Synthetic studies of nucleoside antibiotics: a formal synthesis of (+)-sinefungin

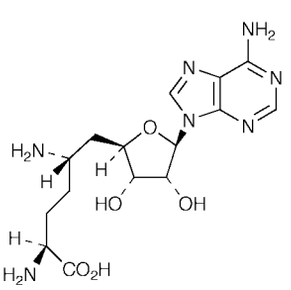
Arun K. Ghosh * and Yong Wang

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607, USA

Received (in Cambridge, UK) 7th September 1999, Accepted 12th October 1999

A formal synthesis of (+)-sinefungin **1** is described. The C-6′ and C-9′ stereogenic centers of sinefungin were constructed stereoselectively by efficient catalytic asymmetric syntheses. The key strategy for the construction of the C-6′ stereocenter involves alkylation of a protected ribose-derived triflate with alkynyl-lithium, Sharpless asymmetric epoxidation of the corresponding allylic alcohol followed by a regioselective epoxide-ring opening with diisopropoxytitanium diazide. The C-9 amino acid stereochemistry was established by a rhodium chiral bisphosphine-catalyzed asymmetric hydrogenation of an α-(acylamino)acrylate derivative. The resulting amino acid derivative has been previously converted to (+)-sinefungin **1**.

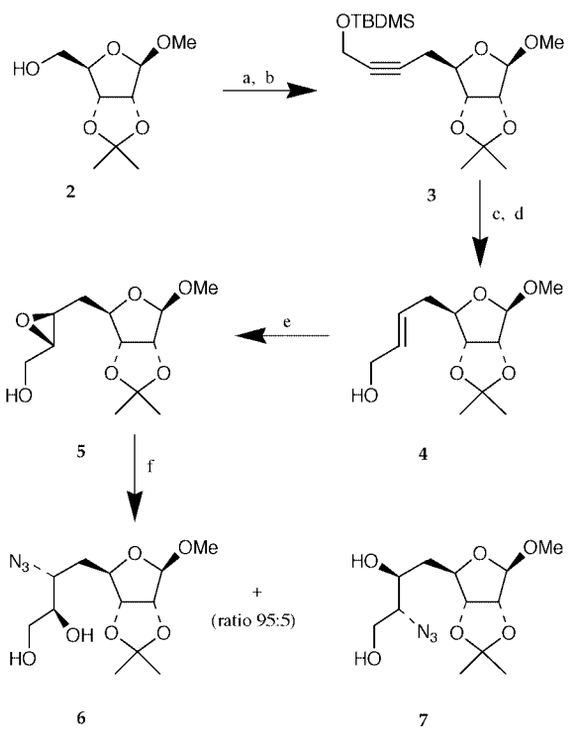
Sinefungin **1**, a novel nucleoside antibiotic isolated from *Streptomyces grisoleus*,[1] has shown many important biological properties including antifungal, antitumor, antiparasitic and antiviral activities.[2] The biological properties of sinefungin stem from inhibition of the *S*-adenoylmethionine (SAM)-dependent methyl transferase enzymes.[3] Clinical use of natural sinefungin is restricted because of its severe *in vivo* toxicity.[4] Thus, total synthesis, structural modifications and biology of sinefungin derivatives have become the subject of much interest over the years. A number of total syntheses of sinefungin have been reported incorporating various strategies for stereocontrol at the C-6′ asymmetric center.[5,6] The synthetic efforts towards sinefungin subsequently led to the preparation of several structural analogues of sinefungin.[7] Recently, we have described a stereoselective synthesis of sinefungin in which both the C-6′ and C-9′ remote chiral centers were constructed by asymmetric syntheses.[8] As part of our continuing interest in sinefungin chemistry, we have now devised a stereocontrolled route to a sinefungin intermediate which has been previously converted to sinefungin by us. The key steps involve an efficient carbon–carbon bond formation between a protected ribose-derived triflate and an alkynyl-lithium, Sharpless asymmetric epoxidation of the corresponding allylic alcohol, followed by a regio- and stereoselective epoxide-ring-opening reaction. The C-9′ amino acid stereochemistry was established by an asymmetric hydrogenation of the corresponding α-(acylamino)-acrylate derivative.



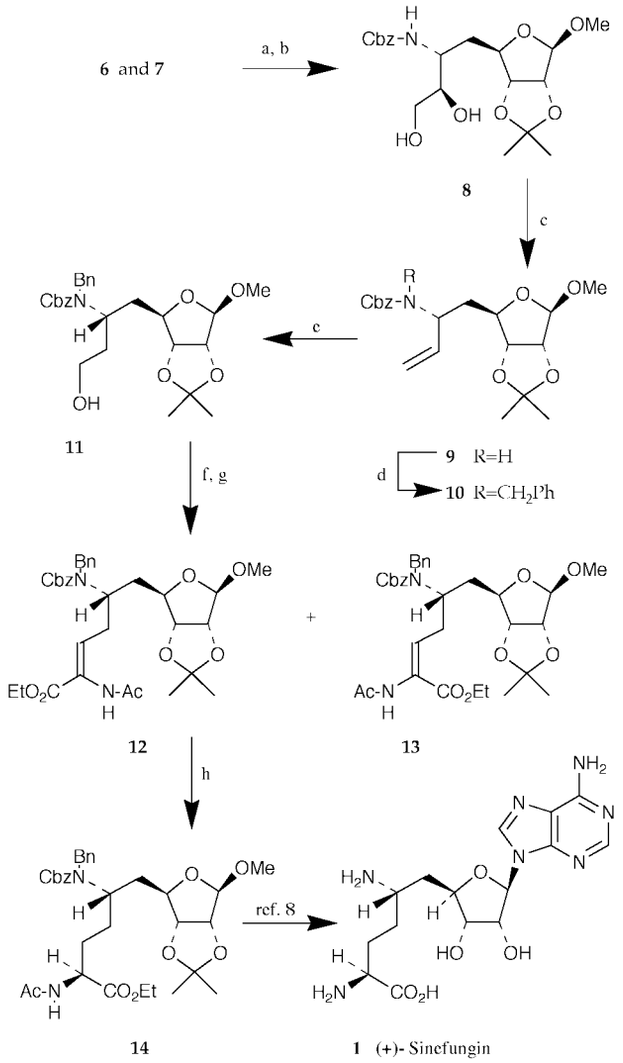
1 (+)-Sinefungin

Results and discussion

As shown in Scheme 1, the known[9] methyl glycoside **2** was readily converted to prop-1-ynyl (propargyl) derivative **3**. The required carbon–carbon bond formation was accomplished by the reaction of the 5′-*O*-triflate of the methyl glycoside **2** and the prop-2-ynyloxysilane-derived alkynyl-lithium $^{t}BuMe_2SiOCH_2C{\equiv}CLi$ which proceeded smoothly in THF in the presence of 1,3-dimethylpropyleneurea (DMPU) at −78 to −20 °C and after 2 h provided the alkyne derivative **3** in 86% yield. The use of HMPA instead of DMPU resulted in significantly lower yield (55%).[10] The removal of the TBDMS group by treatment with *n*-Bu_4NF in THF at 0 °C, followed by LAH reduction of the resulting alkyne in THF at 50 °C for 2 h, furnished exclusively the *E*-allylic alcohol **4** in 77% yield. Sharpless asymmetric epoxidation of **4** with (+)-diethyl



Scheme 1 *Reagents*, *conditions* (*and yields*): (a) Tf_2O, 2,6-lutidine, −78 to 23 °C, 1 h; (b) $TBDMSOCH_2C{\equiv}CLi$, THF, DMPU, −78 to −20 °C, 2 h (86%); (c) *n*-Bu_4NF, THF, 0 °C, 30 min; (d) LAH, THF, 50 °C, 2 h (77%); (e) $^{t}BuOOH$, $Ti(O^{i}Pr)_4$, (+)-DET, CH_2Cl_2, −23 °C, 24 h (88%); (f) $Ti(N_3)_2(O^{i}Pr)_2$, PhH, 75 °C, 15 min (95%).



Scheme 2 *Reagents*, *conditions* (*and yields*): (a) H_2, 10% Pd–C, MeOH, 6 h; (b) CbzCl, $NaHCO_3$, 23 °C, 12 h (90%); (c) Ph_2PC1, imidazole, I_2, PhMe–MeCN (2:1), 90 °C, 4 h (69%); (d) NaH, $PhCH_2Br$, n-Bu_4NI (cat.), THF, 23 °C, 12 h (99%); (e) BH_3·THF, THF, 23 °C, 1 h; then 30% H_2O_2, NaOH (57%); (f) DMSO, $(COC1)_2$, CH_2Cl_2, −60 to −50 °C, 30 min; then $^iPr_2NEt$; (g) $(TMS)_2NK$, THF, 18-crown-6, $(EtO)_2P(O)CH(NHAc)CO_2Et$, −78 to 23 °C, 1 h (79%); (h) H_2, $[Rh(COD)(R,R\text{-DIPAMP})_2]BF_4$, 50 psi, MeOH, 23 °C, 12 h (94%).

L-tartrate [(+)-DET] at −23 °C over 24 h provided the *syn*-epoxide **5** stereoselectively (diastereomeric ratio 96:4 by 400 MHz ^{1}H NMR) in 88% yield.[11] Whereas the MCPBA epoxidation of a ribose-derived allylic alcohol bearing an allylic asymmetric center can provide excellent stereocontrol, the epoxidation of allylic alcohol **4** containing a more remote chiral center resulted in a 2:1 mixture of diastereomers.[12] To install the C-6′ amine functionality, epoxide **5** was exposed to a regio- and stereoselective azide-induced opening reaction as described by Sharpless and co-workers.[13] Thus, treatment of epoxide **5** with diisopropoxytitanium(IV) diazide in benzene at 75 °C for 15 min afforded the azido diols **6** and **7** as an inseparable mixture (19:1) in 95% combined yield. This mixture was subjected to catalytic hydrogenation over 10% Pd–C and the resulting amines were treated with benzyl chloroformate in the presence of aq. $NaHCO_3$ to afford the Cbz-derivative **8**, after silica gel chromatography (Scheme 2). The vicinal diol functionality of **8** was transformed into the corresponding olefin by reaction with chlorodiphenylphosphine, imidazole and iodine in a mixture of toluene and acetonitrile (2:1) at 90 °C for 4 h.[14] The olefin **9** was obtained in 69% yield after silica gel chromatography. As described previously, the protection of the urethane NH is necessary for anomeric adenosylation.[8] Thus, reaction of **9** with sodium hydride and benzyl bromide in the presence of a catalytic amount of n-Bu_4NI furnished the *N*-benzylurethane **10** in 99% yield.

The olefin **10** was hydroborated with borane in THF to furnish alcohol **11** after oxidative work-up with alkaline hydrogen peroxide. Swern oxidation of **11**, followed by immediate exposure of the resulting aldehyde to a Horner–Emmons olefination with the enolate derived from ethyl *N*-acetyl-α-(diethoxyphosphoryl)glycinate[15] and potassium bis(trimethylsilyl)amide in THF at −78 to 23 °C for 1 h, afforded a 1:5.4 mixture of *E*- and *Z*-enamide **12** and **13** in 79% yield (from **11**). This procedure is operationally simple and provided an improvement of yield over the previous conditions.[8] It has been previously demonstrated that (cycloocta-1,5-diene)-[(*R*,*R*)-1,2-ethanediylbis-[(*O*-methoxyphenyl)phenylphosphine]]rhodium tetrafluoroborate $[[Rh(COD)(R,R\text{-DIPAMP})_2]^+BF_4^-]$ catalyst converts both *E*- and *Z*-enamides to an (*S*)-α-amino acid enantioselectively.[16] The *E* and *Z* isomers **12** and **13** were then exposed to asymmetric hydrogenation in the presence of $[Rh(COD)(R,R\text{-DIPAMP})_2]^+BF_4^-$ (10 mol%) catalyst[17] in methanol under 50 psi hydrogen pressure at 23 °C for 12 h to establish the C-9′ stereocenter (9*S*-isomer) stereoselectively. The amino acid derivative **14** {$[\alpha]_D^{23}$ +22.6,† (*c* 1.33, $CHCl_3$)} was isolated in 94% yield. The physical characteristics of the amino acid derivative **14** are identical with the sample made by us previously.[8] The ^{1}H NMR spectrum of **14** revealed the presence of a 4:1 mixture of rotational isomers; however, at coalescence temperature ($T_c \approx 70$ °C in DMSO-d_6) the mixture of peaks merged into one sharp spectrum. The methyl glycoside **14** has been previously converted to (+)-sinefungin by us.[8] The sequence of reactions involved the removal of isopropylidene protection and the methyl acetal by treatment with aq. HCl in 1,4-dioxane, followed by reaction of the triol with acetic anhydride in pyridine to provide the triacetate (70%). Anomeric adenosylation with bis-silyl-*N*-benzoyladenine and TMSOTf afforded the corresponding β-nucleoside (93%). Finally, removal of various protecting groups by a one-pot, three-step procedure involving: (1) reaction with K_2CO_3 in MeOH; (2) removal of methanol and exposure to aq. hydrazine and, (3) catalytic hydrogenation over Pearlman's catalyst [20% $Pd(OH)_2$ on carbon] provided (+)-sinefungin **1** after silica gel chromatography (72%).[8]

Thus a formal stereoselective synthesis of (+)-sinefungin has been accomplished. Our approach utilizes an efficient chain elongation of a protected ribose derivative, Sharpless epoxidation, regio- and stereoselective epoxide opening, and an efficient catalytic hydrogenation. The synthesis is amenable to the preparation of a variety of sinefungin analogues for further biological studies.

Experimental

All mps were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM-400, DPX-400, DRX-500, and Varian VXR-300S spectrometers using tetramethylsilane as the internal standard. IR spectra were recorded on a Matteson Genesis FT-IR spectrometer. Mass spectra were recorded on a Finnigan LCQ mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 spectropolarimeter.† Anhydrous solvents were obtained as follows: dichloromethane and benzene, distillation from CaH_2; THF, distillation from sodium and benzophenone. All other solvents were HPLC grade. Column chromatography was performed with Whatman 240–400 mesh silica gel under a low positive pressure of 5–10 psi.‡ TLC was carried out with E. Merck silica gel 60-F-254 plates.

† $[\alpha]_D$-Values are given in units of 10^{-1} deg cm^2 g^{-1}.
‡ 1 psi = 6894.7 Pa.

Methyl 8-*O*-(*tert*-butyldimethylsilyl)-5,6,7-trideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-oct-6-ynofuranoside 3

To a stirred solution of *tert*-butyldimethyl(prop-2-ynyloxy)-silane (6.30 g, 36.9 mmol) in THF (20 mL) at −78 °C was added *n*-BuLi (23 mL, 36.9 mmol; 1.6 M in hexane) dropwise under nitrogen atmosphere. The resulting mixture was warmed to 0 °C and stirred at this temperature for an additional 2 h before use in the following alkylation step.

In a separate flask, a solution of 2,6-dimethylpyridine (2,6-lutidine) (1.6 mL, 13.5 mmol) in CH_2Cl_2 (20 mL) was stirred at −78 °C and Tf_2O (2.2 mL, 12.9 mmol) was added dropwise over a period of 5 min. The resulting green solution was stirred for 5 min and a solution of alcohol **2** (2.51 g, 12.3 mmol) in CH_2Cl_2 (4 mL) was added. The resulting mixture was stirred at −78 °C for 1 h, the cooling bath was removed, and the mixture was allowed to warm to 23 °C. The mixture was evaporated under reduced pressure and the residue was dissolved in a mixture of THF and DMPU (2:1; 15 mL). The resulting solution was cooled to −78 °C. The above alkynyl-lithium solution was taken up in a syringe and was added to the triflate solution dropwise over a period of 5 min. Stirring was continued at −78 °C for 1 h and the reaction mixture was warmed to −20 °C and stirred at this temperature for an additional 1 h. The reaction mixture was quenched with saturated aq. NH_4Cl and the solution was allowed to warm to 23 °C. The reaction mixture was thoroughly extracted with EtOAc (3 × 50 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed on silica gel (10% EtOAc–hexanes) to afford **3** (R_f 0.85, 25% EtOAc–hexanes) as a colorless oil (3.74 g, 86%); $[\alpha]_D^{23}$ −46 (*c* 2.30, $CHCl_3$); ^{1}H NMR (200 MHz; $CDCl_3$) δ 4.92 (s, 1 H), 4.67 (d, 1 H, *J* 5.9 Hz), 4.57 (d, 1 H, *J* 5.9 Hz), 4.30–4.22 (m, 3 H), 3.30 (s, 3 H), 2.51–2.43 (m, 2 H), 1.44 (s, 3 H), 1.28 (s, 3 H), 0.88 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (50 MHz; $CDCl_3$) δ 112.1, 109.6, 85.1, 85.1, 83.2, 80.7, 80.5, 54.6, 51.7, 26.2, 25.7, 24.8, 24.8, 18.2, −5.3; MS (CI) *m*/*z* 355 (M^+ − H), 325 (M^+ − OMe) (Calc. for $C_{18}H_{32}O_5Si$: C, 60.64; H, 9.05%. Found: C, 60.56; H, 9.08).

Methyl 5,6,7-trideoxy-2,3-*O*-isopropylidene-β-D-ribo-oct-6-enofuranoside 4

To a stirred solution of **3** (3.47 g, 9.73 mmol) in THF (20 mL) at 0 °C was added a solution of *n*-Bu_4NF (12 mL, 12.0 mmol; 1 M in THF). The resulting mixture was stirred at 0 °C for 30 min, then the reaction mixture was quenched with saturated aq. NH_4Cl and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to afford the crude alcohol which was used directly in the following procedure without further purification.

The above alcohol in THF (5 mL) was added dropwise over a period of 5 min to a stirred suspension of LAH (1.90 g, 50.0 mmol) in THF (20 mL) at 0 °C. The resulting reaction mixture was heated at 50 °C for 2 h. After this period, the reaction mixture was cooled to 0 °C and excess of LAH was destroyed by the dropwise addition of EtOAc. Saturated aq. $NaHCO_3$ was then added dropwise. The resulting white suspension was filtered through a pad of Celite and the latter was washed with EtOAc. The filtrate was evaporated to give a residue, which was chromatographed over silica gel (25% EtOAc–hexanes) to afford the desired alcohol **4** (R_f 0.33, 50% EtOAc–hexanes) as a colorless oil (1.82 g, 77%); $[\alpha]_D^{23}$ −42 (*c* 2.30, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.80 –5.64 (m, 2 H), 4.95 (s, 1 H), 4.61 (d, 1 H, *J* 5.9 Hz), 4.56 (d, 1 H, *J* 5.9 Hz), 4.21 (t, 1 H, *J* 7.8 Hz), 4.12 (d, 2 H, *J* 4.9 Hz), 3.34 (s, 3 H), 2.44–2.38 (m, 1 H), 2.32–2.24 (m, 1 H), 1.47 (s, 3 H), 1.31 (s, 3 H); ^{13}C NMR (50 MHz; $CDCl_3$) δ 132.1, 128.0, 112.2, 109.4, 86.5, 85.4, 83.3, 63.4, 54.8, 37.8, 26.4, 24.9; MS (ESI) *m*/*z* 267 (M^+ + Na), 213 (M^+ − OMe); HRMS (FAB) Calc. for $C_{12}H_{20}O_5$: *m*/*z* 244.1311. Found: *m*/*z* 244.1319.

Methyl 6,7-anhydro-5-deoxy-2,3-*O*-isopropylidene-L-*glycero*-β-D-*allo*-octofuranoside 5

To a suspension of powdered 4 Å molecular sieves (1.20 g) in CH_2Cl_2 (25 mL) at −23 °C were sequentially added $Ti(O^iPr)_4$ (0.28 mL, 0.95 mmol) and (+)-DET (0.2 mL, 1.2 mmol) under a nitrogen atmosphere. The resulting mixture was stirred for 15 min at −23 °C and a solution of alcohol **4** (1.12 g, 4.57 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The mixture was stirred for a further 15 min, and *tert*-butyl hydroperoxide (2.8 mL; 5 M in *n*-decane) was added dropwise. The resulting mixture was stirred at −23 °C for 30 min and then put into a freezer at −23 °C for 24 h. After this period, aq. NaOH (4 M) buffered with NaCl (5 mL) was added and the mixture was stirred at 0 °C for 1 h. The mixture was filtered through a Celite pad, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was chromatographed on silica gel (50% EtOAc–hexanes) to furnish the epoxide **5** (R_f 0.20, 50% EtOAc–hexanes) as a colorless oil (1.05 g, 88%); $[\alpha]_D^{23}$ −56.6 (*c* 1.37, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.91 (s, 1 H), 4.57 (d, 1 H, *J* 5.9 Hz), 4.54 (d, 1 H, *J* 5.9 Hz), 4.25 (dd, 1 H, *J* 8.5, 6.0 Hz), 3.83 (dd, 1 H, *J* 12.6, 2.7 Hz), 3.58 (dd, 1 H, *J* 12.6, 4.5 Hz), 3.30 (s, 3 H), 3.04–3.00 (m, 1 H), 2.98–2.96 (m, 1 H), 2.59 (br s, 1 H), 1.99–1.91 (m, 1 H), 1.75–1.69 (m, 1 H), 1.42 (s, 3 H), 1.26 (s, 3 H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 112.4, 109.5, 85.3, 84.2, 83.8, 61.5, 57.9, 54.8, 53.1, 36.5, 26.3, 24.8; MS (ESI) *m*/*z* 283 (M^+ + Na) (Calc. for $C_{12}H_{20}O_6$: C, 55.33; H, 7.75%. Found: C, 55.60; H, 7.67).

Methyl 6-azido-5,6-dideoxy-2,3-*O*-isopropylidene-L-*glycero*-α-L-*talo*-octofuranoside 6

To a stirred solution of $Ti(O^iPr)_4$ (1.55 mL, 5.22 mmol) in dry benzene (30 mL) was added $TMSN_3$ (1.39 mL, 10.44 mmol). The resulting mixture was heated at 75 °C for 12 h. After this period, a solution of epoxide **5** (905 mg, 3.48 mmol) in benzene (3 mL) was added at 75 °C. The resulting mixture was stirred for 15 min, and the mixture was cooled to 23 °C. The reaction mixture was then concentrated under reduced pressure and the residue was diluted with THF (5 mL). Aq. potassium sodium tartrate (20%; 5 mL) was added and the resulting mixture was stirred vigorously at 23 °C for 2 h. After this period, the suspension was diluted with EtOAc (5 mL), filtered through Celite and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated to give a residue, which was chromatographed over silica gel (50% EtOAc–hexanes) to furnish an inseparable mixture of azido diols **6** and **7** (R_f 0.64, EtOAc; isomer ratio 95:5 by 400 MHz ^{1}H NMR) as a colorless oil (1.03 g, 95%); ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.93 (s, 1 H), 4.58 (d, 1 H, *J* 5.9 Hz), 4.54 (d, 1 H, *J* 5.9 Hz), 4.36 (dd, 1 H, *J* 11.5, 3.3 Hz), 3.59–3.72 (m, 4 H), 3.32 (s, 3 H), 1.84–1.77 (m, 1 H), 1.60–1.50 (m, 1 H), 1.45 (s, 3 H), 1.28 (s, 3 H); ^{13}C NMR (50 MHz; $CDCl_3$) δ 112.4, 110.0, 85.1, 84.2, 83.6, 73.9, 63.0, 61.3, 55.3, 35.4, 26.3, 24.8; MS (ESI) *m*/*z* 326 (M^+ + Na) (Calc. for $C_{12}H_{21}N_3O_6$: C, 47.52; H, 6.98%. Found: C, 47.51; H, 7.02).

Methyl 6-(benzyloxycarbonylamino)-5,6-dideoxy-2,3-*O*-isopropylidene-L-*glycero*-α-L-*talo*-octofuranoside 8

To a stirred solution of azide **6** (567 mg, 1.87 mmol) in MeOH (7 mL) was added 10% Pd/C (50 mg). The resulting suspension was stirred under a hydrogen-filled balloon for 6 h. After this period, the mixture was filtered through a Celite pad, and the filter cake was washed thoroughly with EtOAc. Evaporation of

the filtrate gave a residue, which was dissolved in THF (5 mL), and CbzCl (0.32 mL, 2.25 mmol) followed by saturated aq. $NaHCO_3$ (1 mL) were added at 0 °C. The resulting mixture was allowed to warm to 23 °C and stirred at that temperature for 12 h. The mixture was diluted with water and extracted with EtOAc (3 × 10 mL). The organic layers were combined, then dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by silica gel chromatography (75% EtOAc–hexanes) to furnish **8** (R_f 0.43, EtOAc) as a white solid (694 mg, 90%), mp 140–142 °C; $[a]_D^{23}$ +0.4 (*c* 1.47, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.36–7.31 (m, 5 H), 5.62 (d, 1 H, *J* 8.6 Hz), 5.10 (dd, 2 H, *J* 12.2, 8.0 Hz), 4.96 (s, 1 H), 4.61 (d, 1 H, *J* 5.9 Hz), 4.54 (d, 1 H, *J* 5.9 Hz), 4.41 (dd, 1 H, *J* 12.2, 2.5 Hz), 3.88–3.80 (m, 1 H), 3.68–3.62 (m, 2 H), 3.52 (d, 1 H, *J* 8.1 Hz), 3.34 (s, 3 H), 2.95 (br s, 1 H), 1.78–2.04 (m, 3 H), 1.46 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 157.3, 136.1, 128.5, 128.2, 128.0, 112.4, 110.4, 85.1, 84.6, 83.7, 73.0, 67.1, 62.9, 55.6, 50.1, 34.9, 26.4, 24.8; MS (ESI) *m*/*z* 434 (M^+ + Na), 379 (M^+ − OMe) (Calc. for $C_{20}H_{29}NO_8$: C, 58.38; H, 7.10; N, 3.40%. Found: C, 58.13; H, 7.03; N, 3.39).

Methyl 6-(benzyloxycarbonylamino)-5,6,7,8-tetradeoxy-2,3-*O*-isopropylidene-α-L-*talo*-oct-7-enofuranoside 9

To a stirred suspension of **8** (694 mg, 1.69 mmol) in a mixture (2:1) of toluene and acetonitrile (15 mL) at 23 °C were added imidazole (460 mg, 6.76 mmol) and Ph_2PCl (0.67 mL, 3.72 mmol). The resulting mixture was stirred for 5 min and a solution of I_2 (860 mg, 3.38 mmol) in toluene (4 mL) was added dropwise. The resulting mixture was heated at 90 °C for 4 h. After this period, the mixture was cooled to 23 °C, diluted with EtOAc, and washed successively with 10% aq. $Na_2S_2O_3$ and brine. The mixture was extracted with EtOAc (3 × 15 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by silica gel chromatography (25% EtOAc–hexanes) to furnish **9** (R_f 0.29, 25% EtOAc–hexanes) as a white solid (442 mg, 69%), mp 107–108 °C; $[a]_D^{23}$ +13 (*c* 0.48, $CHCl_3$); ^{1}H NMR (200 MHz; $CDCl_3$) δ 7.35–7.26 (m, 5 H), 5.88–5.72 (m, 1 H), 5.32 (d, 1 H, *J* 8.1 Hz), 5.16 (d, 1 H, *J* 18.6 Hz), 5.11 (d, 1 H, *J* 10.5 Hz), 5.10 (s, 2 H), 4.95 (s, 1 H), 4.59 (d, 1 H, *J* 5.9 Hz), 4.52 (d, 1 H, *J* 5.9 Hz), 4.43 (br s, 1 H), 4.32 (dd, 1 H, *J* 10.8, 4.1 Hz), 3.33 (s, 3 H), 1.97–1.82 (m, 1 H), 1.73–1.60 (m, 1 H), 1.45 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR (50 MHz; $CDCl_3$) δ 155.6, 137.8, 136.5, 128.4, 127.9, 115.0, 112.3, 110.0, 85.3, 84.4, 83.7, 66.6, 55.2, 50.8, 39.2, 26.4, 24.9; MS (ESI) *m*/*z* 400 (M^+ + Na); HRMS (FAB) Calc. for $C_{20}H_{27}NO_6$: *m*/*z*, 377.1838. Found: *m*/*z*, 377.1832.

Methyl 6-[benzyl(benzyloxycarbonyl)amino]-5,6,7,8-tetradeoxy-2,3-*O*-isopropylidene-α-L-*talo*-oct-7-enofuranoside 10

To a stirred suspension of NaH (60% oil dispersion; 281 mg, 7.03 mmol) and *n*-Bu_4NI (10 mg) in THF (3 mL) at 23 °C was added a solution of the urethane **9** (442 mg, 1.17 mmol) in THF (2 mL). The mixture was stirred at 23 °C for 1 h and benzyl bromide (0.84 mL, 7.03 mmol) was added. The resulting reaction mixture was stirred at 23 °C for 12 h. The reaction was quenched with saturated aq. NH_4Cl and the mixture was extracted with ethyl acetate. The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification by silica gel chromatography (15% EtOAc–hexanes) gave the *N*-benzyl derivative **10** (R_f 0.53, 25% EtOAc–hexanes) as a colorless oil (546 mg, 99%), $[a]_D^{23}$ −20.3 (*c* 2.90, $CHCl_3$); ^{1}H NMR (400 MHz; DMSO-d_6; 70 °C) δ 7.36–7.21 (m, 10 H), 5.93–5.85 (m, 1 H), 5.18 (s, 2 H), 5.04 (dd, 1 H, *J* 9.7, 1.0 Hz), 5.00 (dd, 1 H, *J* 17.4, 1.0 Hz), 4.84 (s, 1 H), 4.49 (d, 1 H, *J* 5.9 Hz), 4.46 (ABq, 2 H, $\Delta\nu_{AB}$ 88.3 Hz, J_{AB} 15.8 Hz), 4.43 (d, 1 H, *J* 5.9 Hz), 4.41–4.37 (m, 1 H), 3.94 (dd, 1 H, *J* 9.2, 5.7 Hz), 3.21 (s, 3 H), 2.02–1.95 (m, 1 H), 1.79–1.71 (m, 1 H), 1.36 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR (100 MHz; DMSO-d_6; 70 °C) δ 156.6, 139.7, 138.2, 137.7, 129.1, 129.0, 128.6, 128.4, 128.0, 127.7, 117.1, 112.5, 110.1, 85.8, 84.5, 84.2, 67.5, 58.2, 55.2, 50.1, 38.1, 27.3, 25.9; MS (FAB) *m*/*z* 468 (M^+ + H), 436; HRMS (FAB) Calc. for $C_{27}H_{34}NO_6$: *m*/*z*, 468.2386. Found: *m*/*z* 468.2390.

Methyl 6-[benzyl(benzyloxycarbonyl)amino]-5,7-dideoxy-2,3-*O*-isopropylidene-α-L-*talo*-octofuranoside 11

To a stirred solution of the urethane **10** (276 mg, 0.58 mmol) in THF (1 mL) at 23 °C was added BH_3 (1 M solution in THF; 0.87 mL, 0.87 mmol). The mixture was stirred at 23 °C for 1 h. After this period, aqueous 4 M NaOH (0.3 mL) followed by aq. 30% H_2O_2 (0.3 mL) were added. The mixture was stirred at 23 °C for 1 h. The mixture was extracted with ethyl acetate (3 × 15 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by silica gel chromatography to furnish alcohol **11** (R_f 0.42, 50% EtOAc–hexanes) as a colorless oil (159 mg, 57%), $[a]_D^{23}$ +19.9 (*c* 1.58, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.38–7.25 (m, 10 H), 5.21 (s, 2 H), 4.95 (s, 2 H), 4.57 (d, 1 H, *J* 5.8 Hz), 4.44 (d, 1 H, *J* 5.8 Hz), 4.35–4.31 (m, 2 H), 4.13 (dd, 1 H, *J* 11.1, 3.8 Hz), 3.35 (s, 3 H), 3.40–3.27 (m, 2 H), 1.69–1.62 (m, 4 H), 1.45 (s, 3 H), 1.26 (s, 3 H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 157.3, 138.4, 136.3, 128.5, 128.4, 128.0, 128.0, 127.8, 127.4, 112.1, 110.0, 85.4, 84.2, 83.7, 67.4, 58.9, 55.3, 51.6, 37.6, 35.9, 26.4, 24.8; MS (FAB) *m*/*z* 486 (M^+ + H), 454 (M^+ − OMe); HRMS (FAB) Calc. for $C_{27}H_{36}NO_7$: *m*/*z*, 486.2492. Found: *m*/*z*, 486.2481.

Ethyl {methyl 9-acetamido-6-[benzyl(benzyloxycarbonyl)-amino]-5,6,7,8,9-pentadeoxy-2,3-*O*-isopropylidene-α-L-*talo*-dec-8-enofuranosid}uronate 12 and 13

To a stirred solution of DMSO (47 μL, 0.66 mmol) in CH_2Cl_2 (3 mL) at −60 °C was added oxalyl chloride (35 μL, 0.40 mmol) dropwise. After 2 min, alcohol **11** (121 mg, 0.25 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The resulting mixture was stirred at −60 to −50 °C for 30 min and diisopropylethylamine (0.24 mL, 1.33 mmol) was added dropwise. The resulting mixture was stirred at −50 °C for an additional 2 min and then allowed to warm to 23 °C. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethyl acetate, and the organic layer was washed successively with cold aq. $NaHSO_4$ (1 M) and brine, dried over anhydrous Na_2SO_4, and evaporated to give the desired aldehyde. This was used directly without further purification in the following procedure.

To a stirred solution of *N*-acetyl-α-(diethoxyphosphoryl)-glycine ethyl ester (112 mg, 0.4 mmol) and 18-crown-6 (105 mg, 0.4 mmol) in THF (3 mL) at −78 °C was added $KN(TMS)_2$ (0.74 mL; 0.5 M solution in toluene). The mixture was stirred for 15 min and then a solution of the above aldehyde in THF (2 mL) was added dropwise. The resulting solution was stirred at −78 °C for 30 min then allowed to warm to 23 °C and subsequently quenched with saturated aq. NH_4Cl. The reaction mixture was diluted with EtOAc and water and the layers were separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by silica gel chromatography (60% EtOAc–hexanes) to give a mixture (1:5.4) of inseparable enamides **12** and **13** (R_f 0.15, 50% EtOAc–hexanes) as a pale yellow oil (121 mg, 79%); major isomer: ^{1}H NMR (400 MHz; DMSO-d_6; 70 °C) δ 8.65 (s, 1H), 7.37–7.21 (m, 10 H), 6.21 (t, 1 H, *J* 7.1 Hz), 5.14 (s, 2 H), 4.82 (s, 1 H), 4.47 (d, 1 H, *J* 5.9 Hz), 4.44 (ABq, 2 H, $\Delta\nu_{AB}$ 59.8 Hz, J_{AB} 15.7 Hz), 4.36 (d, 1 H, *J* 5.9 Hz), 4.10 (q, 2 H, *J* 7.0 Hz), 4.03–4.01 (m, 1 H), 3.94 (dd, 1 H, *J* 10.2, 4.8 Hz), 3.28 (s, 3H), 2.41 (t, 2 H, *J* 7.2 Hz), 1.98–1.88 (m, 1 H), 1.88 (s, 3 H), 1.64–1.60 (m, 1 H), 1.35 (s, 3 H), 1.21 (s, 3 H), 1.17 (t, 3 H, *J* 7.0 Hz); MS (CI) *m*/*z* 611 (M^+ + H).

Ethyl {methyl 9-acetamido-6-[benzyl(benzyloxycarbonyl)-amino]-5,6,7,8,9-pentadeoxy-2,3-*O*-isopropylidene-D-*glycero*-α-L-*talo*-decofuranosid}uronate 14

In a hydrogenation bottle, the mixture of enamides **12** and **13** (14 mg, 0.023 mmol) was dissolved in methanol (3 mL) and the catalyst $[Rh(COD)(R,R\text{-DIPAMP})_2]^+BF_4^-$ (2 mg) was added. The bottle was then charged with hydrogen to a pressure of 50 psi. The mixture was shaken on a Parr apparatus for 12 h under 50 psi at 23 °C. After this period, the reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography (50% EtOAc–hexanes) to give **14** (R_f 0.16, 50% EtOAc–hexanes) as a colorless oil (13.3 mg, 94%), $[a]_D^{23}$ +22.6 (*c* 1.33, $CHCl_3$) {lit.[8] $[a]_D^{23}$ +24.3 (*c* 0.7, $CHCl_3$)}; ^{1}H NMR (400 MHz; DMSO-d_6; 70 °C) δ 7.85 (d, 1 H, *J* 7.3 Hz), 7.20–7.39 (m, 10 H), 5.13 (s, 2 H), 4.81 (s, 1 H), 4.45 (d, 1 H, *J* 5.9 Hz), 4.41 (ABq, 2 H, $\Delta\nu_{AB}$ 81 Hz, J_{AB} 15.7 Hz), 4.35 (d, 1 H, *J* 5.9 Hz), 4.17–4.15 (m, 1 H), 4.03 (q, 2 H, *J* 7.1 Hz), 3.94–3.91 (m, 2 H), 3.20 (s, 3 H), 1.82 (s, 3 H), 1.70–1.41 (m, 6 H), 1.33 (s, 3 H), 1.21 (s, 3 H), 1.15 (t, 3 H, *J* 7.0 Hz); MS (ESI) *m*/*z* 635 (M^+ + Na), 581 (M^+ − OMe).

Acknowledgements

Financial support of our work by the National Institute of Health (GM 55600) is gratefully acknowledged.

References

1 R. L. Hamil and M. M. Hoehn, *J. Antibiot.*, 1973, **26**, 463.
2 (*a*) R. J. Suhadolnik, *Nucleotides as Biological Probes*, Wiley, New York, 1979, pp. 19–23; (*b*) C. S. G. Pugh, R. T. Borchardt and H. O. Stone, *J. Biol. Chem.*, 1978, **253**, 4075 and references cited therein.
3 (*a*) M. T. McCamnon and L. W. Parks, *J. Bacteriol.*, 1981, **145**, 106; (*b*) R. W. Fuller and R. Nagarajan, *Biochem. Pharmacol.*, 1978, **27**, 1981 and references cited therein.
4 E. Zweygerth, D. Schillinger, W. Kaufmann and D. Roettcher, *Trop. Med. Parasitol.*, 1986, **37**, 255.
5 For synthetic studies, see; (*a*) Y. Mizuno, K. Tsuchida and H. Tampo, *Chem. Pharm. Bull.*, 1984, **32**, 2915; (*b*) A. R. Moorman, T. Martin and R. T. Borchardt, *Carbohydr. Res.*, 1983, **113**, 233; (*c*) J. W. Lyga and J. A. Secrist, III, *J. Org. Chem.*, 1983, **48**, 1982.
6 For total synthesis, see; (*a*) D. H. R. Barton, S. D. Gero, B. Quiclet-Sire and M. Samadi, *J. Chem. Soc., Perkin Trans. 1*, 1991, 983; (*b*) M. P. Maguire, P. L. Feldman and H. Rapoport, *J. Org. Chem.*, 1990, **55**, 948; (*c*) J. G. Buchanan, A. Flinn, P. H. Mundill and R. H. Wightman, *Nucleosides*, *Nucleotides*, 1986, **5**, 313; (*d*) M. Geze, P. Blanchard, J. L. Fourrey and M. Robert-Gero, *J. Am. Chem. Soc.*, 1983, **105**, 7638; (*e*) G. A. Mock and J. G. Moffat, *Nucleic Acids Res.*, 1982, **10**, 6223.
7 For synthesis of sinefungin analogues, see; (*a*) D. H. R. Barton, S. D. Gero, F. Lawrence, M. Robert-Gero, B. Quiclet-Sire and M. Samadi, *J. Med. Chem.*, 1992, **35**, 63; (*b*) D. H. R. Barton, S. D. Gero, G. Negron, B. Quiclet-Sire, M. Samadi and C. Vincent, *Nucleosides*, *Nucleotides*, 1995, **14**, 1619; (*c*) P. Peterli-Roth, M. P. Maguire, E. Leon and H. Rapoport, *J. Org. Chem.*, 1994, **59**, 4186.
8 A. K. Ghosh and W. Liu, *J. Org. Chem.*, 1996, **61**, 6175.
9 (*a*) A. K. Ghosh, S. P. McKee, W. M. Sanders, P. L. Darke, J. A. Zugay, E. A. Emini, W. A. Schleif, J. C. Quintero, J. R. Huff and P. S. Anderson, *Drug Des. Discovery*, 1993, **10**, 77; (*b*) P. A. Levene and E. T. Stiller, *J. Biol. Chem.*, 1934, **104**, 299.
10 H. Kotsuki, I. Kadota and M. Ochi, *Tetrahedron Lett.*, 1990, **31**, 4609.
11 (*a*) R. A. Johnson and K. B. Sharpless, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH Publishers, New York, 1993, pp. 103–158; (*b*) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765.
12 A. K. Ghosh and Y. Wang, *J. Org. Chem.*, 1999, **64**, 2789.
13 M. Caron, P. R. Carlier and K. B. Sharpless, *J. Org. Chem.*, 1988, **53**, 5185.
14 Z. Liu, B. Classon and B. Samuelsson, *J. Org. Chem.*, 1990, **55**, 4273.
15 U. Schmidt, A. Lieberknecht and J. Wild, *Synthesis*, 1984, 53.
16 J. W. Scott, D. D. Keith, G. Nix, Jr., D. R. Parrish, S. Remington, G. P. Roth, J. M. Townsend, D. Valentine, Jr. and R. Yang, *J. Org. Chem.*, 1981, **46**, 5086.
17 (*a*) W. S. Knowles, M. J. Sabacky, B. D. Vineyard and D. J. Weinkauff, *J. Am. Chem. Soc.*, 1975, **97**, 2567; (*b*) B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman and D. J. Weinkauff, *J. Am. Chem. Soc.*, 1977, **99**, 5946.

Paper 9/07228D