mol) added quickly. The solution was kept for 1 h at -40 °C and warmed to room temperature for 1 h. The mixture was poured over 100 mL of 15% HCl and extracted with chloroform. The combined extracts were washed with NaOH and water and dried over $MgSO_4$. Chloroform was evaporated. Product **2a** was obtained after crystallization from ether: mp 136-138 °C; 1.2 g (35% yield); ^{19}F NMR ϕ 51 (s). Anal. Calcd for $C_{13}H_8Cl_2F_2S_2$: C, 46.30; H, 2.39. Found: C, 46.30; H, 2.35.

2. Inhibition by *p*-Dinitrobenzene. The same procedure as above was used. *p*-Dinitrobenzene (0.4 g) was added at -40 °C before the introduction of CF_2BrCl. In these conditions, the formation of the disubstituted product **2a** is completely inhibited.

Condensation of CF_2BrCl with Sodium Thiophenoxide. 1. The same procedure as above was used for the condensation of sodium thiophenoxide with CF_2BrCl. Thiophenol (2.2 g, 0.02 mol) and 6.6 g (0.04 mol) of CF_2BrCl are used. After hydrolysis and workup, a bulb-to-bulb distillation was performed at 0.1 mmHg. The light products $C_6H_5SCF_2Br$ (**3**), $C_6H_5SCF_2Cl$ (**5**), and $C_6H_5SCF_2H$ (**4**) are collected (0.8 g; yield 9% **3**; 5% **5**; 3% **4**): ^{19}F NMR **3** ϕ 21.7 (s); **5** 28.4 (s); **4** (90, d, J_{HF} = 60 Hz). Compounds **3** and **4** have been identified by comparison with authentic samples.[3]

From several experiments we have been able to purify $C_6H_5SCF_2Cl$ (**5**): a spinning-band distillation of the mixture of **3**, **4**, and **5** gave pure **5**: bp 82 °C (30 mm); ^1H NMR δ 7 (m); ^{19}F NMR ϕ 28.4 (s). MS, *m/e* 194-196 (M^+), 159 (M - Cl), 109 (M - CF_2Cl). Anal. Calcd for $C_7H_5ClF_2S$: C, 43.19; H, 2.58. Found: C, 42.76; H, 2.50.

The residue of the bulb-to-bulb distillation was distilled; 1.2 g (43% yield) of compound **6** was obtained: bp 110-115 °C (0.1 mm); ^1H NMR δ 8 (m); ^{19}F NMR ϕ 49 (s); ^{13}C NMR ($CDCl_3$) δ 132.4 (CF_2, t, J_{CF} = 315 Hz). Anal. Calcd for $C_{13}H_{10}F_2S_2$: C, 58.21; H, 3.73; F, 14.18; S, 23.88. Found: C, 58.52; H, 3.95; F, 14.16; S, 23.85.

D. J. Burton[12] gives for **6** the following characteristics: bp 103 °C (1 mm); ^{13}C NMR δ 119.2 (t, J_{CF} = 338.3 Hz).

2. Inhibition by Nitrobenzene. The same procedure as above was used. Nitrobenzene (2.4 g, 0.02 mol) was added at -40 °C before the introduction of CF_2BrCl. After hydrolysis and workup, a bulb-to-bulb distillation was performed. The light products **3**, **4**, **5**, and nitrobenzene are collected (5 g). The three fluorinated derivatives (5 - 2.4 = 2.6 g) are analyzed by ^{19}F NMR, which shows that **3** is the major product (more than 95%); yield in **3**, 52%. Distillation of the residue gives 0.15 g of **6** (yield 5%).

Condensation of CF_2Cl_2 with Sodium Thiophenoxide. Dry DMF (130 mL) was added to sodium hydride (55% in oil, 2.18 g, 0.045 mol) previously washed with hexane. Thiophenol (5 g, 0.045 mol) was added as drops. The mixture was poured into a silica vessel. DMF (150 mL) was added, and argon was bubbled into the solution. The mixture was cooled to -40 °C and CF_2Cl_2 (11 g, 0.09 mol) added. The solution was irradiated at -40 °C for 2 h with a high-pressure mercury lamp (TQ Hanau). Hydrolysis and workup were done as described above.

A bulb-to-bulb distillation gives the light products, 1 g (yield 6% **5**; 6% **4**). The residue was distilled at 0.1 mmHg; 1.3 g of **6** was obtained (yield 22%).

Acknowledgment. We thank Professor M. Chanon for fruitfull discussions.

Registry No. **1a**, 18803-44-6; **2a**, 78840-51-4; **3**, 78031-08-0; **4**, 1535-67-7; **5**, 85554-53-6; **6**, 80351-59-3; CF_2BrCl, 353-59-3; CF_2Cl_2, 75-71-8; C_6H_5SNa, 930-69-8; *p*-chlorothiophenol, 106-54-7; thiophenol, 108-98-5; *p*-dinitrobenzene, 100-25-4.

Synthesis of Chain-Extended and C-6′ Functionalized Precursors of the Nucleoside Antibiotic Sinefungin

John W. Lyga and John A. Secrist III*[1]

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210, and Southern Research Institute, Birmingham, Alabama 35255

Received September 21, 1982

Precursors of sinefungin were prepared by chain extension of the blocked adenosine 5′-aldehyde **4** through a carbon-carbon bond to C-5′. Bond formation was accomplished with variously functionalized stabilized ylides. Employment of 2-oxo-3-(triphenylphosphoranylidene)tetrahydrofuran (**7**) gave a nucleoside lactone (**8**) which was converted in several steps to a C-6′ carboxylic acid (**10c**). A Curtius rearrangement of this acid, quenching with benzyl alcohol, allowed the introduction of a C-6′ amino group, blocked as a urethane (**11a**). The chain-ending (C-8′) alcohol was converted to a leaving group and displaced by azide ion and dibenzyl sodiomalonate.

Sinefungin (**1**, SF; see Chart I), a nucleoside antibiotic isolated from *Streptomyces griseolus*, is one of a number of naturally occurring nucleosides containing amino acid residues.[2] The unique feature of sinefungin is that the bond between the amino acid (ornithine) and the nucleoside (adenosine) is a carbon-carbon bond, thus producing a decose as the carbohydrate moiety. Sinefungin is structurally quite similar to *S*-adenosylmethionine (AdoMet) and *S*-adenosylhomocysteine (AdoHcy), with the sulfur in AdoHcy or methylated sulfur in AdoMet being replaced by $CH(NH_2)$. The spatial orientation of the amino group in sinefungin (*S*) is identical with that of the methyl in AdoMet.[3] It has been suggested on the basis of labeling studies that a preformed adenosine derivative and ornithine or a derivative are close biosynthetic precursors of sinefungin.[4] Sinefungin has been found to have activity against fungi, viruses, parasites, and cancer in vitro[5] and has been reported to have in vivo antiviral activity.[6] The wide range of biologic activity of SF may be due to its strong inhibition of a variety of AdoMet-utilizing methyltransferases[5,7-9] or to the inhibition of an enzyme

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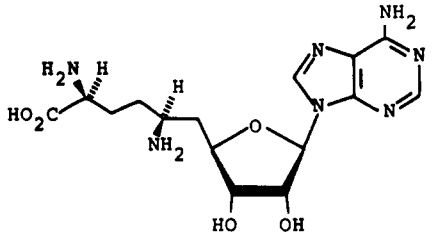
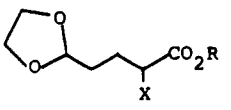
Chart I

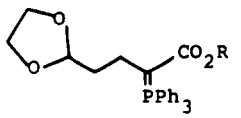


1



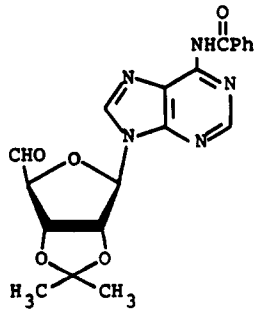
2

a) R = CH_2CH_3, X = H
b) R = CH_2CH_3, X = I
c) R = CH_2CH_3, X = PPh_3I
d) R = CH_2Ph, X = H
e) R = CH_2Ph, X = I
f) R = CH_2Ph, X = PPh_3I

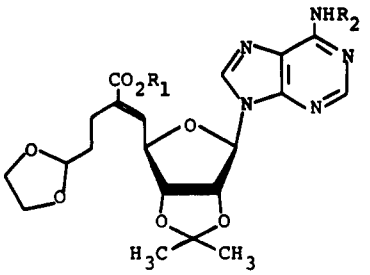


3

a) R = CH_2CH_3
b) R = CH_2Ph

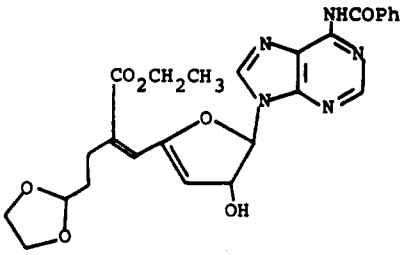


4



5

a) R_1 = CH_2CH_3, R_2 = COPh
b) R_1 = CH_2CH_3, R_2 = H
c) R_1 = CH_2Ph, R_2 = COPh
d) R_1 = H, R_2 = COPh



6

on the polyamine biosynthetic pathway.[10]

In considering synthetic approaches to sinefungin and related compounds with the goal of designing enzyme inhibitors, several challenges must be met, depending upon the variations desired in the SF structure. These include construction of the long-chain carbohydrate unit, incorporation of the α-amino acid at the end of the chain, and development of the amino group at C-6′. We present our initial work in this area, which deals with chain extension and incorporation of the 6′-amino group, thus providing an entry into compounds related to SF and potentially to SF itself.

The most straightforward approach to SF-related compounds would appear to utilize adenosine as one of the starting materials. Thus, the key bond formed would be the 5′–6′ carbon–carbon bond. This provides the dual advantages of dividing the carbohydrate essentially in half and making the site of incorporation of the amino group one allowing for maximum manipulation. Our strategy was to join a suitably functionalized stabilized ylide with an adenosine 5′-aldehyde via a Wittig reaction. Simple monosubstituted stabilized phosphonium ylides have been condensed with nucleoside aldehydes to form chain-extended α,β-unsaturated esters in good yields.[11-13] In our case the ylide must allow for introduction of both an amino acid and the C-6′ amino group. A number of different functional groups would permit eventual elaboration to an amino acid or other desired chain-terminating functionality, but for initial simplicity we felt that a protected aldehyde or alcohol would be best. An ester group attached to the carbon of the ylide to become C-6′ (the carbon adjacent to phosphorus) would not only provide necessary stabilization for the ylide but also allow for later introduction of an amino group, since an ester can be activated and rearranged by various methods to an amine.

The ylide **3**, with an acetal serving as a latent aldehyde (and eventually amino acid if desired), was prepared in standard fashion. Ethyl 5,5-(ethylenedioxy)pentanoate (**2a**) was prepared by a modification of the literature procedure[14] and α iodinated by treatment with lithium diethylamide followed by iodine.[15] Formation of the ylide **3a** was accomplished by warming **2b** with triphenylphosphine in sulfolane to produce the phosphonium salt **2c**, which was then treated with alcoholic potassium hydroxide. Condensation of **3a** with N^6-benzoyl-2′,3′-*O*–

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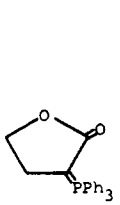
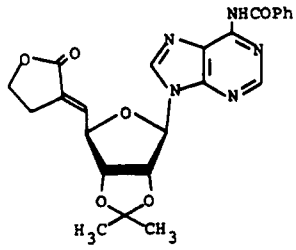
Chart II



7



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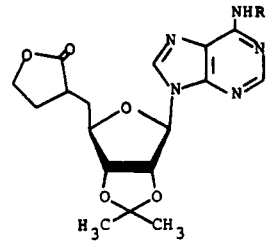
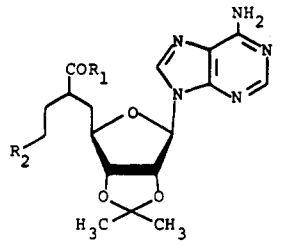


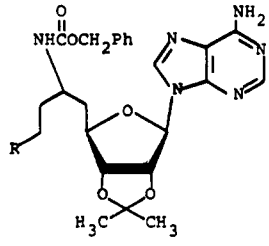
9

a) R = COPh
b) R = H



10

a) R_1 = $O^{\ominus}$, R_2 = OH
b) R_1 = R_2 = OSiTBDP
c) R_1 = OH, R_2 = OSiTBDP
d) R_1 = Cl, R_2 = OSiTBDP
e) R_1 = N_3, R_2 = OSiTBDP



11

a) R = OSiTBDP
b) R = OH
c) R = OSO_2CH_3
d) R = N_3
e) R = $CH(CO_2CH_2Ph)_2$

isopropylideneadenosine 5′-aldehyde (4)[16] at room temperature in acetonitrile afforded adduct **5a** in 70% yield after chromatographic purification. Spectroscopic evidence (^1H and ^{13}C NMR) indicated that only one isomer was produced, to which we have assigned the *E* configuration on the basis of comparative ^1H NMR data in two solvents. A change in solvent from $CDCl_3$ to C_6D_6 produced a downfield shift of the olefinic proton at C-5′ of 0.14 ppm, while all the other protons were observed to have an upfield shift of between 0.07 and 0.78 ppm. As has been seen in similar systems, this result suggests that the olefinic proton is cis to the carbonyl group.[17-19] Debenzoylation with methanol–ammonium hydroxide produced **5b**.

Removal of the 5′–6′ double bond was the next step necessary prior to attempted incorporation of the amino group at C-6′. Although the double bond in the comparable disubstituted α,β-unsaturated nucleoside ester was readily reduced,[11] we have as yet been unable to find satisfactory conditions to carry out this transformation in the trisubstituted case. Since we found in a different system that the double bond of an α,β-unsaturated acid reduced more readily than the corresponding ester,[20] saponification of **5a** was attempted. The major product with a variety of bases was **6**, resulting from initial abstraction of the 4′-proton followed by the elimination of acetone. Considerable literature precedent exists for this pathway.[21] The desired carboxylic acid **5d** was obtained in small amounts by hydrogenolysis of the benzyl ester **5c**, prepared analogously to **5a**,[22] but hydrogenation was still not successful.[23]

To increase the ease of olefinic reduction of a trisubstituted 5′–6′-unsaturated carbonyl compound, we decided to place the double bond exocyclic to a ring, in particular to a five-membered-ring lactone. Thus the ylide necessary is **7**[24] (Chart II), prepared in two steps from α-bromobutyrolactone. Condensation of the ylide **7** with anhydrous **4** in acetonitrile produced one isomer (**8**), assigned the *E* configuration again on the basis of shifts similar to those seen with **5a** in $CDCl_3$ and benzene-d_6.

Hydrogenation of **8** for 40 h in ethanol at 4 atm proceeded smoothly to afford a nearly quantitative yield of the saturated material **9a**. While neither TLC nor ^1H NMR gave evidence of more than one compound, ^{13}C NMR clearly showed that both isomers were present, in about a 2:1 ratio. This mixture was employed for all the remaining transformations. Debenzoylation to **9b** was

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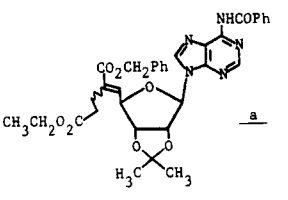
(22) Compound **2d** was prepared by ester exchange with **2a** and benzyl alcohol. Conversion to the salt proceeded as with **2b** and **2c**, affording **2e** and **2f**, but yields were quite low due to competing side reactions. The ylide **3b** was generated in standard fashion.
(23) Compound a was also prepared by employing a phosphonate anion, and extended catalytic hydrogenation resulted in only hydrogenolysis of the benzyl group, with no olefin reduction.



a

(24) Fliszar, S.; Hudson, R. F.; Salvadori, G. *Helv. Chim. Acta* **1963**, *46*, 1580–1588.

accomplished by heating **9a** in ethylene glycol for a short period of time at 110 °C.

Opening of the lactone would then produce a carboxylic acid derivative as the precursor to the 6′-amino and a chain-ending alcohol group for any desired manipulation. The most promising method for introduction of the 6′-amino in a reasonably delicate nucleoside framework appeared to be the Curtius rearrangement, whose relatively mild conditions should not affect the glycosidic linkage.[25-27] Thus, our goals were to open the lactone, blocking the hydroxyl with a selectively removable protecting group, and then introduce the 6′-amino group. Protection of the primary hydroxyl proved necessary to prevent reclosure to the quite stable lactone **9a**.

Treatment of **9b** with 1 equiv of sodium hydroxide gave the hydroxy carboxylate **10a**, which was immediately treated with *tert*-butyldiphenylchlorosilane and imidazole in DMF to produce the bis silyl compound **10b**. Selective saponification of the silyl ester with sodium hydroxide in aqueous THF produced the acid **10c**.

An initial one-pot Curtius rearrangement of **10c** with diphenylphosphoryl azide in triethylamine,[26] although resulting in rearrangement, did not produce the desired product but rather led to the isolation of a nucleoside of unconfirmed structure in low yield. Trimethylsilyl azide[27] produced similar results, so we turned to the classical sequence. Conversion of **10c** to the acid chloride was accomplished with potassium *tert*-butoxide followed by oxalyl chloride or by treating **10c** directly with thionyl chloride. Treatment of **10d** with sodium azide in wet acetone at 0 °C afforded the acyl azide **10e**. Warming of **10e** in toluene effected the rearrangement to the isocyanate, which was trapped as the urethane **11a**. The average yield for this sequence was about 40%.

To demonstrate that **11a** is a viable intermediate for the synthesis of sinefungin-related materials, we have carried out several transformations on the terminal hydroxyl group. Removal of the silyl group was accomplished by treating **11a** with tetra-*n*-butylammonium fluoride in THF. Activation of **11b** with methanesulfonyl chloride (which appeared to produce mainly the mesylate plus a little chloro compound) followed by displacement with sodium azide in Me_2SO produced the azide derivative **11d**. To produce compounds closely related to sinefungin, two more carbons need to be added to the chain. After activation of a small amount of **11b** as above, alkylation with the anion of dibenzyl malonate, one of a number of glycine synthons we might utilize, afforded **11e**, whose structure was confirmed by spectroscopic evidence.

The methodology presented herein allows not only for chain extension with functional group incorporation at C-6′ but also for manipulation at the terminus of the long carbohydrate chain. The synthesis of sinefungin as well as a wide variety of structures based upon sinefungin should now be possible.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 137, 283, or 457 recording spectrometer and were calibrated against the polystyrene absorption peak at 1601 cm^{-1}. The 60-MHz ^1H NMR spectra were recorded on a Varian 360 or 360L instrument, 90-MHz ^1H NMR spectra were recorded on a Varian 390L instrument, and 200-MHz ^1H NMR spectra were recorded on a Bruker WP 200 superconducting instrument. ^{13}C NMR spectra were recorded at 20 MHz on a Bruker WP 80 instrument and at 75 MHz on a Bruker WM 300 instrument. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. ^{13}C NMR spectral assignments were supported by the splitting in off-resonance decoupling experiments. Field-desorption mass spectra (FDMS) were obtained from Southern Research Institute, Birmingham, AL, on a Varian MAT Model 311A double-focussing mass spectrometer, equipped with a combination electron-impact, field-ionization, and field-desorption ion source. High-resolution mass spectra were obtained on a AE1-MS9 spectrometer at 70 eV. Optical rotations were recorded on a Perkin-Elmer Model 141 polarimeter with 1-dm tubes at the sodium D line (589 nm). Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, Atlantic Microlab, Inc., Atlanta, GA, Mr. William Rond or Dr. Ole Mols from the Department of Chemistry of the Ohio State University, or by the Molecular Spectroscopy Section, Southern Research Institute.

Thin-layer chromatography was carried out on precoated glass plates (silica gel F-254, 0.25 mm thickness) from EM Laboratories, Inc. Thick-layer chromatography was performed on glass plates coated to a 2.0-mm thickness with 30 g of silica gel 60 PF-254 (available from EM Laboratories, Inc.) by using calcium sulfate as a binder. HPLC separations were carried out according to the procedure of Loibner and Seidl.[28] Columns and end fittings were purchased from Ace Glass, Inc. (Vineland, NJ). The columns were hand packed with silica gel (230–400 mesh) and driven by a Simplex Milroyal pump, Model D (DC-1-60R), with a controlled volume delivery of 0–45 mL/min (Milton Roy Co., St. Petersburg, FL). Pressures used were usually between 10 and 100 psi. Fractions were analyzed with a Model 153 analytical UV detector equipped with a preparative flow cell (Altex Scientific, Inc., CA) and operating at 254 nm with the references cell open to the atmosphere.

The term "plug filtration" refers to a fast chromatographic technique where the mixture to be separated is applied to a layer of silica gel in a sintered-glass funnel and washed with consecutively more polar solvents under reduced pressure until the desired material is eluted.

Ethyl 5,5-(Ethylenedioxy)pentanoate (2a).[14] A mixture of 40 g (0.154 mol) of ethyl 2-(ethoxycarbonyl)-5,5-(ethylenedioxy)pentanoate,[29] 13 g (0.308 mol) of lithium chloride, 2.8 mL (2.8 g, 0.154 mol) of water, 1 g of powdered glass, and 200 mL of Me_2SO was heated at reflux. After several minutes, a rapid evolution of carbon dioxide was observed which ceased after 3 h. The mixture was heated at 180 °C for an additional 1 h, cooled, and then poured onto 500 mL of ice–water and 200 mL of diethyl ether. The ether layer was separated and washed with two 100 mL portions of water which were combined and back extracted with 100 mL of diethyl ether. The combined ether extracts were washed with 100 mL of saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated at reduced pressure. The residue was distilled at 107 °C (0.8 mmHg) to give 21 g (70%) of a colorless liquid: IR (film) 2967 (s), 1730 (s), 1449, 1404, 1366, 1238 (br), 1148 (br), 1020 (br), 937, 855, 823 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.25 (t, CH_3, 3), 1.75 + 2.34 (m, $CH_2CH_2CH_2$, 6), 3.86 (m, OCH_2CH_2O, 4), 4.09 (q, CH_2, 2), 4.80 (t, H_5, 1); exact mass, m/e 187.0970 [$(M - 1)^+$; calcd m/e 187.0975, $(M - 1)^+$].

Ethyl 5,5-(Ethylenedioxy)-2-iodopentanoate (2b). A solution of 4.8 mL (4.1 g, 0.0293 mol) of cyclohexylisopropylamine dissolved in 25 mL of THF was cooled to -78 °C under an atmosphere of nitrogen and stirred while 22.5 mL (0.0293 mol) of 1.3 M *n*-butyllithium was added over 5 min. The clear solution was stirred at -78 °C for 30 min, and then 5 g (0.0265 mol) of **2a** in 5 mL of THF was added dropwise over 5 min. After being stirred for 5 min, the mixture was warmed slowly to room temperature and then added slowly to a solution of 8.8 g (0.0346 mol) of iodine in 120 mL of THF maintained at -78 °C under an atmosphere of nitrogen. The purple-red solution was stirred at -78 °C for 15 min, warmed to room temperature, and then poured onto 150 mL of diethyl ether and 100 mL of 10% aqueous sodium

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thiosulfate. The clear yellow ether layer was washed with saturated aqueous sodium chloride, dried over magnesium sulfate, treated with charcoal, and concentrated at reduced pressure. The residue was subjected to plug filtration through 100 g of silica gel first with 500 mL of 2:1 petroleum ether–diethyl ether and then with 150 mL of 1:2 petroleum ether–diethyl ether. The solvent was removed at reduced pressure to afford a yellow oil (8 g, 96%), homogeneous on TLC (2:1 diethyl ether–petroleum ether, R_f 0.7), which was suitable for the preparation of **2c**: IR (film) 3020, 1745 (s), 1255, 1140, 1025, 938 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.25 (t, CH_3, 3), 1.55–2.30 (m, CH_2CH_2, 4), 3.86 (m, OCH_2CH_2O, 4), 4.19 (q, CH_2, 2), 4.85 (t, H_5, 1); exact mass, m/e 314.0026 (calcd m/e 314.0017).

[1-(Ethoxycarbonyl)-4,4-(ethylenedioxy)butyl]triphenylphosphonium Iodide (2c). To a solution of the crude iodide **2b** (3.1 g, 0.01 mol) in 5 mL of sulfolane was added 3.4 g (0.013 mol) of triphenylphosphine. The mixture was heated at 60 °C for 4 h, diluted to 10 mL with dichloromethane, and added dropwise with rapid stirring to 600 mL of diethyl ether. The precipitate was collected and dried under reduced pressure to afford 3.4 g (59%) of a white solid: mp 150–151 °C dec; IR (KBr) 3846, 3049, 2941, 2857, 1739 (s), 1435 (s), 1208, 1174, 1134, 990, 939, 872, 749 (s), 722 (s), 682 (s) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.09 (t, CH_3, 3), 2.10–2.30 (m, CH_2CH_2, 4), 3.90 (m, OCH_2CH_2O, 4), 4.05 (q, CH_2, 2), 4.93 (t, H_5, 1), 7.75–7.88 (m, Ph's, 15); FDMS (Me_2SO), m/e 449 [$(M - 1)^+$]. Anal. Calcd for $C_{27}H_{30}IO_4P$: C, 56.26; H, 5.25. Found: C, 56.54; H, 5.40.

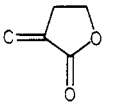
(*E*)-*N*^{6}-Benzoyl-9-[ethyl 5,6-dideoxy-6-[3,3-(ethylenedioxy)propyl]-2,3-*O*-isopropylidene-β-D-*ribo*-hept-5-enofuranosyluronate]adenine (5a). Method A. A solution of 3 g (5.19 mmol) of **2c**, 12 mL of ethanol, and 3 mL of water was stirred at room temperature as 6.5 mL of 0.8 N potassium hydroxide was added. After 30 min, the solution was added dropwise to 300 mL of ice–water with stirring, and then the solid precipitate was filtered and dried in vacuo to afford 1.76 g (76%) of **3a**. The white solid was dissolved in 5 mL of acetonitrile, followed by the addition of 0.98 g (2.39 mmol) of **4** from which the water of hydration had been removed azeotropically with benzene and acetonitrile, followed by conversion to a foam at 0.1 mmHg. The solution was stirred at room temperature under an atmosphere of nitrogen for 15 min and then concentrated at reduced pressure to a tan foam. The crude product was subjected to HPLC (ethyl acetate–THF, 9:1) to afford 0.96 g (69%) of a white foam: IR (KBr) 3390 (br), 3030, 1715 (s), 1613, 1587, 1511, 1482, 1453, 1238, 1205, 1075, 862, 794, 752, 704 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.19 (t, CH_3, 3), 1.39 and 1.65 (2 s, $C(CH_3)_2$, 6), 2.48 and 1.85 (m, $H_{7'}$ and $H_{8'}$, 4), 3.85 (m, OCH_2CH_2O, 4), 4.13 (q, CH_2, 2), 4.81 (t, $H_{9'}$, 1), 5.06 (m, $H_{3'}$ and $H_{4'}$, 2), 5.53 (dd, $H_{2'}$, 1, $J_{1',2'}$ = 1.5 Hz, $J_{2',3'}$ = 5 Hz, 6.15 (d, $H_{1'}$, 1), 6.66 (d, $H_{5'}$, 1, $J_{4',5'}$ = 9 Hz), 7.48–7.90 (m, Ph, 5), 8.05 and 8.75 (2 s, H_8 and H_2, 2), 9.30 (s, NH, 1); ^{13}C NMR (20 MHz, $CDCl_3$), 14.22 (CH_3), 21.90 ($C_{8'}$), 25.49, 27.13, and 114.87 ($C(CH_3)_2$), 33.11 ($C_{7'}$), 60.93 (CH_2O), 64.91 (OCH_2CH_2O), 83.75, 84.57, and 85.30 ($C_{2'}$, $C_{3'}$, $C_{4'}$), 90.98 ($C_{1'}$), 103.80 ($C_{9'}$), 136.03 ($C_{6'}$), 136.96 ($C_{5'}$), 142.39 (C_8), 152.78 (C_2), 123.84, 133.75, and 151.29 (C_4, C_5, C_6), 164.65 (NCOPh), 166.67 (OC); FDMS (Me_2SO), m/e 602 [$(M + Na)^+$], 579 [M^+], 564 [$(M - CH_3)^+$]. Anal. Calcd for $C_{29}H_{33}N_5O_8$: C, 60.10; H, 5.74; N, 12.08. Found: C, 60.19; H, 6.16; N, 11.94.

Method B. A suspension of 0.840 g (1.45 mmol) of **2c** and 2.11 g (1.89 mmol) of potassium *tert*-butoxide in 10 mL of CH_2Cl_2 was stirred rapidly for 1 h and then filtered through Celite. The dark solution was added dropwise to a solution of 0.830 g (1.94 mmol) of **4** in CH_3CN–benzene (a mixture of **4** in 10 mL of CH_3CN and 50 mL of benzene was heated at reflux and 20 mL of solution taken off to remove the water of hydration) at ca. 40 °C. After the mixture was stirred 1 h, solvent was removed under reduced pressure, and the residue was subjected to HPLC as in method A to afford 0.750 g (90%) of a white foam identical with **5a**.

(*Z*,*E*)-*N*^{6}-Benzoyl-9-[ethyl 3,5,6-trideoxy-6-[3,3-(ethylenedioxy)propyl]-β-D-*glycero*-hepta-3,5-dienofuranosyluronate]adenine (6). A solution of 0.2 g (0.345 mmol) of **5a** in 1 mL of ethanol was treated at 0 °C with 0.3 mL of 1.3 M sodium ethoxide. The solution was stirred at room temperature for 4 h, concentrated at reduced pressure, and subjected to thick-layer chromatography (95:5, dichloromethane–methanol) to afford 97 mg (56%) of a tan foam: ^1H NMR (60 MHz, $CDCl_3$) δ 1.30 (t, CH_3, 3), 1.79 and 2.74 (m, $H_{7'}$ and $H_{8'}$, 4), 3.76 (m, OCH_2CH_2O, 4), 4.22 (q, CH_2, 2), 4.70 (t, $H_{9'}$, 1), 5.43 (m, $H_{2'}$, 1), 5.71 (d, $H_{1'}$, 1, $J_{1',2'}$ = 2.5 Hz), 6.67 (d, $H_{3'}$, 1, $J_{2',3'}$ = 2 Hz), 6.95 (s, $H_{5'}$, 1), 7.25–7.49 and 7.85–8.0 (m, Ph, 5), 8.05 and 8.65 (2 s, H_2 and H_8, 2); MS, m/e 521 [M^+], 503 [$(M - H_2O)^+$], 475 [$(M - CH_3CH_2OH)^+$] 448 [$(M - CO_2CH_2CH_3$ or M – dioxolane$)^+$].

2-Oxo-3-(triphenylphosphoranylidene)tetrahydrofuran (7). A solution of 5 g (11.7 mmol) of (2-oxotetrahydro-3-furanyl)triphenylphosphonium bromide[24] in 20 mL of dichloromethane was stirred at room temperature as 1.4 g (12.9 mmol) of potassium *tert*-butoxide was added. After being stirred rapidly at room temperature for 30 min, the suspension was filtered and concentrated at reduced pressure to afford 4 g (100%) of a light brown foam, which was used directly in the next step: ^1H NMR (60 MHz, $CDCl_3$) δ 2.72 (m, H_4, 2), 4.38 (t, H_5, 2, $J_{4,5}$ = 7 Hz), 7.37–7.98 (m, Ph's, 15).

(*E*)-*N*^{6}-Benzoyl-2′,3′-*O*-isopropylidene-5′-*C*-(2-oxotetrahydro-3-furanylidene)-5′-deoxyadenosine (8). A suspension of 11.3 g (26.4 mmol) of **4** (hydrate) in 250 mL of benzene and 50 mL of acetonitrile was heated at reflux, removing the water–benzene azeotrope via a Dean–Stark trap, until a clear solution resulted (1 h). This solution was cooled to 50 °C, and then a solution of 12.5 g (34.4 mmol) of **7** in 50 mL of dichloromethane was added dropwise. After 1 h at 60 °C, the solvent was removed under reduced pressure, and the residue was subjected to plug filtration through silica gel with 9:1 ethyl acetate–dichloromethane to remove the base-line material. The filtrate was concentrated at reduced pressure to afford a white foam which was subjected to HPLC (65:30:5 ethyl acetate–hexane–ethanol) to separate the remaining triphenylphosphine oxide (R_f 0.5) from the product (R_f 0.35), a white foam: 8.6 g (68%); $[\alpha]^{20}_D$ +7.8° (*c* 0.01, methanol); IR (KBr) 3320 (br), 3000, 1761 (s), 1705 (s), 1620, 1590, 1516, 1490, 1460, 1252, 1205, 1080, 1030, 865, 540 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.37 and 1.62 (2 s, $C(CH_3)_2$, 6), 2.87 (dt, $H_{7'}$, 2), 4.87 (m, $H_{4'}$, 1), 5.05 (dd, $H_{3'}$, 1), 5.52 (dd, $H_{2'}$, 1, $J_{2',3'}$ = 4 Hz), 6.23 (d, $H_{1'}$, 1, $J_{1',2'}$ = 2 Hz), 6.78 (dt, $H_{5'}$, 1), 7.85 and 8.05 (m, Ph, 5), 8.20 and 8.73 (s, H_8 and H_2, 2); ^{13}C NMR (20 MHz, $CDCl_3$) δ 24.94 ($C_{7'}$), 25.37, 27.13, and 115.06 (acetonide), 65.54 ($C_{8'}$), 84.23 ($C_{3'}$), 84.78 ($C_{2'}$), 85.08 ($C_{4'}$), 90.30 ($C_{1'}$), 123.92 (C_5), 133.57 (C_6), 135.21 ($C_{5'}$), 142.49 (C_8), 150.02 ($C_{6'}$), 151.29 (C_4), 152.63 (C_2), 165.25 (PhCO), 170.41 (CH_3CO); MS, m/e 477 [M^+], 462 [$(M - CH_3)^+$], 448 [$(M - CHO)^+$], 380 [$(M - I)^+$]. Anal. Calcd for $C_{24}H_{23}N_5O_6$: C, 60.37; H, 4.86; N, 14.67. Found: C, 60.10; H, 5.25; N, 14.29.



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N^6-Benzoyl-2′,3′-*O*-isopropylidene-5′-*C*-(2-oxotetrahydro-3-furanyl)-5′-deoxyadenosine (9a). A mixture of 2 g (4.3 mmol) of **8**, 0.1 g of PtO_2, and 40 mL of ethanol was shaken in a Parr hydrogenator at 60 psi for 50 h. The catalyst was filtered, and the solvent was removed at reduced pressure. The resulting syrup was subjected to HPLC (96:4 dichloromethane–methanol) to remove a small amount of slower moving material and afford 1.8 g (90%) of a white foam: IR (film) 3312 (br), 2995, 2935, 1770 (s), 1705 (s), 1610, 1585, 1513, 1485, 1455, 1255, 1210, 1085, 1023, 855, 730, 705 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.37 and 1.61 (2 s, $C(CH_3)_2$, 6), 2.28 (m, $H_{5'}$, $H_{6'}$, $H_{7'}$, 5), 4.17 (m, $H_{4'}$, $H_{8'}$, 2), 9.55 (s, NH, 1); ^{13}C NMR (20 MHz, $CDCl_3$) (a ca. 2:1 mixture of isomers was present, some signals show uneven doublets which indicate the presence of isomers) δ 25.43, 27.28, 115.01, and 115.10 (acetonide), 28.88 and 29.42 ($C_{5'}$), 33.79 and 34.03 ($C_{7'}$), 36.16 and 36.86 ($C_{8'}$), 66.51 ($C_{8'}$), 83.98 ($C_{3'}$), 85.44 ($C_{4'}$), 90.25 and 90.39 ($C_{1'}$), 123.94 (C_5), 133.65 (C_6), 142.39 and 142.53 (C_8), 151.32 (C_4), 152.73 (C_2), 164.96 (PhCO), 178.56 (CH_3CO); MS, m/e 479 [M^+], 464 [$(M - CH_3)^+$], 450 [$(M - CHO)^+$], 380 [$(M - CH_2$ – lactone$)^+$]. Anal. Calcd for $C_{24}H_{21}N_5O_6 \cdot 0.5H_2O$: C, 59.01; H, 5.36; N, 14.34. Found: C, 59.03; H, 5.62; N, 14.12.

2′,3′-*O*-Isopropylidene-5′-*C*-(2-oxotetrahydro-3-furanyl)-5′-deoxyadenosine (9b). A suspension of 2.6 g (5.42 mmol) of **9a** in 10 mL of ethylene glycol was stirred at 110 °C for 6 h, cooled to room temperature, and then partitioned between dichloromethane (40 mL) and water (40 mL). The organic extract

was washed with saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated at reduced pressure. The resulting syrup was subjected to HPLC (95:5 dichloromethane–methanol) to afford 1.57 g (77%) of a tan foam: IR (KBr) 3335 (br), 3180 (br), 2995, 2940, 1763 (s), 1640 (s), 1595 (s), 1475, 1378, 1210, 1160, 1080, 1022, 865, 800, 650, 518 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.38 and 1.62 (2 s, $C(CH_3)_2$, 6), 1.85–2.85 (m, $H_{5'}$ and $H_{7'}$, 4), 4.02–4.63 (m, $H_{6'}$, $H_{8'}$, 3), 4.93 (dd, $H_{3'}$, 1, $J_{2',3'}$ = 6.8 Hz, $J_{3',4'}$ = 4.5 Hz), 5.52 (dd, $H_{2'}$, 1, $J_{1',2'}$ = 2.5 Hz), 6.10 (d, $H_{1'}$, 1), 6.86 (s, NH_2, 2), 7.95 and 8.32 (s, H_2 and H_8, 2); FDMS (Me_2SO), m/e 398 [$(M + Na)^+$], 375 [M^+], 360 [$(M - CH_3)^+$]; $[\alpha]^{20}_D$ –0.8° (c 0.038, methanol). Anal. Calcd for $C_{17}H_{21}N_5O_5$: C, 54.39; H, 5.64; N, 18.66. Found: C, 54.53; H, 5.59; N, 18.21.

9-[*tert*-Butyldiphenylsilyl 6-(*R*,S)-[2-(*tert*-butyldiphenylsiloxy)ethyl]-2,3-*O*-isopropylidene-5,6-dideoxy-β-D-*ribo*-heptofuranosyluronate]adenine (10b). A solution of 0.114 g (2.85 mmol) of sodium hydroxide in 6 mL of water was added to 1.07 g (2.85 mmol) of **9b** in 10 mL of ethanol. The mixture was heated at 80 °C for 1 h and then concentrated at reduced pressure to give **10a** as a tan solid which was directly silylated: IR (KBr) 3400, 3050, 1660, 1592, 1060, 864 cm^{-1}; ^1H NMR (60 MHz, Me_2SO-d_6) δ 1.30 and 1.50 (2 s, $C(CH_3)_2$, 6), 1.79–2.20 (m, $H_{7'}$, 2), 3.21–3.48 (m, OH, $H_{6'}$, $H_{5'}$, 4), 4.06–4.40 (m, $H_{8'}$, 2), 4.83 (dd, $H_{3'}$, 1), 5.52 (dd, $H_{2'}$, 1), 6.05 (d, $H_{1'}$, 1), 7.37 (s, NH_2, 2), 8.16 and 8.37 (2 s, H_2 and H_8, 2); FDMS (Me_2SO), m/e 438 [$(M + Na)^+$], 415 [M^+], 375 [$(C(CH_3)_2 + Na)^+$].

The carboxylate **10a** was dissolved in 8 mL of DMF followed by the addition of 0.39 g (5.76 mmol) of imidazole. The clear solution was stirred at room temperature as 1.57 mL (1.66 g, 6.05 mol) of *tert*-butyldiphenylchlorosilane was added dropwise, causing a fine precipitate to form. After 5 h of stirring at room temperature the DMF was distilled off at reduced pressure, and the residue was dissolved in 50 mL of dichloromethane. After the mixture was washed with water, the dichloromethane was evaporated at reduced pressure, and the residue was subjected to HPLC (95:5 dichloromethane–methanol) to afford 2.4 g (96%) of a white foam. This material was most conveniently immediately converted to **10c**: IR (KBr) 3580, 3174, 2960 (s), 1733 (s), 1651 (s), 1064, 1480, 1375, 1328, 1211, 1181 (br), 1110 (br), 875, 829, 743, 704 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.03 (s, $C(CH_3)_3$, 9), 1.28 and 1.52 (2 s, $C(CH_3)_2$, 6), 1.99 (m, $H_{5'}$ and $H_{7'}$, 4), 2.89 (m, $H_{6'}$, 1), 3.64 (m, $H_{8'}$, 2), 4.24 (m, $H_{4'}$, 1), 4.83 (dd, $H_{3'}$, 1, $J_{2',3'}$ = 6 Hz, $J_{3',4'}$ = 4 Hz), 5.37 (dd, $H_{2'}$, 1, $J_{1',2'}$ = 2 Hz), 5.85 (s, NH_2, 2), 5.96 (d, $H_{1'}$, 1), 7.30 and 7.52 (2 m, Ph's, 10), 7.78 and 8.27 (2 s, H_2 and H_8, 2); MS, m/e 866, 811, 753, 677.

9-[6-(*R*,*S*)-[2-(*tert*-Butyldiphenylsiloxy)ethyl]-2,3-*O*-isopropylidene-5,6-dideoxy-β-D-*ribo*-heptofuranosyluronic acid]adenine (10c). A mixture of 0.8 g (0.9 mmol) of **10b** in 9 mL of THF was cooled to 0 °C with stirring while 0.360 g (0.9 mmol) of sodium hydroxide in 1 mL of water was added dropwise. The mixture was stirred at 0 °C for 2 h, and then the THF was removed at reduced pressure. The residue was neutralized with glacial acetic acid then partitioned between dichloromethane and water. The organic extract was washed with 10 mL of saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated at reduced pressure. The residue was subjected to HPLC (93:7 dichloromethane–methanol) to afford 0.51 g (90%) of a white foam shown to be a 3:1 mixture of isomers (6*S* + 6*R*): IR (KBr) 3320 (br), 3180 (br), 3060 (br), 2920, 2850, 1960, 1895, 1700 (s), 1640 (s), 1600, 1470, 1425 (s), 1380, 1330, 1200 (br), 1090 (br), 865, 820, 740, 720, 700, 605, 540, 505 cm^{-1}; ^1H NMR for isomer 1 (200 MHz, $CDCl_3$) δ 1.05 (s, $C(CH_3)_3$, 9), 1.35 and 1.60 (2 s, $C(CH_3)_2$, 6), 2.22 (m, $H_{5'}$, 2), 2.89 (m, $H_{6'}$, 1), 3.77 (t, $H_{8'}$, 2, $J_{7',8'}$ = 6.06 Hz), 4.36 (q, $H_{4'}$, 1), 4.92 (dd, $H_{3'}$, 1), 5.28 (dd, $H_{2'}$, 1, $J_{2',3'}$ = 6.62 Hz, $J_{1',2'}$ = 2.94 Hz, $J_{3',4'}$ = 4.04 Hz), 6.04 (d, $H_{1'}$, 1), 6.42 (s, NH_2, 2), 7.64 and 7.38 (2 m, Ph, 10), 7.91 and 8.21 (2 s, H_2 + H_8, 2); ^1H NMR for isomer 2 (selected signals, 200 MHz, $CDCl_3$) δ 3.07 ($H_{6'}$), 4.79 ($H_{3'}$), 5.41 ($H_{2'}$), 6.09 ($H_{1'}$), 6.53 (NH_2), 7.83 and 8.16 (H_2 and H_8); FDMS (Me_2SO), m/e 632 [$(M+1)^+$], 587 [$(M - CO_2)^+$], 574 [$(M - t\text{-}Bu)^+$]; $[\alpha]^{20}_D$ +10.7° (c 0.0021, methanol). Anal. Calcd for $C_{33}H_{41}N_5O_6Si$: C, 62.73; H, 6.54; N, 11.08. Found: C, 62.34; H, 6.74; N, 10.95.

9-[6-[(Benzyloxycarbonyl)amino]-5,6,7-trideoxy-8-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-β-D-*allo*- and -α-L-*talo*-octofuranosyl]adenine (11a). Method A. To a solution of 0.2 g (0.317 mmol) of **10c** in 3 mL of methanol was added 0.035 g (0.317 mmol) of potassium *tert*-butoxide, the resulting solution was stirred for 15 min, and then the solvent was removed under reduced pressure. The crude solid was dried in vacuo overnight, dissolved in 10 mL of dry benzene, and treated with 0.034 mL (0.052 g, 0.412 mmol) of oxalyl chloride. After 30 min, the yellow solution was concentrated under reduced pressure and dried in vacuo. The acid chloride **10d** was dissolved in 10 mL of dry acetone and cooled to 0 °C as a solution of 0.062 g (0.953 mmol) of sodium azide in 0.5 mL of water was added dropwise. After the mixture was stirred at 0 °C for 90 min, the acetone was removed under a stream of nitrogen, and the residue was diluted with 20 mL of toluene and 5 mL of water. The organic extract was dried over magnesium sulfate and filtered into a 100-mL flask [IR (toluene) azide band at 2143 cm^{-1}]. To this clear solution was added 0.34 mL (0.32 g, 0.00317 mol) of benzyl alcohol, and the mixture was heated at reflux for 4 h. The solvent was removed at reduced pressure, and the residue was subjected to thick-layer chromatography (95:5 dichloromethane–methanol) to yield 0.114 (49%) of a white foam (yields varied between 10% and 60%).

Method B. A solution of 0.2 g (0.317 mmol) of **10c** and 2 mL of thionyl chloride was stirred at room temperature for 1 h, and then the excess thionyl chloride was removed under a stream of nitrogen. The residue was kept under vacuum for 2 h to remove all traces of hydrogen chloride. The crude acid chloride was treated as in method A to afford similar yields: IR (KBr) 3400 (br), 3120 (br), 2930, 1710 (s), 1640 (s), 1600, 1245, 1110, 1085, 700 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.00 (s, $C(CH_3)_3$, 9), 1.36 and 1.58 (2 s, $C(CH_3)_2$, 6), 1.70 (m, 2 $H_{5'}$, 2), 1.98 (m, 2 $H_{7'}$, 2), 3.68 (m, 2 $H_{8'}$, 2), 3.94 (m, $H_{6'}$, 1), 4.27 (m, $H_{4'}$, 1), 4.89 (m, $H_{3'}$, 1), 5.02 (s, CH_2Ph, 2), 5.38 (m, $H_{2'}$, 1), 5.50 (s, NH_2, 2), 6.00 (d, $H_{1'}$, 1), 7.26–7.64 (m, Ph, 15), 7.84 and 8.32 (2 s, H_2 and H_8, 2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.45, 27.24, 114.68 and 114.75 (acetonide), 26.85 and 26.99 (C-5′), 37.91 and 38.15 (C-7′), 47.03 and 47.13 (C-6′), 61.01 (CH_2Ph), 66.43 (C-8′), 83.88 (C-3′), 83.96 and 84.27 (C-2′), 84.47 and 84.56 (C-4′), 90.31 and 90.50 (C-1′), 120.39 (C-5), 139.86 and 139.96 (C-8), 149.47 and 149.40 (C-4), 153.18 (C-2), 155.68 (C-6), 155.92 (C=O); FDMS (Me_2SO) m/e 736 [M^+], 679 [$(M - t\text{-}Bu)^+$]; $[\alpha]^{20}_D$ +8.9° (c 0.00718 methanol). Anal. Calcd for $C_{40}H_{48}N_6O_6Si$: C, 65.19; H, 6.57; N, 11.40. Found: C, 65.13; H, 6.97; N, 11.69.

9-[6-[(Benzyloxycarbonyl)amino]-5,6,7-trideoxy-2,3-*O*-isopropylidene-β-D-*allo*- and -α-L-*talo*-octofuranosyl]adenine (11b). A solution of 0.12 g (0.163 mmol) of **11a** and 2 mL of THF was stirred under nitrogen at room temperature as 0.33 mL (0.326 mmol) of 1 M tetrabutylammonium fluoride was added. The solution was stirred at room temperature for 45 min, and then 5 mL of water and 5 mL of dichloromethane were added. The organic extract was dried over magnesium sulfate and concentrated at reduced pressure, and the residue was subjected to thick-layer chromatography (95:5 dichloromethane–methanol) to yield 0.05 g (62%) of a white foam, which was taken up in CH_3OH–H_2O and lyophilized to a white powder: IR (KBr) 3340 (br), 2935, 1705, 1642, 1375, 1250, 1210, 1080 (br), 865, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.40 and 1.62 (2 s, $C(CH_3)_2$, 6), 1.90 (m, 2 $H_{5'}$, 2), 2.80 (m, 2 $H_{7'}$, 1), 3.62 (m, 2 $H_{8'}$, 2), 4.06 (m, $H_{6'}$, 1), 4.38 (m, $H_{4'}$, 1), 4.94 (m, $H_{3'}$, 1), 5.08 (s, CH_2Ph, 2), 5.47 (m, $H_{2'}$, 1), 5.60 (s, NH_2, 2), 6.03 (d, $H_{1'}$, 1), 7.33 (m, Ph, 5), 7.82 and 8.37 (2 s, H_2 and H_8, 2); FDMS (Me_2SO), m/e 498 (M^+). Anal. Calcd for $C_{24}H_{30}N_6O_6{\cdot}H_2O$: C, 55.80; H, 6.24; N, 16.27. Found: C, 56.17; H, 6.31; N, 15.85.

9-[8-Azido-6-[(benzyloxycarbonyl)amino]-5,6,7,8-tetradeoxy-2,3-*O*-isopropylidene-β-D-*allo*- and -α-L-*talo*-octafuranosyl]adenine (11d). A solution of 0.070 g (0.14 mmol) of **11b**, 2 mL of dichloromethane and 0.051 mL (0.0379 g, 0.365 mmol) of triethylamine was stirred at room temperature, as 0.014 mL (0.021 g, 0.183 mmol) of methanesulfonyl chloride was added under an atmosphere of nitrogen. After 1 h at room temperature, the solvent was removed under reduced pressure to afford a tacky foam: FDMS (Me_2SO), m/e 577 [$(M + 1)^+$], 481 [$(M - OSO_2CH_3)^+$].

A solution of 0.017 g (0.29 mmol) of the mesylate **11c** in 1 mL of dry Me_2SO was treated with 0.046 g (0.702 mmol) of sodium azide in 2 mL of Me_2SO, and the mixture was heated at 60 °C for 1 h. Water (5 mL) and dichloromethane (15 mL) were added, and the organic extract was separated, dried over magnesium sulfate, and then concentrated at reduced pressure. The residue

was subjected to HPLC (95:5 dichloromethane–methanol) to afford 0.069 g (89%) of a hygroscopic tan foam, which was dissolved in H_2O–THF and lyophilized to provide material for analysis: IR (film) 2120 cm^{-1} (N_3); ^1H NMR (200 MHz, $CDCl_3$) δ 1.32 and 1.56 (2 s, $C(CH_3)_2$, 6), 2.11 (m, 2 $H_{5'}$, 2), 2.95 (q, 2 $H_{7'}$, 2), 3.20 (t, 2 $H_{8'}$, 2), 3.77 (m, $H_{6'}$, 1), 4.28 (m, $H_{4'}$, 1), 4.86 (m, $H_{3'}$, 1), 5.00 (s, CH_2Ph, 2), 5.40 (m, $H_{2'}$, 1), 5.52 (s, NH_2, 2), 5.94 (br s, $H_{1'}$, 1), 7.22 (s, Ph, 5), 7.77 and 8.22 (2 s, H_2 and H_8, 2); FDMS (Me_2SO), *m/e* 524 [$(M + 1)^+$], 523 [M^+], 481 [$(M - N_3)^+$]. Anal. Calcd for $C_{24}H_{29}N_9O_5 \cdot 1.6H_2O$: C, 52.19; H, 5.88; N, 22.82. Found: C, 52.27; H, 5.70; N, 22.51.

9-[Benzyl 9-(benzyloxycarbonyl)-6-[(benzyloxycarbonyl)amino]-5,6,7,8,9-pentadeoxy-2,3-*O*-isopropylidene-β-D-*allo*- and -α-L-*talo*-decafuranosyluronate]adenine (11e). A solution of 0.6 mL (0.068 g, 0.237 mmol) of dibenzyl malonate and 2 mL of DMF was treated at room temperature with 0.01 g (0.237 mmol) of sodium hydride 60% oil dispersion. After the evolution of hydrogen ceased, a solution of 0.038 g (0.067 mmol) of **11c**, formed as described in the synthesis of **11d**, in 2 mL of DMF was added, and the mixture was heated at 80 °C for 3 h. After the solvent was removed at reduced pressure, the residue was dissolved in dichloromethane and washed with water. The organic extract was dried over magnesium sulfate and concentrated at reduced pressure. The residue was subjected to thick-layer chromatography (95:5 dichloromethane–methanol) to afford 0.011 g (22%) of a tan foam: ^1H NMR (200 MHz, $CDCl_3$) δ 1.34 and 1.59 (2 s, $C(CH_3)_2$, 6), 2.00 (m, 2 $H_{5'}$, 2 $H_{7'}$, 2 $H_{8'}$, 6), 3.47 (t, $H_{9'}$, 1), 3.51 (m, $H_{6'}$, 1), 4.29 (m, $H_{4'}$, 1), 5.04 (m, $H_{3'}$, 1), 5.11 (s, CH_2Ph, 4), 5.47 (m, $H_{2'}$, 1), 5.75 (br s, NH_2, 2), 6.01 (br s, $H_{1'}$, 1), 7.28 (m, Ph and H_2 or H_8, 16), 8.33 (s, H_2 or H_8, 1); FDMS (Me_2SO), *m/e* 788 [$(M + Na)^+$], 765 [$(M + 1)^+$], 764 [M^+].

Registry No. **1**, 58944-73-3; **2a**, 38049-07-9; **2b**, 85680-98-4; **2c**, 85680-99-5; **3a**, 85681-00-1; **4**, 43077-06-1; **5a**, 85681-01-2; **6**, 85681-02-3; **7**, 34932-07-5; **8**, 85681-03-4; **9a**, 85681-04-5; **9b**, 85681-05-6; (*R*)-**10a**, 85681-07-8; (*S*)-**10a**, 85681-10-3; (*R*)-**10b**, 85681-06-7; (*S*)-**10b**, 85701-31-1; (*R*)-**10c**, 85681-08-9; (*S*)-**10c**, 85681-09-0; (*R*)-**10d**, 85681-11-4; (*S*)-**10d**, 85681-12-5; β-D-*allo*-**11a**, 85681-13-6; α-L-*talo*-**11a**, 85681-14-7; β-D-*allo*-**11b**, 85681-15-8; α-L-*talo*-**11b**, 85701-32-2; β-D-*allo*-**11c**, 85681-18-1; α-L-*talo*-**11c**, 85681-19-2; β-D-*allo*-**11d**, 85681-16-9; α-L-*talo*-**11d**, 85681-17-0; β-D-*allo*-**11e**, 85681-20-5; α-L-*talo*-**11e**, 85701-33-3; *a*, 85681-21-6; ethyl 2-(ethoxycarbonyl)-5,5-(ethylenedioxy)pentanoate, 23985-06-0; (2-oxotetrahydro-3-furanyl)triphenylphosphonium bromide, 28228-78-6; dibenzyl malonate, 15014-25-2.

Total Synthesis of β-Santalol

Dennis Solas and Joseph Wolinsky*

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

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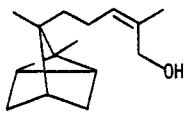
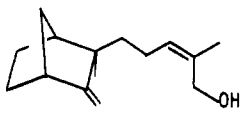
A synthesis of β-santalol (**2**) is described by using camphenesultone (**4**) as the starting material. Alkylation of the sultone **4** with the tetrahydropyranyl ether of 2-bromoethanol (**11**) followed by reaction with phenyllithium and desulfurization with sodium amalgam produced the monoprotected diol **16**. The intermediate **1** was converted to bicycloekasantalal which has been previously transformed into β-santalol (**2**).

There has been considerable interest in recent years in developing syntheses of α-santalol (**1**)[1] and β-santalol (**2**),[2] the main constituents of East Indian sandalwood oil,[3] which are highly prized for their fragrance.



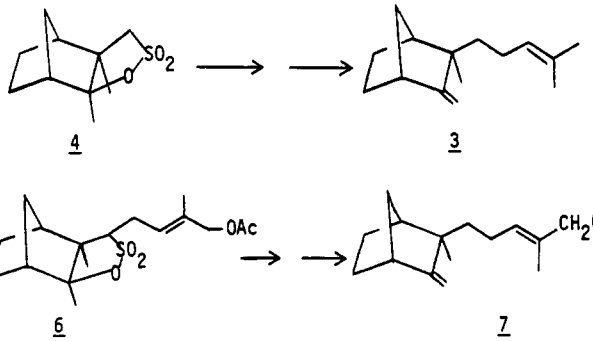
1



2

Work on the construction of β-santalol (**2**) in our laboratory started years ago and resulted in a successful total synthesis of β-santalene (**3**),[4] one of the minor sesquiterpene components of sandalwood oil, on using camphenesultone (**4**) as starting material.

While the alkylation of sultone **4** with *trans*-1-acetoxy-4-bromo-2-methyl-2-butene (**5**)[5] proved successful, attempts to convert the resulting acetate **6** to *trans*-β-santalol (**7**) were disappointing, especially with regard to the very low yields obtained in the desulfurization of **6** on using aluminum hydride–lithium aluminum hydride.[4,6]



4 **3** **6** **7**

We have now turned to a stepwise construction of the allylic alcohol side chain and report a route to bicycloekasantalal (**8**) which has been previously transformed into β-santalol (**2**) with high stereoselectivity.[2b]

In this work, camphenesultone (**4**) was prepared from *d*-10-camphorsulfonic acid (**9**), in 54% overall yield, by reduction with sodium borohydride and conversion to sultone **10** with *p*-toluensulfonyl chloride in pyridine followed by pyrolysis at 126 °C[7] (Scheme I).

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