A Radical-Based Strategy for the Synthesis of Higher Homologues of Sinefungin

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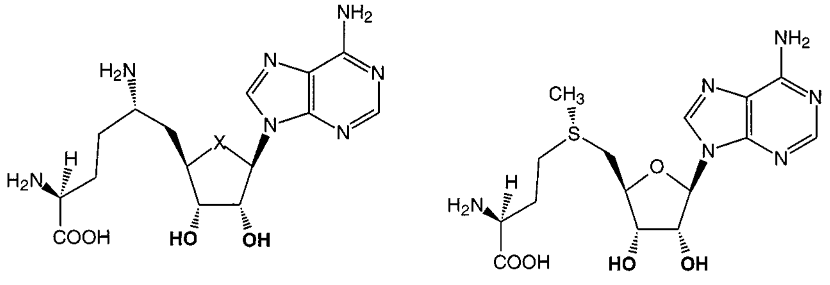
Homosinefungin **5**, which can be considered as an analogue of *S*-adenosylmethionine (SAM) and of *S*-adenosylhomocysteine (SAH), has been synthesized by means of a sequence in which the key step was the addition of a radical, produced by the simple treatment of an iodide precursor with a zinc-copper couple, to suitably activated olefins.

Introduction

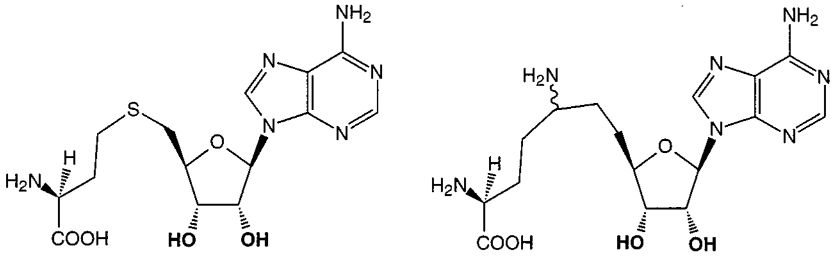
Sinefungin **1** is a natural complex nucleoside[1] in which an ornithine residue is linked to the 5' end of adenosine by a carbon-carbon bond. Accordingly, it bears a close structural resemblance to both *S*-adenosylmethionine (SAM) **2** and *S*-adenosylhomocysteine (SAH) **3**. The antibiotic, which was isolated from various cultures of *Streptomyces,*[2] was shown to exhibit a variety of biological effects including antiviral, antifungal,[3] and antiparasitic[4] activities. Unfortunately, sinefungin **1** was found to be nephrotoxic and this fact has led research groups to prepare structurally related analogues (Figure 1). For example, we recently described an original approach to the synthesis of carbocyclic sinefungin **4**[5] by a new type of radical C–C bond forming reaction.[6]

We now report a short synthesis of homosinefungin **5** based on the same radical chemistry. Hopefully, this new analogue of SAM and SAH might inhibit various enzymes including SAM-transferase, SAM-decarboxylase, and SAH-hydrolase.



Sinefungin **1** (X= O)
Carbasinefungin **4** (X= CH_2)

SAM **2**



SAH **3**

Homosinefungin **5**

Figure 1

Results and Discussion

Our synthesis of homosinefungin **5** (outlined in Scheme 1) started from methyl 5-deoxy-5-iodo-2,3-*O*-isopropylideneriboside **6**, which is known to generate a radical in the presence of Zn/CuI which in turn readily undergoes addition to electron deficient olefins.[6] In our hands, application of

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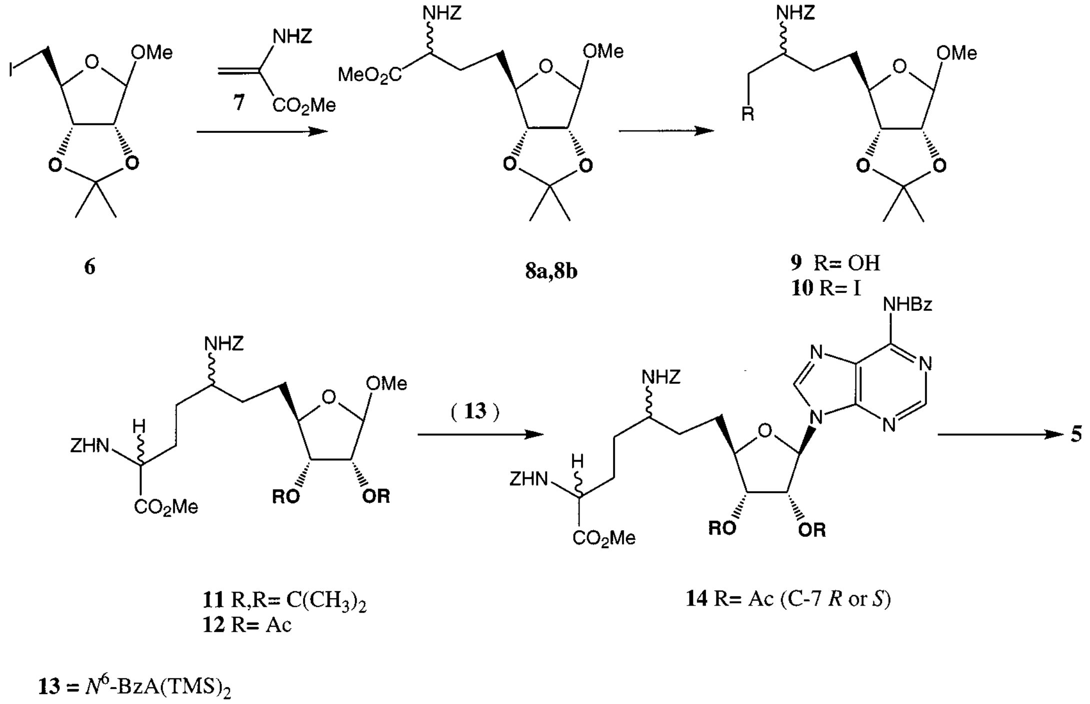


6

8a,8b

9 R= OH
10 R= I

11 R,R= $C(CH_3)_2$
12 R= Ac

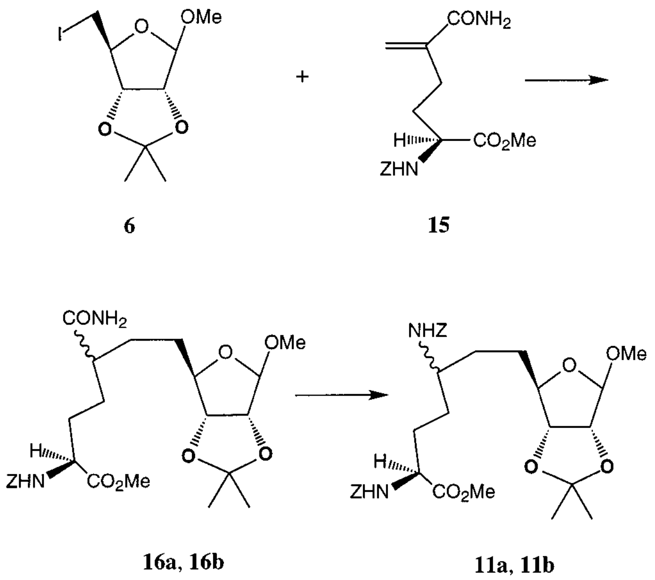
14 R= Ac (C-7 *R* or *S*)

13 = N^6-BzA(TMS)$_2$

Scheme 1

these reaction conditions to the acrylate **7**[7] afforded a mixture of separable octose derivatives **8a** (less polar isomer) and **8b** (more polar isomer). However, the configuration at C-7 has not been yet established. Reduction of **8a** in the presence of $NaBH_4$/LiCl gave the hydroxy derivative **9** and subsequent treatment of **9** with methyltriphenoxyphosphonium iodide led to iodide **10** in 75% yield. Again, the radical derived from **10** was added to olefin **6** to give **11** as a mixture of two stereoisomers in 50% yield, although in this instance these could not be separated. Final adenylation was accomplished by a modification of the method of Vorbruggen.[8] The acetonide protecting group of **11** was first removed by treatment with aqueous dioxane/HCl to give a diol intermediate which was acetylated with acetic anhydride/sodium acetate to provide **12** in 58% yield. Subsequent reaction of **12** with persilylated N^6-benzoyladenine (**13**) in the presence of trimethylsilyl triflate[8b] gave **14** as a mixture of two stereoisomers at C-10 in 34% yield. Complete deprotection of compound **14** was accomplished in two steps, i.e. by initial treatment with methanolic ammonia followed by hydrogenolysis of the Cbz group (H_2, 10% Pd/C) to furnish **5** in 60% overall yield.

Alternatively, we proposed to explore a more convergent route to obtain intermediate **11** with the naturally observed chirality at position C-10. Thus, compounds **15**[5,9] and **6** were combined under our usual radical conditions to produce **16** (two stereoisomers at C-7) in 18% yield. Amide derivatives **16a** and **16b** were separated by HPLC and submitted separately to Hofmann degradation with [bis(trifluoroacetoxy)iodo]benzene.[10,11] The amines thus formed were immediately converted into the benzyloxycarbonyl derivatives **11a** and **11b**, which were isolated both in 40% yield (Scheme 2). However, as in the case of compounds **8a** and **8b**, their respective configurations at C-7' have not been determined.



6 **15**

16a, 16b **11a, 11b**

Scheme 2

In conclusion, we have developed a simple sequence which in a few steps leads to **5** a higher analogue of sinefungin **1**. The new nucleoside differs from the parent compound by the side chain which contains a supplementary methylene group next to the ribose moiety. The strategy employed to synthesize **5** might be extended to obtain various other sinefungin analogues with other modified side chains.

Experimental Section

^1H and ^{13}C NMR spectra were recorded on Bruker WP 200 SY and AC 300 spectrometers. Chemical shifts (δ) are reported in ppm. – Electron impact (EI) mass spectra were measured with an AEI MS 50 mass spectrometer. Fast atom bombardment (FAB) mass spectra, using glycerol (or thioglycerol) matrices, were obtained with a Kratos MS 80 instrument. – Microanalyses were performed by the Service de Microanalyse de l'ICSN-CNRS. – Column chromatography was carried out on Silica gel Kieselgel 60. Silicagel TLC was performed on Schleicher and Schuell plates with UV light for visualization. Analytical and preparative HPLC wee accomplished on Intersil 5μ silica columns.

Methyl [7-(Benzyloxycarbonyl)amino-5,6,7-trideoxy-2,3-*O*-(isopropylidene)-7-methoxycarbonyl-β-D-heptaribofuranose (8). – A solution of 5-iodoribose **6** (2 g; 6.36 mmol) in THF/H_2O (8:2) (10 mL) under a nitrogen atmosphere was treated (in 5 portions) with a solid mixture composed of CuI (1.46 g; 9.6 mmol) and Zn powder (2 g; 32 mmol) followed by a solution of the acrylate **7** (4.49 g; 19.1 mmol) in THF (10 mL). The reaction mixture was stirred with a vibromixer until disappearance of the starting material, then diluted with ether, filtered through Celite and the resulting solution washed with brine. Evaporation of the solvents gave a residue which was chromatographed on silica gel (heptane/ethyl acetate 2:1) to yield a mixture (3.0 g; 67%) of the two C-7 epimers **8a** and **8b** as a colourless oil. The epimers were then separated by HPLC (elution with heptane/ethyl acetate/CH_2Cl_2, 60:33:7). – ***Isomer* 8a:** $[\alpha]_D$ = –23 (*c* = 1.7, $CHCl_3$). – EIMS: *m/z*: 423 [M^+], 392 [M – 31]. – ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34 (s, 5 H, Ph), 5.36 (m, 1 H, NH), 5.10 (s, 2 H, CH_2Ph), 4.92 (s, 1 H, H-1), 4.59 (d, 1 H, H-2, J_{2-3} = 6 Hz), 4.50 (d, 1 H, H-3), 4.41 (m, 1 H, H-7), 4.11 (m, 1 H, H-4), 3.74 (s, 3 H, OCH_3), 3.32 (s, 3 H, OMe), 2.06 (m, 2 H, 2 H-5), 1.75 (m, 2 H, H-6a), 1.46 (s, 3 H, CH_3 isop), 1.30 (s, 3 H, CH_3 isop). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 179.3 ($COCH_2Ph$), 159.7 ($COCH_3$), 128.6 (Ph), 112.6 (Cq), 109.8 (C-1), 86.6 (C-2), 85.5 (C-3), 84.3 (C-4), 67.1 (CH_2Ph), 55.1 (OCH_3), 53.9 (C-7), 52.4 (OMe), 31.0 (C-5), 29.7 (C-6), 26.6 and 25.2 (2 CH_3 isop). – $C_{21}H_{29}NO_8$ (423.47): calcd. C 59.50, H 6.85, N 3.30; found C 59.59, H 6.65, N 2.99. – ***Isomer* 8b:** $[\alpha]_D$ = –32 (*c* = 1.7, $CHCl_3$). – ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33 (s, 5 H, Ph), 5.34 (m, 1 H, NH), 5.08 (s, 2 H, CH_2Ph), 4.92 (s, 1 H, H-1), 4.57 (d, 1 H, H-2, J_{2-3} = 6 Hz), 4.48 (d, 1 H, H-3), 4.40 (m, 1 H, H-7), 4.10 (m, 1 H, H-4), 3.74 (s, 3 H, OCH_3), 3.28 (s, 3 H, OMe), 1.90 (m, 2 H, 2 H-5), 1.57 (m, 2 H, H-6a), 1.46 (s, 3 H, CH_3 isop), 1.30 (s, 3 H, CH_3 isop). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 179.1 ($COCH_2Ph$), 159.7 ($COCH_3$), 128.1 (Ph), 112.3 (Cq), 109.8 (C-1), 86.2 (C-2), 85.4 (C-3), 84.1 (C-4), 66.9 (CH_2Ph), 55.0 (OCH_3), 53.7 (C-7), 52.2 (OMe), 30.8 (C-5), 29.3 (C-6), 26.4 and 25.0 (2 CH_3 isop).

Methyl [7-(Benzyloxycarbonyl)amino-5,6,7-trideoxy-2,3-*O*-(isopropylidene)-β-D-octaribofuranose (9): A solution of **8** (3.0 g; 7.22 mmol) in anhydrous THF (25 mL) at 0 °C was treated with LiCl (3 g; 72.2 mmol) and $NaBH_4$ (2.87 g; 72.2 mmol). The mixture was stirred for 3 min, anhydrous methanol (30 mL) added and the mixture stirred for a further 5h at room temperature. The solvents were removed in vacuo, the residue dissolved in ethyl acetate, washed successively with saturated NH_4Cl solution and brine, and dried. The solvent was evaporated to give a residue, which was purified by silica gel column chromatography (heptane/ethyl acetate, 1:1) to yield **9** (1.3 g, 85%) as an oil. – EIMS; *m/z*: 364 [M – 31]$^+$. – ^1H NMR (250 MHz, $CDCl_3$): δ = 7.34 (s, 5 H, Ph), 5.09 (s, 2 H, CH_2Ph), 5.10 (s, 1 H, NH), 4.92 (s, 1 H, H-1), 4.59 (d, 1 H, H-2, J_{2-3} = 6 Hz), 4.51 (d, 1 H, H-3, J_{3-2} = 6 Hz), 4.14 (dd, 1 H, H-7, J_{7-8} = 3 Hz, J_{7-6} = 5 Hz), 3.66 (dd, 1 H, H-4, J_{4-5} = 5 Hz, $J_{4-5'}$ = 8 Hz), 3.59 (m, 2 H, 2H-8), 3.31 (s, 3 H, OMe), 2.56 (s, 1 H, OH), 1.6–1.5 (m, 4 H, 2H-5 and 2H-6), 1.46 (s, 3 H, CH_3 isop), 1.30 (s, 3 H, CH_3 isop). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 179.2 (CO), 128.6 (Ph), 112.5 (Cq), 109.8 (C-1), 87.0 (C-2), 86.8 (C-3), 85.5 (C-4), 66.9 (CH_2Ph), 65.3 (C-8), 55.1 (OCH_3), 53.3 (C-7), 28.4 (C-6), 26.6 and 25.1 (2 CH_3 isop). –$C_{20}H_{29}NO_7$ (395.46): calcd. C 60.75, H 7.34, N 3.54; found C 60.51, H 7.53, N 3.54.

Methyl [7-(Benzyloxycarbonyl)amino-5,6,7,8-tetradeoxy-8-iodo-2,3-*O*-(isopropylidene)-β-D-octaribofuranose (10): A solution of **9** (2 g, 5.16 mmol) in DMF (20 mL) containing methyltriphenoxyphosphonium iodide (4.6 g, 10.32 mmol) was stirred at room temperature under a nitrogen atmosphere for 18 h. The solution was evaporated to dryness, and the residue dissolved in dichloromethane (20 mL). The solution was successively washed with saturated sodium thiosulfate (2 × 10 mL), $NaHCO_3$ (2 × 10 mL), brine and dried. The solvent was evaporated to give a residue, which was purified by silica gel column chromatography (heptane/ethyl acetate, 2:1) to yield **10** (1.9 g, 75%) as an oil. – EIMS; *m/z*: 505 [M]$^+$, 490 [M – 15]. – ^1H NMR (250 MHz, $CDCl_3$): δ = 7.35 (s, 5 H, Ph), 5.10 (s, 2 H, CH_2Ph), 4.89 (br. s, 1 H, NH), 4.83 (s, 1 H, H-1), 4.60 (d, 1 H, H-2, J_{2-3} = 6 Hz), 4.51 (d, 1 H, H-3, J_{3-2} = 6 Hz), 4.12 (m, 1 H, H-4), 3.43 (m, 2 H, 2H-8), 3.40 (m, 1 H, H-7), 3.34 (s, 3 H, OMe), 1.73–1.57 (m, 4 H, 2H-5 and 2H-6), 1.47 (s, 3 H, CH_3 isop), 1.31 (s, 3 H, CH_3 isop). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 179.2 (CO), 128.6 (Ph), 112.5 (Cq), 109.8 (C-1), 86.8 (C-2), 85.5 (C-3), 84.2 (C-4), 67.0 (CH_2Ph), 55.5 (OCH_3), 50.6 (C-7), 32.1 (C-5), 31.6 (C-6), 26.6 and 25.1 (2 CH_3 isop), 13.7 (C-8). – $C_{20}H_{28}NO_6I$ (505.35): calcd. C 47.52, H 5.54, N 2.77; found C 47.75, H 5.64, N 2.56.

Methyl [7,10-Bis(benzyloxycarbonyl)amino-5,6,7,8,9,10-hexadeoxy-2,3-*O*-(isopropylidene)-10-methoxycarbonyl-β-D-decaribofuranose (11): A solution of **10** (0.5 g; 1.0 mmol) in THF/H_2O (8:2) (2 mL), under a nitrogen atmosphere, was treated successively with CuI (0.35 g; 2.4 mmol), Zn powder (0.5 g; 8 mmol) and then a solution of the acrylate **7**[7] (0.94 g; 4 mmol) in THF (2 mL). The reaction mixture was stirred with a vibromixer until disappearance of the starting material, then diluted with ether, filtered through Celite and the resulting solution washed with brine. Evaporation of the solvents gave a residue which was chromatographed on a silica gel column to yield **11** (0.3 g; 50%) as a mixture of C-10 stereoisomers. – EIMS; *m/z*: 614 [M^+], 583 [M – 31], 555 [M – CO_2CH_3]. – ^1H NMR (250 MHz, $CDCl_3$): δ = 7.32 (s, 5 H, Ph), 5.32 (m, 1 H, NH), 5.09 (s, 2 H, CH_2Ph), 5.07 (s, 2 H, CH_2Ph), 4.91 (s, 1 H, H-1), 4.90 (m, 1 H, NH), 4.57 (d, 1 H, H-2, J_{2-3} = 6 Hz), 4.47 (d, 1 H, H-3, J_{3-2} = 6 Hz), 4.34 (m, 1 H, H-7), 4.09 (dd, 1 H, H-4, J_{4-5} = 5 Hz, $J_{4-5'}$ = 5 Hz), 3.70 (s, 3 H, OCH_3), 3.63 (m, 1 H, H-10), 3.29 (s, 3 H, OMe), 1.73 (m, 8 H, 2H-5, 2H-6, 2H-8 and 2H-9), 1.46 (s, 3 H, CH_3 isop), 1.29 (s, 3 H, CH_3 isop). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 176.9 (CO), 156.0 (CO_2CH_3), 128.5 (Ph), 112.3 (Cq), 109.6 (C-1), 87.2 (C-2), 86.4 (C-3), 84.1 (C-4), 69.3 (CH_2Ph), 66.8 (CH_2Ph), 55.0 (OCH_3), 53.9 (C-7), 52.1 (OMe), 50.7 (C-10), 32.3–29.1 (C-5, C-6, C-8 and C-9), 26.5 (CH_3 isop), 24.9 (CH_3 isop). – $C_{32}H_{42}N_2O_{10}$ (614.68): calcd. C 62.54, H 7.16, N 4.56; found C 61.99, H 6.96, N 4.41.

Methyl [2,3-Di-*O*-acetyl-7,10-bis(benzyloxycarbonyl)amino-5,6,7,8,9,10-hexadeoxy-10-methoxycarbonyl]-β-D-decaribofuranose

(12): A solution of **11** (500 mg, 0.8 mmol) in dioxane (10 mL) was treated with 0.5 mL of 4N HCl. The biphasic mixture was stirred at 22 °C for 40 h, partitioned between 20 mL of ethyl acetate and 20 mL of 0.25 N $NaHPO_4$, and the aqueous phase back-extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried and evaporated to give 375 mg of a crude oil which was dissolved in 50 mL of acetic anhydride containing 0.93 g (11.3 mmol) of sodium acetate. The mixture was stirred at 50 °C for 16 h., volatiles removed in vacuo,the residue coevaporated twice with xylene and finally partitioned between water (50 mL) and ethyl acetate (100 mL). The organic layer was washed with saturated $NaHCO_3$ (30 mL), brine (30 mL) and dried. Evaporation of the solvent gave a residue which was purified by silica gel column chromatography (heptane/ethyl acetate, 7:3) to give 307 mg of pure **12** (58%) as an oil. – EIMS; *m*/*z*: 659 $[M + 1]^+$. – ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35 (s, 5 H, Ph), 5.32 (m, 1 H, NH), 5.11 (s, 4 H, 2 CH_2Ph), 4.85 (s, 1 H, H-1), 4.82 (d, 1 H, H-2, J_{2-3} = 5 Hz), 4.60 (d, 1 H, H-3, J_{3-2} = 5 Hz), 4.32 (m, 1 H, H-7), 4.09 (dd, 1 H, H-4, J_{4-5} = 5 Hz, $J_{4-5'}$ = 5 Hz), 3.75 (s, 3 H, OCH_3), 3.68 (m, 1 H, H-10), 3.37 (s, 3 H, OMe), 2.12 (s, 3 H, OAc), 2.05 (s, 3 H, OAc), 1.94 (m, 8 H, 2H-5, 2 H-6, 2H-8, 2 H-9). – ^{13}C NMR (69.72 MHz, $CDCl_3$): δ = 176.4 (CO), 169.8 (OAc), 156.8 (OAc), 128.6 (Ph), 106.2 (C-1), 80.6 (C-2), 80.3 (C-3), 75.2 (C-4), 67.2 (CH_2Ph), 66.8 (*C*H_2Ph), 55.4 (OCH_3), 54.8 (C-7), 52.7 (OMe), 50.3 (C-10), 31.5 (C-5), 31.3 (C-6), 30.8 (C-8) 29.4 (C-9), 20.7 (CH_3). – $C_{33}H_{42}N_2O_{12}$ (658.70): calcd. C 60.18, H 6.30, N 4.20; found C 59.70, H 6.41, N 4.13.

9-[2,3-Di-*O*-acetyl-7,10-bis(benzyloxycarbonyl)amino-5,6,7,8,9,10-hexadeoxy-10-methoxycarbonyl-]-β-D-decaribofuranosyl]-*N6*-benzoyladenine (14): *N*^{6}-Benzoyl-*N*^{6},*N*^{9}-bis(trimethylsilyl)adenine **13** (177 mg, 0.27 mmol) was added to a solution of **12** (92 mg, 0.14 mmol) in 5 mL of 1,2-dichloroethane (DCE) and 0.3 mL of a 25% solution of trimethylsilyl triflate in DCE, and the mixture heated under reflux for 48 h. It was then diluted with dichloromethane and washed with saturated brine. The organic phase was evaporated and the residue dissolved in ethyl acetate. The solution was kept in the refrigerator overnight to precipitate excess *N*^{6}-benzoyladenine. The filtrate was evaporated to give a residue which was chromatographed on a silica gel column to give 46 mg (38%) of **14** as mixture of two C-10 stereoisomers. – FABMS; *m*/*z*: 866 $[M + 1]^+$. – ^1H NMR (250 MHz, CD_3OD): δ = 8.80 (s, 1 H, H-2), 8.23 (s, 1 H, H-8), 7.60–7.30 (s, 5 H, 3 Ph), 5.40 (m, 1 H, NH), 4.85 (d, 1 H, H-1’, $J_{2'-1'}$ = 4 Hz), 4.82 (dd 1 H, H-2’, $J_{2'-3'}$ = 6 Hz), 4.50 (d, 1 H, H-3’, $J_{3'-2'}$ = 3 Hz), 4.30 (m, 1 H, H-7’), 4.10 (dd, 1 H, H-4’, $J_{4'-5'}$ = 5 Hz, $J_{4'-5''}$ = 8 Hz), 3.68 (m, 1 H, H-10’), 3.30 (s, 3 H, COMe), 2.10 (s, 3 H, OAc), 2.05 (s, 3 H, OAc), 1.99 (m, 8 H, 2H-5’, 2H-6’, 2H-8’, 2H-9’). – ^{13}C NMR (62.89 MHz, CD_3OD): δ = 179.0 (CO), 169.8 (OAc), 151.9 (C-6), 151.7 (C-2), 149.3 (C-4), 143.7 (C-8), 133.4 (C-5), 128.5 (Ph), 90.4 (C-1’), 84.6 (C-4’), 84.6 (C-3’), 84.0 (C-2’), 49.3 (C-10’), 48.5 (C-7’), 34.9 (C-5’), 34.1 (C-6’) 33.5 (C-8’), 32.6 (C-9’), 20.7 (CH_3), 20.1 (CH_3). – $C_{44}H_{47}N_7O_{12}$ (865.90): calcd. C 60.91, H 5.10, N 10.92; found C 61.00, H 5.42, N 11.33.

Homosinefungin (5): Derivative **14** (60 mg; 0.07 mmol) was hydrogenated overnight in methanol over 10% Pd/C (72 mg) at 2 atm pressure. After filtration through Celite, the solvent was removed and the residue washed with ether. The residue was then kept in a solution of methanol containing ammonium hydroxide 30% (1/1) (1 mL) for 16 h at room temperature. After evaporation of the solvent under reduced pressure, the residue was purified by chromatography on silica gel to afford **5** (15.7 mg, 57%) as an inseparable mixture of diastereoisomers (foam). – FABMS; *m*/*z*: 396 $[M + 1]^+$. – ^1H NMR (300 MHz, D_2O): δ = 8.22 (s, 1 H, H-2), 8.17 (s, 1 H, H-8), 6.01 (d, 1 H, H-1’, $J_{1'-2'}$ = 4 Hz), 4.76 (dd, 1 H, H-2’, $J_{2'-1'}$ = 4 Hz, $J_{2'-3'}$ = 6 Hz), 4.35 (d, 1 H, H-3’, $J_{3'-2'}$ = 6 Hz, $J_{3'-4'}$ = 4 Hz), 4.31 (dd 1 H, H-4’, $J_{4'-3'}$ = 4 Hz, $J_{4'-5''}$ = 7 Hz), 3.79 (m, 1 H, H-10’), 3.68 (m, 1 H, H-7’), 2.20 (t, 2 H, 2H-5’), 1.97–1.82 (m, 6 H, 2H-6’, 2H-8’, 2H-9’). – $C_{16}H_{25}N_7O_5$ (395.43): calcd. C 47.90, H 5.93, N 24.92; found C 48.51, H 6.31, N 24.92.

Methyl [10-(benzyloxycarbonyl)amino-7-carboxamido-5,6,7,8,9,10-hexadeoxy-2,3-*O*-(isopropylidene)-10-methoxycarbonyl-]-β-D-decaribofuranose (16): A solution of 5-iodoribose **6** (2 g; 6.36 mmol) in THF/H_2O (8/2) (10 mL) under a nitrogen atmosphere was treated (in 5 portions) with a solid mixture composed of CuI (1.46 g; 9.6 mmol) and Zn powder (2 g; 32 mmol) followed by a solution of acrylate **15**[5,9] (4.49 g; 19.1 mmol) in THF (10 mL). The reaction mixture was stirred with a vibromixer until disappearance of the starting material, diluted with ether, the suspension filtered through Celite and the resulting solution washed with brine. Evaporation of the organic phase gave a residue which was chromatographed on a silica gel column to yield **16** a mixture of two isomers (3.0 g; 67%). Separation by HPLC (silica) with heptane/ethyl acetate (2:1) gave **16a** (less polar isomer) and **16b** (more polar isomer). – ***Isomer* 16a:** EIMS; *m*/*z*: 509 $[M + 1]^+$. – ^1H NMR (250 MHz, $CDCl_3$): δ = 7.60 (s, 5 H, Ph), 5.60–5.43 (br, 2 H, NH), 5.10 (s, 2 H, CH_2Ph), 5.07 (s, 1 H, H-1), 4.56 (d, 1 H, H-2, J_{2-3} = 6 Hz), 4.45 (d, 1 H, H-3, J_{3-2} = 6 Hz), 4.44 (d, 1 H, H-10), 4.12 (t, 1 H, H-4, J_{4-3} = 2 Hz, J_{4-5} = 5 Hz, $J_{4-3'}$ = 8 Hz), 3.89 (m, 2 H, 2H-5), 3.82 (m, 1 H, H-7), 3.75 (s, 3 H, CO_2CH_3), 3.65 (m, 1 H, H-10), 3.32 (s, 3 H, OCH_3), 1.97–1.86 (m, 6 H, 2H-6, 2H-8, 2H-9), 1.39 (s, CH_3 isop), 1.13 (s, 3 H, CH_3 isop). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 180.0 ($CONH_2$), 170.0 (*C*O_2CH_3), 165.0 ($COCH_3$), 128.5 (Ph), 112.3 (Cq), 109.9 (C-1), 86.0, 85.3, 83.8 (C-2, C-3, C-4), 55.6 (OCH_3), 53.9 (C-7), 50.7 (C-10), 32.3 (C-5), 29.7 (C-6), 29.3 (C-9), 27.7 (C-8), 26.6 (CH_3 isop), 25.1 (CH_3 isop). – $C_{25}H_{36}N_2O_9$ (508.56): calcd. C 59.05, H 7.08, N 5.50; found C 58.90, H 7.10, N 5.10. – ***Isomer* 16b:** ^1H NMR (250 MHz, $CDCl_3$): δ = 7.62 (s, 5 H, Ph), 5.62–5.43 (br, 2 H, NH), 5.12 (s, 2 H, CH_2Ph), 5.07 (s, 1 H, H-1), 4.59 (d, 1 H, H-2, J_{2-3} = 6 Hz), 4.46 (d, 1 H, H-3, J_{3-2} = 6 Hz), 4.44 (d, 1 H, H-10), 4.15 (t, 1 H, H-4, J_{4-3} = 2 Hz, J_{4-5} = 5 Hz, $J_{4-3'}$ = 8 Hz), 3.89 (m, 2 H, 2H-5), 3.85 (m, 1 H, H-7), 3.77 (s, 3 H, CO_2CH_3), 3.65 (m, 1 H, H-10), 3.32 (s, 3 H, OCH_3), 1.97–1.86 (m, 6 H, 2H-6, 2H-8,2H-9), 1.40 (s, CH_3 isop), 1.15 (s, 3 H, CH_3 isop). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 180.0 ($CONH_2$), 173.0 (*C*O_2CH_3), 165.0 ($COCH_3$), 128.5 (Ph), 114.0 (Cq), 110.0 (C-1), 89.0, 86.0, 85.0 (C-2, C-3, C-4), 56.0 (OCH_3), 55.0 (C-7), 50.7 (C-10), 33.0 (C-5), 30.2 (C-6), 29.8 (C-9), 27.7 (C-8), 27.7 (CH_3 isop), 25.6 (CH_3 isop). – $C_{25}H_{36}N_2O_9$ (508.56): calcd. C 59.05, H 7.08, N 5.50; found C 59.25, H 7.18, N 5.27.

Methyl [7,10-Bis(benzyloxycarbonyl)amino-5,6,7,8,9,10-hexadeoxy-2,3-*O*-(isopropylidene)-10-methoxycarbonyl-]-β-D-decaribofuranose (11). – The amide **16** (100 mg; 0.25 mmol) in a mixture of dimethylformamide (1 mL) and water (1 mL) was treated with [bis(trifluoroacetoxy)iodo]benzene (155 mg; 0.36 mmol). The mixture was stirred at room temperature for 30 min, pyridine (0.04 mL) added and stirred for a further 4 h at room temperature. The solvent was removed under reduced pressure and the resulting crude amine treated at 0°C with benzyl chloroformate (63 mg; 29 mmol) in dioxane/H_2O/triethylamine (2:1:1). The mixture was stirred for 4 h at room temperature, solvents removed under reduced pressure and the residue purified on a silica gel column (heptane/ethyl acetate, 2:1) to afford 48 mg (40%) of a mixture of isomers **11a** and **11b**. Separation by HPLC gave the pure isomers. – ***Isomer* 16a:** ^1H NMR (250 MHz, $CDCl_3$): δ = 7.35 (s, 10 H, Ph), 5.32 (br, 1 H, NH), 5.10 (s, 4 H, CH_2Ph), 4.93 (br, 1 H, NH), 4.78 (s, 1 H, H-1), 4.60 (d, 1 H, H-2, J_{3-2} = 6 Hz), 4.51 (d, 1 H, H-3, J_{3-2} = 6 Hz), 4.12

(m, 1 H, H-7), 3.83 (m, 1 H, H-4), 3.70 (s, 3 H, CO_2CH_3), 3.41 (m, 1 H, H-8), 3.29 (s, 3 H, OCH_3), 3.23 (m, 1 H, H-8'), 1.70–1.57 (m, 4 H, 2 H-5, 2 H-6), 1.47 (s, CH_3 isop), 1.31 (s, 3 H, CH_3 isop). ***Isomer* 16a:** ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.35 (s, 10 H, Ph), 5.30 (br, 1 H, NH), 5.10 (s, 4 H, CH_2Ph), 4.93 (br, 1 H, NH), 4.64 (s, 1 H, H-1), 4.60 (d, 1 H, H-2, J_{3-2} = 6 Hz), 4.51 (d, 1 H, H-3, J_{3-2} = 6 Hz), 4.12 (m, 1 H, H-7), 3.83 (m, 1 H, H-4), 3.70 (s, 3 H, CO_2CH_3), 3.41 (m, 1 H, H-8), 3.28 (s, 3 H, OCH_3), 3.21 (m, 1 H, H-8'), 1.73–1.57 (m, 4 H, 2H-5, 2H-6), 1.47 (s, CH_3 isop), 1.31 (s, 3 H, CH_3 isop).

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