidinone as the chiral auxiliary (single isomer, 81% yield in the alkylation step). The stereochemical course of such an alkylation process has been well established previously.[15] The observed diastereoselectivity and isolated yields of the asymmetric alkylation process in both cases

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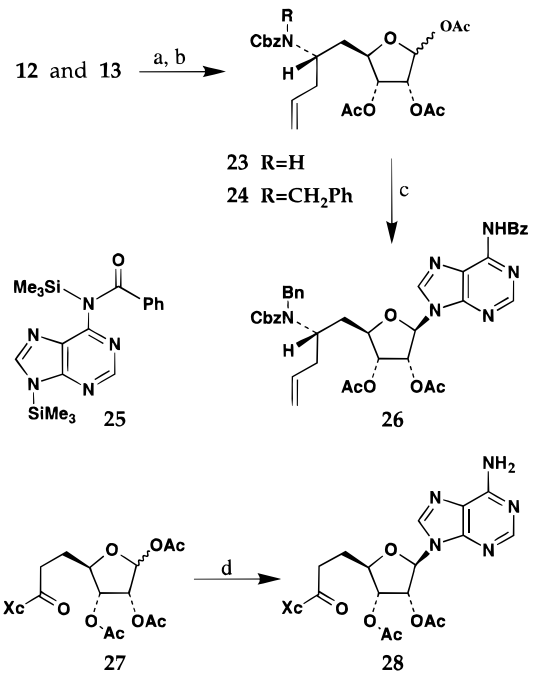
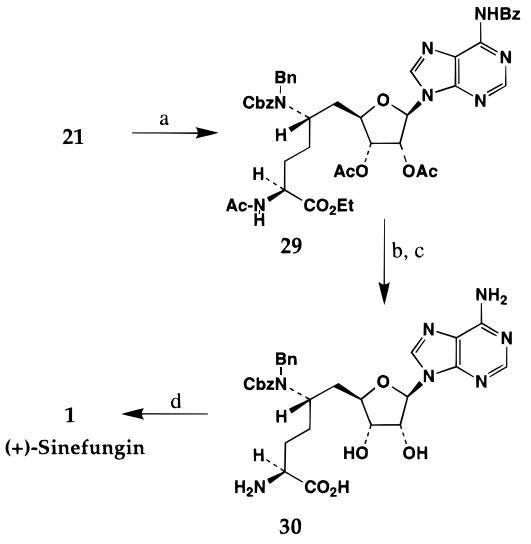
Scheme 4[a]



[a] Key: (a) aqueous HCl, dioxane, 23 °C; (b) Ac_2O, pyridine, 0 °C to 23 °C, 10 h; (c) TMSOTf, silyl N^6-benzoyladenine **25**, $ClCH_2CH_2Cl$, 23 °C, 3 h; (d) $SnCl_4$, adenine, CH_3CN, 23 °C.

Scheme 5[a]



[a] Key: (a) TMSOTf, silyl N^6-benzoyladenine **22**, $ClCH_2CH_2Cl$, 45 °C, 2 h; (b) K_2CO_3, MeOH, 23 °C, 8 h; (c) NH_2NH_2, H_2O, 23 °C, 2 h and then H_3O^+ (pH 7.0); (d) H_2, 20% $Pd(OH)_2$−C, MeOH, 48 h.

are quite comparable. Thus, the constrained chiral oxazolidinone **8** complements the chiral oxazolidinone derived from the L-phenylalaninol.

For conversion of the carboxylic acid to the correponding protected amine derivative, a Curtius rearrangement was sought.[16] Thus, the above acid **11** without further purification was exposed to 1.2 equiv of diphenyl phosphorazidate and 1.2 equiv of triethylamine in refluxing toluene for 2 h. Benzyl alcohol (2 equiv) was added, and the resulting mixture was heated at a reflux for 12 h to furnish the urethane **12** (Cbz-derivative) in 79% yield (from **10**) after silica gel chromatography. The stereochemistry of the urethane bearing chiral center in **12** was assigned based upon the fact that the Curtius rearrangement proceeds with retention of configuration of the migrating carbon atom.[17] For the anomeric adenosylation reaction, it was necessary to convert the urethane NH as its *N*-benzyl urethane **13.** This was accomplished by *N*-benzylation of **12** with sodium hydride and benzyl bromide in a mixture of THF/DMF (10:1) at 23 °C for 12 h to provide **13**. To elaborate the C-9 amino acid stereochemistry, the *N*-benzyl urethane **13** was then transformed into the corresponding α-(acylamino)acrylate derivatives **16** and **17**. Thus, ozonolysis of the terminal olefin of **13** in a mixture (1:1) of methanol and CH_2Cl_2 at −78 °C followed by reductive workup with dimethyl sulfide afforded the corresponding aldehyde which was exposed to a Horner−Emmons type olefination with the enolate derived from ethyl *N*-acetyl-α-(diethylphosphonyl)glycinate[18] and KO*t*Bu in CH_2Cl_2 at −78 °C to 23 °C for 5 h. This provided a 1:5 mixture of *E* and *Z*-enamides **16** and **17** in 64% yield (from **12**) after silica gel chromatography. Determination of the isomer ratio by ^{1}H-NMR ($CDCl_3$ or DMSO-d_6) was complicated due to the presence of the Cbz-protecting group which resulted in a number of rotational isomers at 23 °C. When the temperature was raised, the rotation about the N−C bond became appreciable and at coalescence temperature (T_c, *ca.* 74 °C in DMSO-d_6), the mixture of broad peaks merged into sharp peaks corresponding to major and minor isomers (1:5 mixture by ^{1}H-NMR integration) **16** and **17**. The eneamides **14** and **15** derived from **12**, however, revealed the presence of a 1:6 mixture of the corresponding *E*- and *Z*-enamide by ^{1}H-NMR (400 MHz) in $CDCl_3$. Identification of the *E*- and *Z*-isomers derived from **12** or **13** was made by ^{1}H-NMR (400 MHz, $CDCl_3$) spectroscopy. The vinylic chemical shift value (6.6 ppm) for the *Z*-isomer **17** is about 0.3 ppm upfield relative to the *E*-isomer **16** (6.9 ppm) which is characteristic of the double bond configuration of the *E*- and *Z*-enamido ester.[19] The *E*,*Z*-isomers **14** and **15** or **16** and **17** were inseparable by chromatography. Since "Rh-(*R*,*R*)-DIPAMP" based asymmetric hydrogenation of both *E*- and *Z*-isomers is well known[20] to provide the *S*-enantiomer with excellent enantiomeric excess, the mixture was utilized in the subsequent reaction. Thus, asymmetric hydrogenation of the mixture of enamides (**16** and **17**; 1:5 mixture) was carried out in methanol in the presence of $[Rh(COD)(R,R\text{-DIPAMP})_2]^+BF_4^-$ (6 mol %) catalyst[21] at 23 °C under 50 psi hydrogen pressure for 10 h to provide the 9-*S*-isomer **18**. The ^{1}H-NMR of **18** was again complicated by the presence of a 4:1 mixture of rotational isomers. At coalescence temperature (T_c, *ca.* 70 °C in DMSO-d_6), the mixture of peaks merged into one sharp

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spectrum. The removal of both *N*-benzyl and Cbz-group by a catalytic hydrogenation over $Pd(OH)_2$−C in methanol afforded the corresponding amine whose ^{1}H-NMR (400 MHz) revealed the presence of a single isomer. Further reaction of the amine with benzyl chloroformate in the presence of triethylamine and a catalytic amount of DMAP furnished the Cbz-derivative **19**.[22] The ^{13}C-NMR analysis of **19** has also established the presence of a single isomer. In order to have access to the C-9(*R*)-diastereomer, asymmetric hydrogenation of the mixture of eneamides (**14** and **15**) was accomplished in methanol in the presence of [Rh(norbornadiene)(*S,S*)-Chiraphos)]$^+$ClO_4^- (6 mol %) as the catalyst[23] to provide **22** in 95% isolated yield. The diastereomeric excess of various asymmetric hydrogenation processes was determined by HPLC analysis using a Daicel OD column[24] with 10% 2-propanol in hexane as the eluent. The optical purity of **18** was determined to be >98% by HPLC. Further HPLC analysis of **19** derived from **18** has established the diastereomeric excess to be 98%.[25] The asymmetric hydrogenation of eneamides **14** and **15** with [Rh(COD)-(*R,R*-DIPAMP)$_2$]$^+$BF_4^- has also provided **19** with 98% de (by HPLC). The ^{1}H-NMR and ^{13}C-NMR, however, revealed one isomer. In contrast, the diastereomeric excess of C-9(*R*)-diastereomer **22** was found to be 81% by HPLC.

After introduction of appropriate chirality at the C-6 and C-9 positions corresponding to (+)-sinefungin structure, the next synthetic plan was to incorporate adenine at the anomeric position. The removal of the isopropylidene group as well as the methyl acetal was effected by treatment of **18** with aqueous HCl and dioxane at 23 °C for 12 h, providing the corresponding triol. Without further purification, the resulting triol was exposed to acetic anhydride in pyridine at 0 °C to 23 °C for 10 h to furnish the triacetate **21** (3:2 mixture of anomers by ^{1}H-NMR) in 70% yield after chromatography. The mixture of anomers was difficult to separate by silica gel chromatography and was utilized for the subsequent adenosylation reaction. For initial anomeric adenosylation, urethane **20** (1:1 mixture of anomers) was employed; however, no desired product was obtained under a variety of reagents and reaction conditions. Treatment of **20** with excess of adenine and $SnCl_4$ in acetonitrile[26] at 23 °C to 60 °C did not yield any adenosylation product, and the starting triacetates **20** were found to be destroyed under these reaction conditions. Similarly, attempts to effect the adenosylation reaction of **23** derived from **12** under a variety of reagents and reaction conditions were unsuccessful. The mixture (1:1) of anomeric acetates **24** derived from the *N*-benzyl urethane derivative **13**, however, underwent adenylation smoothly under Vorbrüggen[27] reaction conditions. Anomeric adenosylation of **24** was effectively carried out as follows: N^6-benzoyladenine was treated with TMSCl in hexamethyldisilazane at reflux for 5 h and the resulting bis-silyl-*N*-benzoyladenine **25** (1.2 equiv)[27] was reacted with triacetate **24** in the presence of 1.2 equiv of TMSOTf in dichloroethane at 23 °C for 3 h to afford the protected β-nucleoside **26** in 98% yield after silica gel chromatography. Slight modification of the above reaction conditions proved to be optimum for the adenosylation of anomers **21**. Thus, reaction of the mixture (1:1) of anomers **21** with 4 equiv of bis-silyl-*N*-benzoyladenine **25** and 4 equiv of TMSOTf in dichloroethane at 45 °C for 2 h furnished the protected sinefungin derivative **29** in 93% yield after silica gel chromatography. In contrast, adenosylation of **21** with adenine and $SnCl_4$ in acetonitrile at 23 °C to 60 °C under a variety of conditions afforded only a trace amount of N^6-debenzoyl derivative of **29**. Similarly, reactions of anomeric acetates **24** with $SnCl_4$ provided only a small amount of desired adenosylation product (5−8% yield). On the other hand, adenosylation of the mixture of anomeric acetates **27** provided the corresponding β-nucleoside **28** in 58% yield after chromatography.[28] Thus, it is apparent that the substitutent at C-6 has a pronounced effect on the adenosylation reaction; however, the exact role is not clear.

To complete the synthesis of sinefungin, we needed to remove various protecting groups in **29**. This was accomplished in one pot by a three-step sequence. Thus, exposure of **29** with K_2CO_3 in methanol at 23 °C for 8 h followed by removal of methanol and treatment with 5 equiv of aqueous hydrazine at 23 °C for 2 h effected the hydrolysis of esters, benzoyl amide as well as acetamide functionalities affording the sinefungin derivative **30**.[29] Subsequent removal of the carbobenzyloxy and *N*-benzyl protecting groups of **30** was carried out after evaporation of solvent from the above reaction mixture under reduced pressure followed by hydrogenation of the residue in methanol in the presence of $Pd(OH)_2$/C (20% wt) under atmospheric hydrogen for 48 h. The resulting crude sinefungin was purified by silica gel chromatography (eluent, MeOH:$CHCl_3$:NH_4OH = 3:5:1) to furnish the synthetic (+)-sinefungin **1** (α_D^{23} +13.4; *c*, 0.12, H_2O; lit.[9a] α_D^{23} +12.4 ± 0.2°; *c*, 0.227, H_2O) with ^{1}H-NMR (400 MHz) spectroscopic data in full agreement with the ^{1}H-NMR spectra of both natural and synthetic (+)-sinefungin kindly provided by Professor Henry Rapoport.

Conclusion

A concise synthesis of (+)-sinefungin has been accomplished in a stereocontrolled fashion from D-ribose. The key steps in the synthesis are a diastereoselective alkylation and Curtius rearrangement to set the C-6 amine functionality. A chiral bisphosphine−rhodium-catalyzed asymmetric hydrogenation of an α-(acylamino)-acrylate derivative is used to set the C-9 amino acid stereochemistry. Diastereoselective alkylation of a (1*S*,2*R*)-1-amino-2-indanol-derived oxazolidinone is noteworthy. Since both enantiomers of *cis*-1-amino-2-indanols are commercially available,[30] the present asym-

(22) For HPLC analysis, a mixture of C-9 diastereomers were prepared by hydrogenation of the mixture of enamides **14** and **15** over 5% Pd−C in methanol under a hydrogen filled balloon at 23 °C for 8 h. This has afforded a mixture (60:40) of **19** and **22** in 78% isolated yield.

(23) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262.

(24) Daicel OD column was purchased from Chiral Technologies, 730 Springdale Dr., Exton, PA.

(25) Isocratic normal phase HPLC analysis on a Chiralcel OD column (25 cm) using 10% 2-propanol in hexane as eluant (flow rate: 1.1 mL/min) and UV detection at 254 nm indicated that both diastereomers could be cleanly separated. Retention times for diastereomer **19**: 17.10 min and diastereomer **22**: 20.67 min.

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(28) The presence of azide functionality at C-6 also does not interfere with the adenosylation reaction under this conditions. Rapoport has reported[9a] 59% yield of the corresponding β-nucleoside by a $SnCl_4$-catalyzed adenosylation reaction of the anomeric acetates containing C-6 azide and C-9 amino acid protected as *p*-toluenesulfonamide and *tert*-butyl ester.

(29) The ^{1}H-NMR (D_2O) of a crude sample of **30** indicated the absence of benzoyl, acetyl, and ethyl ester groups.

metric alkylation would provide access to either stereochemistry at C-6. Similarly, with choice of chiral catalyst, asymmetric hydrogenation of the α-(acylamino)-acrylate derivative would enable one to obtain either stereoisomer at C-9. The current synthesis is flexible and therefore provides a convenient access to the synthesis of various sinefungin analogues for biological evaluation. Further study of the chemistry and biology of sinefungin is an active area of research in our laboratory.

Experimental Section

All melting points were recorded and uncorrected. Analytical HPLC analyses were performed on a Daicel OD column (4.6 mm × 25 cm) with 10% *i*PrOH/hexane as the solvent, flow rate 1.1 mL/min, λ 254 nm). Anhydrous solvents were obtained as follows: 1,2-dichloroethane was first refluxed for 2 h over P_2O_5 and then followed by distillation; tetrahydrofuran distillation from sodium and benzophenone; methylene chloride, distillation from P_2O_5; trimethylchlorosilane, pyridine, and dimethoxyethane distillation from CaH_2. All other solvents were HPLC grade. N^6-Benzoyladenine was recrystallized from MeOH. Column chromatography was performed with Whatman 240−400 mesh silica gel under low pressure of 5−10 psi. Thin-layer chromatography (TLC) was carried out with E. Merck silica gel 60 F-254 plates.

Methyl 2,3-*O*-Isopropylidene-β-D-ribofuranoside 5. Powdered D-ribose (5.85 g, 39 mmol) and anhydrous cuprous sulfate (12.4 g) were suspended in a mixture of acetone (110 mL) and methanol (32 mL) containing a catalytic amount of concentrated sulfuric acid (0.2 mL). The resulting mixture was stirred at 40 °C for 48 h. After this period, the mixture was filtered and the filter cake was washed with a mixture of acetone and methanol (1:1 mixture, 100 mL). The resulting solution was neutralized with saturated $NaHCO_3$ aqueous solution, and the methanol and acetone were removed under reduced pressure. The residue was extracted with EtOAc (3 × 50 mL). The combined EtOAc layers were washed with brine and dried (Na_2SO_4). Concentration and chromatography (25%EtOAc/hexanes) provided **5** as an oil (5.69 g, 72%). $[\alpha]_D^{23}$ −73.8 (*c* 1.1, $CHCl_3$); lit.[31] $[\alpha]_D^{23}$ −78.5 (*c* 2.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ; 1.31 (s, 3 H), 1.47 (s, 3 H), 3.25 (br s, 1 H), 3.43 (s, 3 H), 3.60 (dd, 1 H, *J* = 12.5, 3.1 Hz), 3.69 (dd, 1 H, *J* = 12.5, 2.2Hz), 4.43 (t, 1 H, *J* = 2.6 Hz), 4.57 (d, 1 H, *J* = 5.9 Hz), 4.83 (d, 1 H, *J* = 5.9 Hz), 4.97 (s, 1 H); IR (neat) 3458, 2988, 2940, 1383, 1210, 1093, 1044, 870 cm^{-1}.

***trans*-Ethyl [Methyl 5,6-dideoxy-2,3-*O*-(1-methylethylidene)-β-D-*ribo*-hept-5-enofuranosid]uronate (6).** To a stirred solution of DMSO (3.9 mL) in dry CH_2Cl_2 (45 mL) at −60 °C was added oxalyl chloride (2.4 mL) over a period of 5 min. The resulting mixture was stirred for additional 3 min and then the alcohol **5** (3.74 g, 18.3 mmol) in CH_2Cl_2 (30 mL) was added over 2 min. The mixture was stirred at −60 °C for 2 h. After this period, the reaction was quenched with triethylamine (10 mL), and the resulting mixture was stirred for an additional 5 min at −60 °C and then allowed to warm to 23 °C. The reaction mixture was diluted with water (20 mL), the resulting mixture was concentrated under reduced pressure, and the residue was extracted with EtOAc (3 × 50 mL). The combined EtOAc layers were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude aldehyde which was used directly without further purification.

To suspension of NaH (60%, 1.47 g, 36.8 mmol) in THF (100 mL) at 0 °C was added triethyl phosphonoacetate (7.3 mL, 36.8 mmol) dropwise over a period of 5 min. The resulting reaction mixture was allowed to warm up to 23 °C and was stirred for another 40 min. After this period, the reaction mixture was cooled to 0 °C and the above crude aldehyde in THF (20 mL) was added. The reaction mixture was stirred for 5 min and then allowed to warm up to 23 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent provided a residue which was chromatographed over silica gel (10% EtOAc/hexanes) to provide the title ester **6** as a clear oil (3.53 g, 72%). $[\alpha]_D^{23}$ −38.3 (*c* 1.3, $CHCl_3$); ^{1}H-NMR($CDCl_3$) δ ; 1.29 (t, 3 H, *J* = 7.2 Hz), 1.30 (s, 3 H), 1.50 (s, 3 H), 3.37 (s, 3 H), 4.20 (q, 2 H, *J* = 7.1 Hz), 4.60 (d, 1 H, *J* = 5.9 Hz), 4.66 (d, 1 H, *J* = 5.9 Hz), 4.75 (d, 1 H, *J* = 7.1 Hz), 5.01 (s, 1 H), 5.99 (d, 1 H, *J* = 15.5 Hz), 6.88 (dd, 1 H, *J* = 15.7,7.1 Hz); IR (neat) 2984, 2938, 1722, 1372, 1177, 1092, 981, 868 cm^{-1}; MS (CI) *m*/*z* 273 (M^+ + H), 257 (M^+ − Me), 241 (M^+ − OMe), 214.

Methyl 5,6-Dideoxy-2,3-*O*-(1-methylethylidene)-β-D-*ribo*-heptofuranosiduronic acid 7. To a solution of **6** (3.27 g, 12 mmol) in ethyl acetate (200 mL) was suspended 10% Pd/C (490 mg). The resulting mixture was hydrogenated under a hydrogen-filled balloon for 9 h. After this period, the mixture was filtered through a Celite pad, and the Celite pad was washed with additional ethyl acetate (50 mL). Evaporation of the solvent under reduced pressure gave a residue which was chromatographed over silica gel to furnish the corresponding saturated ester as an oil (3.29 g, 99%). $[\alpha]_D^{23}$ −34.3 (*c* 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ; 1.22 (t, 3 H, *J* = 7.1 Hz), 1.27 (s, 3 H), 1.43 (s, 3 H), 1.85 (m, 2 H), 2.42 (m, 2 H), 3.31 (s, 3 H), 4.10 (m, 3 H), 4.51 (d, 1 H, *J* = 5.9 Hz), 4.59 (d, 1 H, *J* = 5.9 Hz), 4.91 (s, 1 H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ; 14.08, 24.84, 26.35, 30.10, 30.90, 54.97, 60.32, 83.91, 85.35, 86.06, 109.56, 112.17, 172.83; IR (neat) 2983, 2937, 1720, 1372, 1209, 1162, 1093, 869 cm^{-1}; MS (CI) *m*/*z* 275 (M^+ + H), 259 (M^+ − Me), 243 (M^+ − OMe), 216.

To a mixture of the above ester (2.2 g, 8.03 mmol) in water (50 mL) and THF (10 mL) at 23 °C was added solid $LiOH \cdot H_2O$ (1 g, 24 mmol), and the resulting reaction mixture was stirred for 12 h. After this period, the solvents were removed under reduced pressure, and the residue was cooled down to 0 °C and carefully acidified with 10% citric acid to pH 4. The mixture was thoroughly extracted with ethyl acetate (3 × 70 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give the title acid as an oil (1.98 g, 100%) which was used for the next reaction without further purification. $[\alpha]_D^{23}$ −37.9° (*c* 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ; 1.30 (s, 3 H), 1.46 (s, 3 H), 1.87 (dd, 2 H, *J* = 15.0, 7.6 Hz), 2.50 (m, 2 H), 3.34 (s, 3 H), 4.20 (t, 1 H, *J* = 7.7 Hz), 4.53 (d, 1 H, *J* = 5.9 Hz), 4.61 (d, 1 H, *J* = 5.9 Hz), 4.95 (s, 1 H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ; 24.84, 26.35, 29.81, 30.61, 55.09, 83.90, 85.33, 85.85, 109.65, 112.31, 178.99. IR (neat) 3200−3600, 2989, 2937, 1714, 1383, 1210, 1092, 962, 866 cm^{-1}; MS (CI) *m*/*z* 247 (M^+ + H), 231 (M^+ − Me), 229 (M^+ − OH), 215 (M^+ − OMe), 157.

***N*-[Methyl 5,6-dideoxy-2,3-*O*-(1-methylethylidene)-β-D-*ribo*-heptofuranosiduronyl]-(4*S*,5*R*)-indano[1,2-*d*]oxazolidin-2-one 9.** To a stirred solution of **7** (1.82 g, 7.5 mmol) in dry THF (50 mL) at −15 °C was added triethylamine (2 mL) followed by trimethylacetyl chloride (1 mL). After 15 min, the reaction slurry was allowed to warm up to 0 °C over 20 min and then recooled to −78 °C. In a separate flask, the (4*S*,5*R*)-indano[1,2-*d*]oxazolidin-2-one **8** (1.43 g, 8 mmol) was dissolved in dry THF (75 mL), and the resulting solution was cooled to −60 °C. To this cold solution, was added *n*-butyllithium (1.6 M in hexane, 5.1 mL) over a period of 15 min. After stirring for 10 min, the solution was taken up in a syringe and added to the white slurry prepared as described above. After the mixture was stirred for 1 h at −78 °C, 1 N sodium bisulfate (30 mL) was added and the reaction was allowed to warm to 23 °C. The resulting reaction mixture was concentrated under reduced pressure, and the residue was extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure and purification by silica gel chromatography (25% EtOAc/hexanes) provided the oxazolidinone **9** as an oil (2.1 g, 70%). $[\alpha]_D^{23}$ +158.2 (*c* 1.7, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ; 1.31 (s, 3 H), 1.47 (s, 3 H), 1.95 (m, 2 H), 3.09 (m, 2 H), 3.33 (s, 3 H), 3.48 (d, 2 H, *J* = 3.4 Hz),

(30) Available from Aldrich Chemical Co., Milwaukee, WI and Sepracor Inc., Marlborough, MA 01752.

(31) Boullais, C.; Zylber, N.; Zylber, J.; Guilhem, J.; Gaudemfr, A. *Tetrahedron* **1983**, *39*, 759.

4.25 (dd, 1 H, J = 9.0, 6.3 Hz), 4.60 (dd, 2 H, J = 8.1, 6.0 Hz), 4.94 (s, 1 H), 5.28 (m, 1 H), 5.91 (d, 1 H, J = 7.0 Hz), 7.27 (m, 3 H), 7.60 (d, 1 H, J = 7.6 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ; 24.95, 26.42, 29.29, 31.95, 37.92, 55.14, 62.99, 78.05, 84.00, 85.42, 85.89, 109.66, 112.21, 125.12, 127.14, 128.06, 129.78, 139.00, 139.41, 152.88, 172.74; IR (neat) 2985, 2935, 1784, 1689, 1364, 1192, 1107, 869, 757 cm^{-1}; MS (CI) m/z 404 (MH^+), 388 (M^+ − Me), 372 (M^+ − OMe), 314, 285, 204. Anal. Calcd for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.35; H, 5.99; N, 3.67.

***N*-[Methyl 5,6-dideoxy-2,3-*O*-(1-methylethylidene)-6(*S*)-allyl-β-D-*ribo*-heptofuranosiduronyl]-(4*S*,5*R*)-indano[1,2-*d*]oxazolidin-2-one 10.** To a stirred solution of **9** (1 g, 2.5 mmol) in dry THF (100 mL) at −78 °C was added lithium hexamethyldisilazide (1 M in hexane, 3.75 mL). The resulting solution was stirred at −78 °C for 1 h, and then allyl iodide (0.45 mL, 5 mmol) was added. The reaction mixture was stirred for 3 h, and then it was allowed to warm to −40 °C over 3 h. After this period, the reaction was quenched with saturated aqueous NH_4Cl (20 mL), and the resulting mixture was warmed up to 23 °C. The reaction mixture was concentrated under reduced pressure, and the residue was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporation of the solvent provided a residue which was purified by silica gel chromatography (25% EtOAc/hexanes) to afford the allylation product **10** (855 mg, 78% yield) as an oil. $[\alpha]_D^{23}$ +118 (*c* 0.6, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ; 1.30 (s, 3 H), 1.47 (s, 3 H), 1.75 (m, 1 H), 2.05 (m, 1 H), 2.25 (m, 1 H), 2.41 (m, 1 H), 3.38 (s, 5 H), 4.12 (m, 1 H), 4.23 (dd, 1 H, J = 10.9, 4.5 Hz), 4.58 (dd, 2 H, J = 12.1, 6.0 Hz), 4.95 (m, 3 H), 5.27 (m, 1 H), 5.68 (m, 1 H), 5.95 (d, 1 H, J = 6.9 Hz), 7.20−7.38 (m, 3 H), 7.54 (d, 1 H, J = 7.6 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ; 24.82, 26.39, 35.63, 37.10, 37.79, 38.92, 55.53, 63.04, 77.96, 84.32, 84.44, 85.37, 109.94, 112.09, 117.67, 125.06, 127.01, 127.98, 129.68, 134.22, 139.16, 139.37, 152.50, 175.29. IR (neat) 2979, 2935, 1779, 1695, 1360, 1189, 1088, 758 cm^{-1}; MS (CI) m/z 444 (M^+ + H), 412 (M^+ − OMe), 354, 325, 269. Anal. Calcd for $C_{24}H_{29}NO_7$: C, 65.00; H, 6.59; N, 3.16. Found: C, 64.81; H, 6.63; N, 3.30.

Methyl 5,6-Dideoxy-2,3-*O*-(1-methylethylidene)-6(*S*)-allyl-β-D-*ribo*-heptofuranosiduronic Acid 11. To a stirred solution of **10** (775 mg, 1.75 mmol) in a mixture of THF (30 mL) and water (10 mL) at 0 °C was added solid $LiOH·H_2O$ (145 mg, 3.5 mmol) followed by hydrogen peroxide (30%, 0.7 mL). The resulting mixture was stirred for 1 h at 0 °C and then 3 h at 23 °C. After this period, the reaction was quenched with 1.5 M aqueous Na_2SO_3 solution (1.5 mL) followed by saturated aqueous $NaHCO_3$ solution (10 mL). The mixture was concentrated under reduced pressure. The remaining residue was diluted with water (25 mL) and then extracted with dichloromethane (2 × 25 mL) to remove the chiral auxiliary. The aqueous phase was carefully acidified with 1 N HCl to pH 1 and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The resulting residue was purified by silica gel chromatography (25% EtOAc/hexanes) to afford the title acid **11** (498 mg, 98%) as an oil. $[\alpha]_D^{23}$ −19.5° (*c* 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ; 1.30 (s, 3 H), 1.47 (s, 3 H), 1.73 (m, 1 H), 1.85 (m, 1 H), 2.30 (m, 1 H), 2.43 (m, 1 H), 2.75 (m, 1 H), 3.35 (s, 3 H), 4.28 (dd, 1 H, J = 11.2, 4.1 Hz), 4.53 (d, 1 H, J = 5.9 Hz), 4.61 (d, 1 H, J = 5.9 Hz), 4.95 (s, 1 H), 5.60 (m, 2 H), 5.75 (m, 1 H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ; 24.83, 26.33, 36.23, 36.68, 41.63, 55.28, 84.30, 84.73, 85.37, 109.97, 112.25, 117.55, 134.42, 180.42; IR (neat) 3150, 3077, 2982, 2937, 1737, 1708, 1441, 1374, 1193, 1093, 1060, 963, 869 cm^{-1}; MS (CI) m/z 287 (M^+ + H), 271 (M^+ − Me), 269 (M^+ − OH), 255 (M^+ − OMe), 229, 214, 197, 157 Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.74. Found: C, 58.56; H, 7.82.

6(*S*)-Allyl-*N*-[(phenylmethoxy)carbonyl][methyl 5,6-dideoxy-2,3-*O*-(1-methylethylidene)-β-D-*ribo*-heptofuranosid]uramine 12. To a stirred solution of acid **11** (440 mg, 1.55 mmol) in dry toluene (50 mL) were added diphenyl phosphorazidate (0.4 mL, 1.85 mmol) and triethylamine (0.25 mL, 1.85 mmol). The resulting mixture was heated at reflux for 2 h, and then benzyl alcohol (0.3 mL, 3.1 mmol) was added. Stirring and refluxing were continued for an additional 12 h. After this period, the reaction was cooled to 23 °C, and the solvents were evaporated under reduced pressure. The resulting residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The layers were separated, and the organic phase was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave a residue which was chromatographed over silica gel (5% EtOAc/benzene) to furnish **12** (475 mg, 79%) as a white foam. $[\alpha]_D^{23}$ +3.9 (*c* 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ; 1.30 (s, 3 H), 1.47 (s, 3 H), 1.59 (m, 1 H), 1.80 (m, 1 H), 2.30 (m, 2 H), 3.34 (s, 3 H), 3.95 (m, 1 H), 4.33 (dd, 1 H, J = 11.0, 3.8 Hz), 4.53 (d, 1 H, J = 5.9 Hz), 4.59 (d, 1 H, J = 5.9 Hz), 4.89 (d, 1 H, J = 9.0 Hz), 4.96 (s, 1 H), 5.08 (m, 4 H), 5.75 (m, 1 H), 7.33 (m, 5 H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ; 24.87, 26.38, 39.08, 39.47, 48.18, 55.23, 66.49, 83.72, 84.44, 85.36, 109.15, 112.27, 118.11, 127.96, 128.38, 128.40, 133.89, 136.52, 155.73; IR (neat) 3360, 2919, 1698, 1520, 1265, 1212, 1108, 1057, 964, 870, 695 cm^{-1}; MS (CI) m/z 392 (M^+ + H), 360 (M^+ − OMe), 350, 316. Anal. Calcd for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.35; H, 7.54; N, 3.51.

6(*S*)-Allyl-*N*-(phenylmethyl)-*N*-[(phenylmethoxy)carbonyl][methyl 5,6-dideoxy-2,3-*O*-(1-methylethylidene)-β-D-*ribo*-heptofuranosid]uramine 13. To a stirred suspension of NaH (60%, 290 mg) in a mixture (10:1) of THF−DMF (50 mL) at 23 °C was added the urethane **12** (475 mg, 1.2 mmol) in THF (2 mL). The mixture was stirred at 23 °C for 1 h. After this period, benzyl bromide (1.25 g, 7.3 mmol) followed by tetrabutylammonium iodide (25 mg) were added, and the resulting reaction mixture was stirred for an additional 10 h at 23 °C. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was concentrated under reduced pressure to a small volume. The residue was extracted with ethyl acetate (3 × 50 mL), and the combined extracts were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification of the residue by silica gel chromatography (10% EtOAc/hexanes) provided the *N*-benzyl derivative **13** (510 mg, 87%) as an oil. $[\alpha]_D^{23}$ +27.0 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (major, $CDCl_3$, 400 MHz) δ; 1.29 (s, 3 H), 1.47 (s, 3 H), 1.70 (m, 1 H), 2.01 (m, 1 H), 2.36 (m, 2 H), 3.32 (s, 3 H), 3.86 (br s, 1 H), 4.27 (m, 2 H), 4.50 (m, 2 H), 4.69 (d, 1 H, J = 15.8 Hz), 4.90 (m, 3 H), 5.15 (d, 1 H, J = 5.0 Hz), 5.21 (s, 1 H), 5.49 (m, 1 H), 7.18-7.45 (m, 10 H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ; 24.81, 26.36, 36.75, 37.88, 38.67, 55.26, 56.02, 66.89, 67.40, 83.90, 84.25, 85.44, 109.92, 112.06, 117.08, 127.17, 127.79, 128.02, 128.14, 128.32, 135.15, 136.56, 138.48, 155.50; IR (neat) 2985, 2933, 1697, 1454, 1371, 1230, 1089, 1010, 869, 750, 699 cm^{-1}; MS (CI) m/z 482 (M^+ + H), 450 (M^+ − OMe), 440, 408. Anal. Calcd for $C_{28}H_{35}NO_6$: C, 69.83; H, 7.33; N, 2.91. Found: C, 70.06; H, 7.29; N, 2.94.

Ethyl [Methyl 9-(*N*-acetylamino-6(*S*)-[*N*-(phenylmethyl)-*N*-[(phenylmethoxy)carbonyl]amino]-5,6,7,8,9-pentadeoxy-2,3-*O*-(1-methylethylidene)-β-D-*ribo*-dec-8-enofuranosid]-uronate 16 and 17. To a stirred solution of **13** (445 mg, 0.9 mmol) in a mixture of methanol (100 mL) and CH_2Cl_2 (100 mL) at −78 °C was bubbled through a stream of ozonized oxygen until the blue color persisted (10 min). After the solution was flushed with nitrogen for 5 min, dimethyl sulfide (1.5 mL) was added to the reaction mixture at −78 °C. The dry ice bath was removed and the reaction mixture was allowed to warm to 23 °C. Evaporation of the solvent under reduced pressure gave the crude aldehyde which was used directly without further purification. In a separate flask, potassium *tert*-butoxide (330 mg, 2.8 mmol) was suspended in dry CH_2Cl_2 (5 mL) at −78 °C, and to it was added a solution of *N*-acyl-α-(diethylphosphonyl)glycine ethyl ester (780 mg, 2.8 mmol) in CH_2Cl_2 (10 mL). The resulting mixture was stirred for 1 h at −78 °C, and then the crude aldehyde in CH_2Cl_2 (15 mL) was added dropwise for 5 min. The reaction mixture was continued to stir at −78 °C for an additional 20 min, the cooling bath was removed and the reaction was allowed to warm to 23 °C and stirred for another 4 h. After this period, the reaction was quenched with saturated aqueous NH_4Cl solution, and the two layers were separated. The aqueous layer was

extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave a residue which was chromatographed over silical gel (50% ethy acetate/hexane) to furnish the mixture (1:5) of olefins **16** and **17** (418 mg, 74% from compound **13**) as an oil. ^{1}H-NMR (major isomer $CDCl_3$, 400 MHz) δ; 1.25 (t, 3 H, J = 7.0 Hz), 1.30 (s, 3 H), 1.46 (s, 3 H), 1.67 (t, 1 H, J = 11.2 Hz), 1.90 (m, 1 H), 2.01 (s, 3 H), 2.27 (m, 1 H), 2.62 (m, 1 H), 3.33 (s, 3 H), 3.85 (br s, 1 H), 4.11 (q, 2 H, J = 7.0 Hz), 4.20 (m, 2 H), 4.45 (d, 2 H, J = 5.8 Hz), 4.97 (s, 1 H), 5.19 (m, 2 H), 5.85 (br s, 1 H), 6.33 (br s, 1 H), 7.10−7.40 (m, 10 H); IR (neat) 3310, 2983, 2937, 1694, 1498, 1454, 1372, 1232, 1092, 1027, 869, 753, 702 cm^{-1}; MS (CI) m/z 611 (M^+ + H), 579 (M^+ − OMe), 537, 533, 440. Anal. Calcd for $C_{33}H_{42}N_2O_9$: C, 64.90; H, 6.93; N, 4.59. Found: C, 64.71; H, 6.78; N, 4.62.

Ethyl [Methyl 9-(*N*-acetylamino)-6(*S*)-[*N*-[(phenylmethoxy)carbonyl]amino]-5,6,7,8,9-pentadeoxy-2,3-*O*-(1-methylethylidene)-*β*-D-*ribo*-dec-8-enofuranosid]uronate 14 and 15. Following the procedure described above for **16** and **17**, urethane **12** (228 mg, 0.58 mmol) was converted to a mixture (1:6) of eneamides **14** and **15** (230 mg, 76% yield). ^{1}H-NMR (major isomer, $CDCl_3$, 400 MHz) δ; 1.25 (t, 3 H, J = 7.1 Hz), 1.30 (s, 3 H), 1.45 (s, 3 H), 1.75 (m, 2 H), 2.05 (s, 3 H), 2.40 (m, 2 H), 3.31 (s, 3 H), 3.90 (m, 1 H), 4.20 (q, 2 H, J = 7.1 Hz), 4.30 (m, 1 H), 4.57 (dd, 2 H, J = 6.0, 13.9 Hz), 4.94 (s, 1 H), 5.08 (s, 2 H), 5.77 (d, 1 H, J = 8.4 Hz), 6.55 (t, 1 H, J = 4.8 Hz), 7.2−7.4 (m, 5 H); IR (neat) 3384, 2983, 2298, 1244, 851, 755 cm^{-1}; MS (CI) m/z 521 (M^+ + H), 489 (M^+ − OMe), 447, 443, 350.

Ethyl [Methyl 9(*S*)-(*N*-acetylamino)-6(*S*)-[*N*-(phenylmethyl)-*N*-[(phenylmethoxy)carbonyl]amino]-5,6,7,8,9-pentadeoxy-2,3-*O*-(1-methylethylidene)-*β*-D-*ribo*-decofuranosid]uronate 18. In a hydrogenation bottle, the mixture (1:5) of enamide **16** and **17** (305 mg, 0.5 mmol) was dissolved in methanol (10 mL) and the catalyst [Rh(COD)(*R*,*R*-DIPAMP)]$^+BF_4^-$ (15 mg) was added to it. The bottle was then thoroughly flushed with nitrogen and charged with hydrogen to a pressure of 50 psig. The mixture was shaken on a Parr apparatus for 10 h under 50 psig at 23 °C. After this period, the solvent was removed by rotary evaporation and the residue was passed through a short silica gel column (50% ethyl acetate/hexane) to give the title hydrogenation product **18** (290 mg, 95%) as an oil. $[\alpha]_D^{23}$ +24.3 (c 0.7, $CHCl_3$); ^{1}H-NMR (DMSO-d_6, 70 °C, 400 MHz) δ; 1.15 (t, 3 H, J = 7.1 Hz), 1.21 (s, 3 H), 1.33 (s, 3 H), 1.35−1.66 (m, 6 H), 1.82 (s, 3 H), 3.20 (s, 3 H), 3.90 (m, 2 H), 4.03 (q, 2 H, J = 7.1 Hz), 4.15 (m, 1 H), 4.35 (s, 1 H), 4.41 (AB q, 2 H, $\Delta\nu_{AB}$ = 81 Hz, J_{AB} = 15.7 Hz), 4.45 (d, 1 H J = 5.9 Hz), 4.81 (s, 1 H), 5.13 (s, 2 H), 7.20−7.39 (m,10 H), 7.85 (d, 1 H, J = 7.3 Hz); IR (neat) 3300−3600, 2937, 2242, 1738, 1686, 1540, 1454, 1209, 1093, 1026, 870, 752, 700 cm^{-1}; MS (CI) m/z 613 (M^+ + H), 582 (M^+ + H − OMe), 581 (M^+ − OMe), 537, 445 Anal. Calcd for $C_{33}H_{44}N_2O_9$: C, 64.71; H, 7.19; N, 4.58. Found: C, 64.22; H, 7.34; N, 4.42.

Ethyl [Methyl 9(*S*)-(*N*-acetylamino)-6(*S*)-[(phenylmethoxy)carbonyl]amino]-5,6,7,8,9-pentadeoxy-2,3-*O*-(1-methylethylidene)-*β*-D-*ribo*-decofuranosid]uronate 19. To a stirred solution of **18** (20 mg, 0.033 mmol) in methanol (2 mL) was suspended 20 wt % $Pd(OH)_2$/C (5 mg) at 23 °C. The resulting mixture was hydrogenated under hydrogen-filled balloon for 12 h. The reaction mixture was then filtered through a pad of Celite, and the Celite pad was washed with methanol (10 mL). Evaporation of the solvent provided the crude amine. Without further purification, the amine was dissolved in $CHCl_3$ (3 mL) and benzyl chloroformate (17 mg, 1 mmol) followed by the addition of triethylamine (10 mg, 1 mmol) and DMAP (4 mg, 0.033 mmol). The resulting mixture was stirred at 23 °C for 12 h. After this period, the solution was concentrated, and the residue was chromatographed over silica gel (75%ethyl acetate/hexane) to give **19** (5 mg, 29% from **18**) as an oil. $[\alpha]_D^{23}$ +16.3 (c 0.84, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ; 1.25 (t, J = 7.1 Hz, 3 H), 1.28 (s, 3 H), 1.45 (s, 3 H), 1.53 (m, 3 H), 1.70 (m, 2 H), 1.83 (m, 1 H), 1.97 (s, 3 H), 3.31 (s, 3 H), 3.79 (m, 1 H), 4.15 (q, 2 H, J = 7.0 Hz), 4.28 (dd, 1 H, J = 11.0, 3.4 Hz), 4.50 (d, J = 5.9 Hz, 1 H), 4.55 (m, 2 H), 4.94 (s, 1 H), 5.03 (d, 1 H, J = 9.2 Hz), 5.08 (s, 2 H), 6.30 (d, 1 H, J = 7.8 Hz), 7.23−7.35 (m, 5 H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ; 14.05, 22.98, 24.83, 26.36, 28.89, 31.12, 39.80, 48.48, 51.90, 55.27, 61.42, 66.56, 83.66, 84.40, 85.27, 110.00, 112.28, 127.95, 127.99, 128.40, 136.42, 155.92, 169.90, 172.26; IR (neat) 3300−3400, 2940, 2241, 1733, 1708, 1651, 1537, 1454, 1372, 1256, 1092, 1026, 877 cm^{-1}; MS (CI) c/z 523 (M^+ + H), 492, 447, 355.

Ethyl 9(*S*)-(*N*-Acetylamino)-6(*S*)-[*N*-(phenylmethyl)-*N*-[(phenylmethoxy)carbonyl]amino]-5,6,7,8,9-pentadeoxy-1,2,3-tri-*O*-acetyl-*β*-D-*ribo*-decofuranosid]uronate and Its C-1 Epimer 21. To a stirred solution of **18** (208 mg, 0.34 mmol) in dioxane (24 mL) at 23 °C, aqueous 4 N HCl (8 mL) was added. The resulting mixture was stirred at 23 °C for 12 h. After this period, the reaction mixture was cooled to 0 °C, and the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was concentrated under reduced pressure, and the remaining residue was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to provide the corresponding triol. The above triol, without further purification was dissolved in dry pyridine (8 mL) and cooled to 0 °C, and acetic anhydride (692 mg, 6.8 mmol) was added. The resulting reaction mixture was stirred at 0 °C to 23 °C for 10 h. After this period, the reaction mixture was concentrated under reduced pressure, and saturated aqueous $NaHCO_3$ solution was added. The mixture was extracted with ethyl acetate (2 × 50 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by silica gel chromatography (75% EtOAc/hexanes) to provide the mixture (3:2) of anomeric acetates **21** (164 mg, 70% from compound **18**) as an oil. $[\alpha]_D^{23}$ +29.0 (c 1.1, $CHCl_3$); ^{1}H-NMR (DMSO-d_6, 70 °C, 400 MHz) δ; 1.15 (t, 3 H, J = 7.1 Hz), 1.40−1.70 (m, 6 H), 1.84 (s, 3 H), 1.95 (s, 1.5 H), 1.99 (s, 3 H), 2.00 (s, 3 H), 2.05 (s, 1.5 H), 3.95 (m, 2 H), 4.06 (q, 2 H, J = 7.1 Hz), 4.13 (m, 1 H), 4.25 (dd, 1 H, J = 15.6, 10.0 Hz), 4.47 (d, 1 H, J = 15.7 Hz), 4.83 (t, 1 H, J = 5.8 Hz, major), 4.90 (t, 1 H, J = 5.4 Hz, minor), 5.11 (s, 2 H), 5.20 (m, 1 H), 5.95 (s, 1 H, β-anomer), 6.23 (d, 1 H, J = 4.7 Hz, α-anomer), 7.18−7.38 (m, 10 H), 7.82 (br s, 1 H); IR (neat) 3323, 2957, 2203, 1739, 1689, 1372, 1223, 1011, 763, 701 cm^{-1}. MS (CI) m/z 685 (M^+ + H), 653, 626, 625, 565. Anal. Calcd for $C_{35}H_{44}N_2O_{12}$: C, 61.39; H, 6.48; N, 4.09. Found: C, 60.95; H, 6.51; N, 4.34.

Ethyl [Methyl 9(*R*)-(*N*-acetylamino)-6(*S*)-[(phenylmethoxy)carbonyl]amino]-5,6,7,8,9-pentadeoxy-2,3-*O*-(1-methylethylidene)-*β*-D-*ribo*-decofuranosid]uronate 22. In a hydrogenation bottle, the mixture (1:6) of enamide **14** and **15** (30 mg, 0.058 mmol) was dissolved in methanol (5 mL), and the catalyst (*S*,*S*)-CHIRAPHOS (10 mg) was added to it. The bottle was then thoroughly flushed with nitrogen and then charged with hydrogen to a pressure of 50 psig. The mixture was shaken on a Parr apparatus for 10 h under 50 psig at 23 °C. After this period, the solvent was removed by rotary evaporation, and the residue was passed through a short silica gel column (75% ethyl acetate/hexane) to give the title hydrogenation product **22** (29 mg, 96%) as an oil. $[\alpha]_D^{23}$ −16.0 (c 0.3, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ; 1.26 (t, 3 H, J = 7.2 Hz), 1.30 (s, 3 H), 1.47 (s, 3 H), 1.5−2.0 (m, 6 H), 2.04 (s, 3 H), 3.32 (s, 3 H), 3.90 (m, 1 H), 4.18 (q, 2 H, J = 7.1 Hz), 4.29 (dd, 1 H, J = 3.3, 11.2 Hz), 4.51 (d, 1 H, J = 5.9 Hz), 4.95 (d, 1 H, J = 7.6 Hz), 7.36 (m, 5 H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ; 14.06, 23.05, 24.84, 26.37, 28.59, 31.46, 40.04, 48.60, 52.40, 55.27, 61.44, 66.69, 83.64, 84.40, 85.28, 110.34, 112.35, 127.96, 128.01, 128.42, 136.37, 156.17, 170.06, 172.17; MS (CI) c/z 523 (M^+ + H), 491, 449, 352.

6(*S*)-Allyl-*N*-(phenylmethyl)-*N*-[(phenylmethoxy)carbonyl][methyl 5,6-dideoxy-1,2,3-tri-*O*-acetyl-*β*-D-*ribo*-heptofuranosid]uramine 24 and Its C-1 Epimer. Following the procedure described above for **21**, *N*-benzyl urethane **13** (214 mg, 0.44 mmol) was converted to a mixture (1:1) of anomeric acetates **24** (288.5 mg, 93% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ; 1.64 (m, 1 H), 2.03 (s, 3 H), 2.09 (s, 3 H), 2.10 (s, 3 H), 2.20 (m, 2 H), 2.36 (m, 1 H), 3.80−4.20 (series of m, 3 H), 4.65 (m, 1 H), 4.77−5.07 (m, 3 H), 5.17 (s, 2 H), 5.26 (m, 1 H), 5.50 (m, 1 H), 6.08 (d, 1 H, J = 5.9 Hz, β-anomer), 6.32 (d, 1 H, J = 4.5 Hz, α-anomer), 7.15−7.40 (m, 10 H).

6(*S*)-Allyl-1-[6-*N*-benzoyl-9*H*-purin-9-yl]-2,3-di-*O*-acetyl-*N*-(phenylmethyl)-*N*-[(phenylmethoxy)carbonyl]-*β*-D-*ribo*-heptofuranosid]uramine 26. To a stirred suspension of N^6-benzoyladenine (17.9 mg, 0.075 mmol) in 1,1,1,3,3,3-hexamethyldisilazane (1.5 mL) at 23 °C was added trimethylchlorosilane (0.3 mL), and the resulting mixture was heated at reflux for 5 h. The reaction mixture was cooled to 23 °C, and the solvent was removed under reduced pressure to provide the crude silylated N^6-benzoyladenine **25.** Dry 1,2-dichloroethane (2 mL) followed by the mixture of anomeric acetates **24** (32 mg, 0.057 mmol) dissolved in 1,2-dichloroethane (2 mL) was added to the silylated N^6-benzoyladenine **25** at 23 °C. The resulting mixture was then treated with TMSOTf (16.7 mg, 0.075 mmol) in 1,2-dichloroethane (0.2 mL). The reaction mixture was stirred at 23 °C for 3 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (1 mL), and the resulting mixture was extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was chromatographed over silica gel (2% MeOH/$CHCl_3$) to furnish the nucleoside derivative **26** (42 mg, 98%) as an oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ; 1.80 (m, 1 H), 2.04 (s, 6 H), 2.16−2.45 (m, 3 H), 4.00 (m, 2 H), 4.35 (m, 1 H), 4.55 (m, 1 H), 4.95 (m, 3 H), 5.19 (s, 2 H), 5.30 (s, 1 H), 5.55 (br m, 1 H), 5.91 (s, 1 H), 7.12−7.40 (m, 10 H), 7.52 (t, J = 7.7 Hz, 2 H), 7.60 (t, J = 7.7 Hz, 1 H), 8.00 (d, J = 7.7 Hz, 2 H), 8.77 (s, 1 H), 9.09 (s, 1 H).

***N*-[5,6-Dideoxy-1,2,3-tri-*O*-acetyl-*β*-D-*ribo*-heptofuranuronyl]-(4*S*,5*R*)-indano[1,2-*d*]oxazolidin-2-one 27 and Its C-1 Epimer.** Following the procedure described above for **21**, oxazolidinone **9** (181 mg, 0.45 mmol) was converted to a mixture (3:1) of anomeric acetates **27** (148 mg, 69% yield). ^{1}H-NMR (major anomer, $CDCl_3$, 400 MHz) δ; 1.90−2.20 (m, 2 H), 2.05 (s, 3 H), 2.10 (s, 3 H), 2.13 (s, 3 H), 3.05 (m, 2 H), 3.39 (m, 2 H), 4.31 (m, 1 H), 5.20 (dd, 1 H, J = 4.8, 7.4 Hz), 5.30 (m, 1 H), 5.92 (d, 1 H, J = 6.9 Hz), 6.11 (s, 1 H), 7.20−7.35 (m, 3 H), 7.60 (d, 1 H, J = 7.4 Hz); IR (neat) 3422, 1769, 1747, 1693, 1649, 1366, 1220, 1010, 757 cm^{-1}; MS (CI) m/z 476 (M^+ + H), 416, 356.

***N*-[1-[9-Adenyl]-2,3-di-*O*-acetyl-5,6-dideoxy-*β*-D-*ribo*-heptofuranuronyl]-(4*S*,5*R*)-indano[1,2-*d*]oxazolidin-2-one 28.** To a stirred solution of **27** (74.2 mg, 0.156 mmol) in dry acetonitrile (3 mL) at 23 °C under nitrogen were added adenine (21.1 mg, 0.156 mmol) and $SnCl_4$ (0.16 mL, 1.0 M solution in CH_2Cl_2, Aldrich). The resulting mixture was stirred at 25 °C for 3 h. After this period, $CHCl_3$ (20 mL) followed by aqueous $NaHCO_3$ solution (5 mL) were added. The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (2 × 10 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was chromatographed over silica gel (5% MeOH/$CHCl_3$) to furnish the nucleoside derivative **28** (49.8 mg, 58%) as an oil. $[\alpha]_D^{23}$ +107.9 (*c* 1.05, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ; 2.05 (s, 3 H), 2.11 (s, 3 H), 2.25 (dd, 2 H, J = 7, 14 Hz), 3.08 (m, 2 H), 3.37 (s, 2 H), 4.32 (dd, 1 H, J = 6.1, 12.3 Hz), 5.70 (m, 1 H), 5.52 (t, 1 H, J = 5.4 Hz), 5.90 (t, 2 H, J = 5.4 Hz), 5.95 (s, 2 H), 6.06 (d, 1 H, J = 5.0 Hz), 7.18−7.34 (m, 3 H), 7.56 (d, 1 H, J = 7.7 Hz), 7.95 (s, 1 H), 8.30 (s, 1 H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ; 20.36, 20.49, 27.30, 31.27, 37.89, 62.93, 73.05, 73.29, 77.15, 78.14, 81.03, 86.31, 120.05, 125.11, 127.11,-128.07, 129.82, 138.81, 139.21, 139.34, 149.56, 152.87, 155.26, 169.39, 169.62, 172.47; IR (neat) 3404, 1757, 1632, 1364, 1240, 753 cm^{-1}; MS (CI) m/z: 551 (M^+ + H), 416, 357.

Ethyl 2,3-Di-*O*-acetyl-1,5,6,7,8,9-hexadeoxy-1-[6-*N*-benzoyl-9*H*-purin-9-yl]-9(*S*)-(*N*-acetylamino)-6(*S*)-[*N*-(phenylmethyl)-*N*-[(phenylmethoxy)carbonyl]amino]-*β*-D-*ribo*-decofuranuronate 29. To a stirred suspension of N^6-benzoyladenine (56 mg, 0.24 mmol) in 1,1,1,3,3,3-hexamethyldisilazane (4 mL) at 23 °C, was added trimethylchlorosilane (0.4 mL) and the resulting mixture was heated at reflux for 5 h. The reaction mixture was cooled to 23 °C, and the solvent was removed under reduced pressure to provide the crude silylated N^6-benzoyladenine **25.** Dry 1,2-dichloroethane (4 mL) followed by a mixture of anomeric acetates **21** (40 mg, 0.058 mmol) dissolved in 1,2-dichloroethane (8 mL) was added to the silylated N^6-benzoyladenine **25** at 23 °C. The resulting mixture was then treated with TMSOTf (0.044 mL, 0.24 mmol) in 1,2-dichloroethane (0.4 mL). The reaction mixture was heated at 45 °C for 2 h. After this period, the mixture was cooled to 23 °C and the reaction was quenched with saturated aqueous $NaHCO_3$ (4 mL), and the resulting mixture was extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was chromatographed over silica gel (2% MeOH/$CHCl_3$) to furnish the nucleoside derivative **29** (46 mg, 93%) as an oil. $[\alpha]_D^{23}$ +4.9 (*c* 0.6, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 70 °C, 400 MHz) δ; 1.12 (t, 3 H, J = 7.1 Hz), 1.20−1.70 (series of m, 6 H), 1.82 (s, 3 H), 2.00 (s, 3 H), 2.05 (s, 3 H), 3.90 (m, 2 H), 4.01 (q, 2 H, J = 7.1 Hz), 4.12 (m, 1 H), 4.40 (AB q, 2 H, $\Delta\nu$ = 60 Hz, J = 15.6 Hz), 5.10 (d, 2 H, J = 7.0 Hz), 5.20 (t, 1 H, J = 5.0 Hz), 6.00 (t, 1 H, J = 5.5 Hz), 6.12 (d, 1 H, J = 5.5 Hz), 7.18−7.38 (m, 10 H), 7.55 (t, 2 H, J = 7.5 Hz), 7.65 (d, 1 H, J = 7.4 Hz), 7.80 (m, 1 H), 8.04 (d, 2 H, J = 7.4 Hz), 8.60 (s, 1 H), 8.71 (s, 1 H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ; 14.04, 20.33, 20.51, 23.09, 29.59, 51.57, 61.41, 67.49, 72.92, 73.26, 79.07, 86.79, 124.92, 127.32, 127.82, 127.89, 128.39, 128.80, 132.82, 136.33, 142.14, 149.60, 151.45, 152.49, 169.28, 169.42, 169.80, 172.06; IR (neat) 3301, 2928, 1745, 1693, 1454, 1245, 1096, 752, 701 cm^{-1}; MS (CI) m/z 864 (M^+ + H), 625 (M^+ − N^6-benzoyladenine), 565, 523. Anal. Calcd for $C_{45}H_{49}N_7O_{11}$: C, 62.56; H, 5.72; N, 11.35. Found: C, 62.25; H, 5.78; N, 11.23.

(+)-Sinefungin (1). To a stirred solution of the nucleoside **29** (23.2 mg, 0.027 mmol) in methanol (10 mL) was added solid potassium carbonate (18.6 mg, 0.135 mmol). The resulting mixture was stirred at 23 °C for 8 h. After this period, the reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in water (10 mL), and hydrazine (4.3 mg, 0.13 mmol) was added. The reaction mixture was then stirred at 23 °C for 2 h, and the water was removed under reduced pressure. The residue was diluted with water (1 mL) and neutralized with 1 N aqueous HCl to pH 7 to provide **30**.[29] The resulting mixture was concentrated under reduced pressure, the residue was dissolved in MeOH (10 mL), and 20% $Pd(OH)_2$/C (30 mg) was added to the solution. The resulting mixture was hydrogenated under a balloon filled with hydrogen for 48 h. The reaction mixture was then filtered through a pad of Celite, and the Celite pad was washed with MeOH (30 mL). The filtrate was concentrated under reduced pressure to leave a residue which was chromatographed over silica gel using a mixture of methanol, chloroform, and ammonium hydroxide (MeOH:$CHCl_3$:NH_4OH = 3:5:1) as the eluent to provide the synthetic sinefungin (7.4 mg, 72% from **29**); $[\alpha]_D^{23}$ +13.4 (*c*, 0.12 H_2O); lit.[9a] α_D^{23} +12.4 ± 0.2°; *c*, 0.227, H_2O).

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