Expedient Synthesis of Natural (*S*)-Sinefungin and of its C-6′ Epimer†

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Sinefungin **1a** and 6-*epi*-sinefungin **1b** have been prepared from adenosine and L-aspartic acid. The key step in the synthesis was the coupling of the radical derived from **14** with the unsaturated amide **13**. The latter was obtained by a radical reaction from L-aspartic acid and olefin **11**. Thus the carbon skeleton is constructed in two radical coupling reactions.

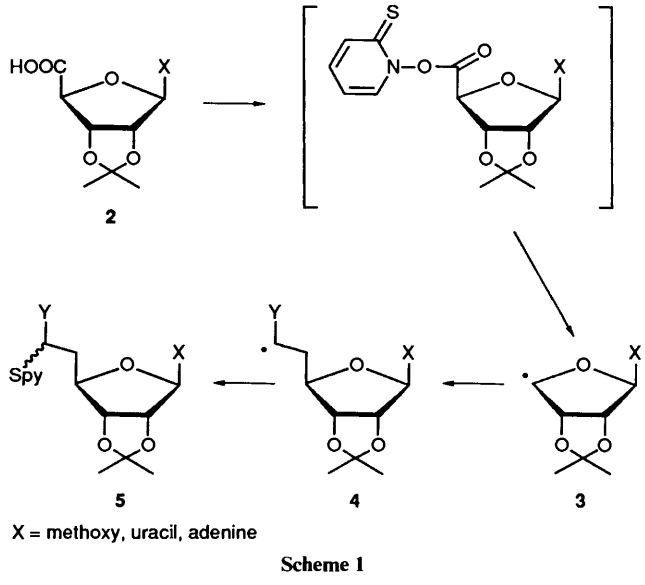
Natural sinefungin **1a** is a nucleosidic antibiotic which was isolated in 1973 from a strain of *Streptomyces grisoleus*.[1] Later, it was obtained from *Streptomyces incarnatus*.[2] Its structure **1a** is composed of an adenosine unit which has been attached at the C-5′ position an ornithine residue. The asymmetric centre at C-6′ is *S* in configuration, as has been confirmed in a recent synthesis by Rapoport[3] and in agreement with our own synthesis.

Natural sinefungin shows a wide variety of biological activities. It is a powerful antifungal agent and is particularly efficient against *Candida albicans*. It has also been shown to be active against various viruses.[4] It also possesses a powerful anti-parasite activity, especially against several species of *Leishmania*.[5] Finally, its strong activity against the AIDS virus is of great interest.[6]

Two syntheses of sinefungin have already been published.[3,7] We now wish to report a new and simple synthesis which affords the whole carbon skeleton in a few steps. The synthesis lends itself to modification of both the ornithine and the adenosine parts of the molecule. Since sinefungin has serious secondary effects (nephrotoxicity in the dog, toxicity for bone marrow cells), the preparation of analogues has become a major research activity.

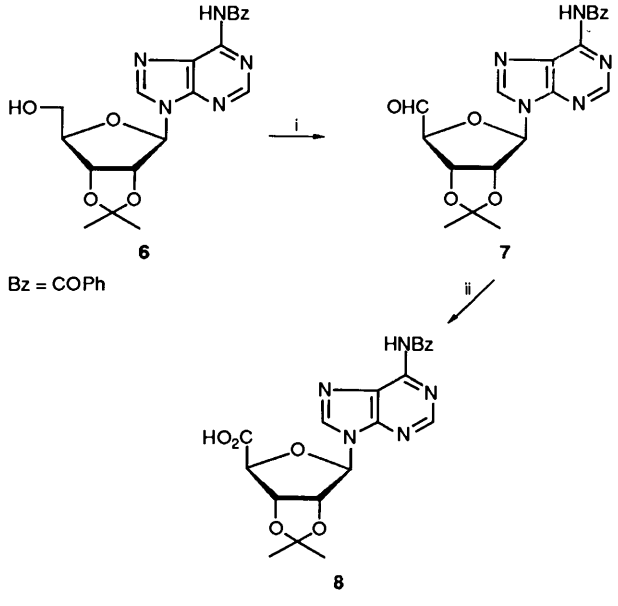
Results and Discussion

Previous syntheses[3,7] of sinefungin have reposed on known types of ionic chemistry. Our new synthesis constructs the carbon skeleton by two simple radical reactions. Such reactions proceed at room temperature under neutral conditions.[8] We have recently shown[9] that the 2,3-dimethyl ketals of D-ribose derivatives with, or without, the basic group of the nucleoside added, confer a high degree of stereoselectivity to radical chemistry at C-4′. This is usually based on the photolysis of the *N*-hydroxy-2-thiopyridone derivative of the appropriate 5′-carboxylic acid. Thus (Scheme 1) the acid **2** affords the radical **3**, generated *via* the intermediate ester, which adds to the appropriate electron deficient olefin to give **4**. This radical then reacts[10] with the thiocarbonyl derivative of the precursor to give the 2-thiopyridyl derivative **5** as a mixture of stereoisomers. In contrast, the radical at the 4′ position reacts very stereoselectively[9] and only one configuration (less hindered-side attack) is seen. An intermediate like **5** is readily reduced by tin hydride reagents with removal of the 2-thiopyridyl residue, or oxidised, and the resulting sulphoxide group eliminated by pyrolysis, to give an olefin.



Scheme 1

For the synthesis of natural sinefungin **1a** admixed with its *R* epimer **1b** at C-6′, we chose two intermediates, the acid **8** (Scheme 2) and the olefin **13** (Scheme 3).



Scheme 2 *Reagents and conditions*: i, DMSO–DCC, Cl_2CHCO_2H, room temperature; ii, MCPBA, CH_2Cl_2, room temperature

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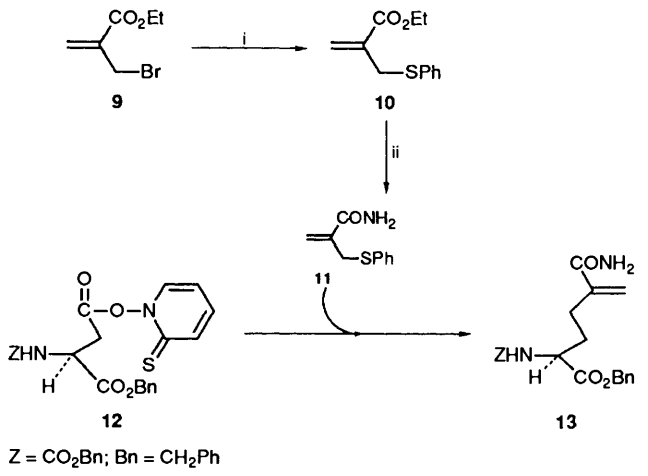


Scheme 3 *Reagents:* i, $(PhS)_2/NaBH_4$; ii, $MeAlClNH_2$, benzene

The crystalline acid **8** was prepared[11] from **6** through the aldehyde **7** and further oxidation with *m*-chloroperbenzoic acid in 70% overall yield.

The unknown olefin **13** was prepared in the following way. The known[13] derivative of L-aspartic acid **12** was added to the olefin **11** to furnish the expected[13] derivative **13** (62% isolated). The olefin **11** in turn had been prepared (Scheme 3) from the α-bromomethylacrylate[14] **9** by displacement with thiophenol (70%). Then the ester function was converted to amide **11** (82%) using the amide of methylchloroaluminium, prepared *in situ* from trimethylaluminium and ammonium chloride in benzene at room temperature.[15]

From **8**, the *N*-hydroxy-2-thiopyridone derivative **14** (Scheme 4) was prepared in tetrahydrofuran (THF) by the usual mixed anhydride method.[13,16] The irradiation of **14** in the presence of the olefin **13** gave the addition product **15** (45%) as a mixture of two stereoisomers at C-6′ as well as the usual rearrangement product **16** (20%). The adduct **15** was reduced with tributyltin hydride in benzene under reflux with an initiator. The two reduction products **17a** and **17b**, epimeric at C-6′, were separated by medium pressure chromatography over silica gel. The less polar was **17a** (38%) and the more polar turned out to be **17b** (36%). These two amides were treated separately with [bis(trifluoroacetoxy)iodo]benzene in DMF–water in the presence of pyridine at room temperature.[17] The amines thus formed were at once converted to their *tert*-butoxycarbonyl derivatives, which were both isolated in crystalline form: **18a** (60%), **18b** (68%). The compound **18a** was deprotected by successive hydrogenolysis, treatment with ammonia in methanol and acidic hydrolysis to furnish sinefungin **1a** with the same ^1H NMR spectrum (400 MHz) and optical rotation as described in the literature for natural sinefungin. In the same way, the derivative **18b** afforded 6′-*epi*-sinefungin **1b** with a distinct ^1H NMR spectrum and optical rotation.

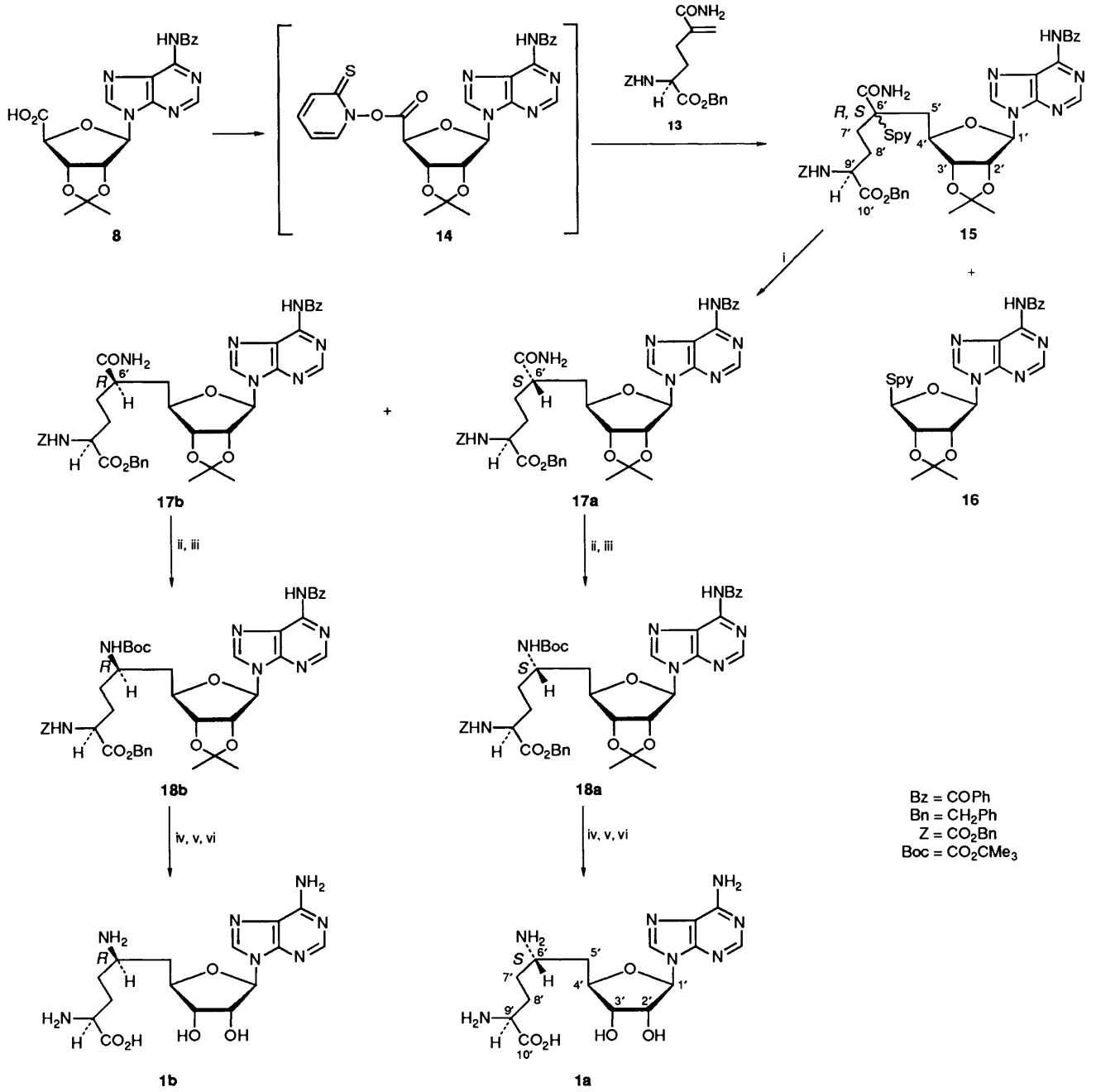
Experimental

General.—Column chromatography was carried out on silica gel 60 (0.040–0.063 mm). Thin layer analytical plates were $60F_{254}$ (Merck). Unless stated otherwise ^1H and ^{13}C NMR spectra were recorded on Brücker WP200 SY (200 MHz) or on HS80 (80 MHz). Chemical shifts (δ) are expressed in ppm from Me_4Si as internal standard. Coupling constants J are in Hz. Most spectra were taken in $CDCl_3$; in other cases the solvent is specified. M.p.s were taken on a Reicher apparatus and are not corrected. Infra-red spectra were recorded on a Perkin-Elmer 297. Routine mass spectra were recorded on an AEI MS50, AEI MS9 and Kratos MS80 (for FAB spectra). Mass spectra at high resolution were determined at the Service for Mass Spectra of the C.N.R.S. at Vernaison. Elementary analyses were carried out at the I.C.S.N.

Synthesis of the Uronic Acid **8**.—To a solution of the alcohol **6** (9.8 g, 24 mmol) and dicyclohexylcarbodiimide (14.88 g, 72 mmol) in dimethylsulphoxide (54 cm^3) was added drop by drop at 0 °C dichloroacetic acid (0.96 cm^3, 12 mmol). The reaction mixture was stirred at room temperature for 1.5 h. The dicyclohexylurea formed was filtered off, and the solution extracted with hexane (4 × 100 cm^3) to remove the excess of dicyclohexylcarbodiimide. The solution of dimethylsulphoxide was diluted with $CHCl_3$ (400 cm^3) and then extracted with water (2 × 200 cm^3). The residual organic phase was dried over sodium sulphate, filtered and evaporated under reduced pressure. The residue (aldehyde **7**) was taken up in CH_2Cl_2 (240 cm^3, dry). To this was added *m*-chloroperbenzoic acid (8.25 g, 48 mmol). The mixture was stirred at room temperature for 30 min. The CH_2Cl_2 was removed under reduced pressure and the residue repeatedly triturated with ether. The residue was the acid **8** (7.14 g). Recrystallised from ethanol, this (70%) had m.p. 235–238 °C; $[\alpha]_D^{20}$ −61.2° (*c* 0.5; DMF); ν_{max}(Nujol)/cm^{-1} 3327, 1720, 1690 and 1595; δ_H(200 MHz in [$^2H_5$]pyridine) 8.95 (1 H, s, 2-H), 8.76 (1 H, s, 8-H), 8.16, 7.36 (5 H, m, Ph), 6.76 (1 H, s, 1′-H), 5.96 (1 H, d, 2′-H, $J_{2',3'}$ 6), 5.7 (1 H, d, 3′-H, $J_{3',2'}$ 6), 5.2 (1 H, s, 4′-H), 1.51 and 1.3 (6 H, 2 × s, CMe_2); *m/z* (FAB) 426 (MH^+) (Found: C, 55.1; H, 4.6; N, 15.9. $C_{20}H_{19}N_5O_6 \cdot 0.5H_2O$ requires C, 55.3; H, 4.6; N, 16.1%).

Ethyl 2-Phenylthiomethylacrylate **10**.—To a solution of diphenyl disulphide (11.9 g, 55 mmol) in absolute ethanol (200 cm^3) was added at 0 °C sodium borohydride (4.18 g, 110 mmol). The reaction mixture was stirred under argon for 30 min. This solution was then added under argon to ethyl 2-bromomethylacrylate **9** (19.2 g, 100 mmol) in ethanol (100 cm^3) at −30 °C. After being stirred for 18 h at room temperature under argon, the ethanol was evaporated under reduced pressure. The residue in ether (300 cm^3) was washed successively with water (100 cm^3) and saturated brine (2 × 50 cm^3), dried ($MgSO_4$) and filtered. Evaporation under reduced pressure and chromatography on silica (EtOAc–hexane, 1:9) gave *ethyl 2-phenylthiomethylacrylate* **10** as a colourless oil (76%), δ_H(80 MHz in $CDCl_3$) 7.25 (5 H, m, Ph), 6.11 (1 H, s, HC=C), 5.5 (1 H, s, HC=C), 4.2 (2 H, q, CH_2, *J* 7), 3.73 (2 H, s, CH_2S) and 1.28 (3 H, t, Me, *J* 7); *m/z* (EI) 222 ($M^{\cdot+}$) (Found: C, 64.7; H, 6.4; S, 14.6. $C_{12}H_{14}O_2S$ requires C, 64.9; H, 6.3; S, 14.4%).

2-Phenylthiomethylacrylamide **11**.—A suspension of ammonium chloride (10.7 g, 200 mmol) in anhydrous benzene (200 cm^3) was added dropwise under argon at 0 °C to trimethylaluminium (2 mol dm^{-3}) in toluene (100 cm^3, 200 mmol). The reaction mixture was stirred at room temperature for 2 h and then added under argon to the ester **10** (14.65 g, 66 mmol) in anhydrous benzene (300 cm^3). The reaction mixture was stirred at 50 °C under argon for 16 h, cooled to 0 °C and hydrochloric acid (5%; 50 cm^3) was added. The organic phase was separated. The aqueous layer was extracted with ethyl acetate (3 × 150 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure. The residue was chromatographed over silica gel (ethyl acetate–hexane, 1:1) to give the crystalline *amide* **11** (10.4 g, 82%), m.p. (from CH_2Cl_2–hexane) 84–86 °C. This had ν_{max}(Nujol)/cm^{-1} 3399, 3178, 1669, 1655, 1641, 1600, 748 and 692; *m/z* (EI) 193 ($M^{\cdot+}$); δ_H 7.25 (5 H, m, Ph), 6.08 (2 H, br s, $CONH_2$), 5.68 (1 H, s, HC=C), 5.31 (1 H, s, HC=C) and 3.76 (2 H, s, CH_2) (Found: C, 62.0; H, 5.7; N, 7.3; S, 16.6. $C_{10}H_{11}NOS$ requires C, 62.15; H, 5.7; N, 7.25; S, 16.6%).



Scheme 4 *Reagents and conditions:* i, Bu_3SnH, AIBN; ii, $(CF_3CO_2)_2IC_6H_5$, py, DMF–H_2O (1:1), room temperature; iii, Boc_2O, Et_3N, DMF, room temperature; iv, 10% Pd/C, H_2, EtOH; v, NH_3/ MeOH; vi, CF_3CO_2H/H_2O

Synthesis of the Ester Amide **13**.—To 1-benzyl *N*-benzyloxycarbonylaspartate (4.28 g, 12 mmol) in anhydrous THF (10 cm^3) was added *N*-methylmorpholine (1.32 cm^3, 12 mmol) and isobutyl chloroformate (1.68 cm^3, 12 mmol) under argon at 0 °C. The mixture was stirred for 15 min and the sodium salt of *N*-hydroxy-2-thiopyridone (2.14 g, 14.4 mmol) was added. The reaction mixture was stirred at 0 °C, sheltered from light (aluminium foil), for 1 h. TLC revealed the yellow spot characteristic of the acylated *N*-hydroxy-2-thiopyridone derivatives. Then olefin **11** (11.6 g, 60 mmol) was added and the solution irradiated with a tungsten lamp (250 W) for 20 min (until disappearance of intermediate). After addition of CH_2Cl_2, the solution was washed successively with saturated sodium hydrogen carbonate, water and then brine. The organic phase was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. Chromatography of the product over silica gel (ethyl acetate–hexane, 6:4) gave the *olefin* **13** (2.95 g, 62%) as crystals, m.p. (from CH_2Cl_2–hexane) 93–95 °C; $[\alpha]_D^{20}$ +1.6° (*c* 0.5; $CHCl_3$). This compound had ν_{max}(Nujol)/cm^{-1} 1758, 1743, 1690, 1655, 1604 and 1535; *m/z* (CI) 397 (MH^+); δ_H(80 MHz; $CDCl_3$) 7.28 (10 H, s, 2 × Ph), 5.82 (2 H, br s, $CONH_2$), 5.6 (1 H, s, 6-H), 5.26 (1 H, s, 6′-H), 5.12 (2 H, s, CH_2 of benzyl), 5.06 (2 H, s, CH_2 of benzyl), 4.35 (1 H, m, 2-H) and 2.27–1.95 (4 H, m, 3-H_2 and 4-H_2) (Found: C, 66.45; H, 5.85; N, 7.25. $C_{22}H_{24}N_2O_5$ requires C, 66.65; H, 6.05; N, 7.05%).

Synthesis of Coupled Derivative **15**.—To the acid **8** (1 mmol) in anhydrous THF (12 cm^3) was added *N*-methylmorpholine (0.11 cm^3, 1 mmol) and isobutyl chloroformate (0.14 cm^3, 1 mmol). The solution was stirred for 15 min at 0 °C under argon and the sodium salt of *N*-hydroxy-2-thiopyridone (0.178 g, 1.2 mmol) was added. The reaction mixture was stirred under argon at 0 °C for 30 min with exclusion of light (aluminium foil) to form **14**. Then the olefin **13** (2.376 g, 6 mmol) was added and the

yellow solution was irradiated with a tungsten lamp (250 W) at 0 °C for 30 min. The reaction mixture was diluted with $CHCl_3$ (100 cm^3) and washed with saturated aqueous sodium hydrogen carbonate (50 cm^3) and with water (50 cm^3). The organic phase was dried ($MgSO_4$) and, after filtration, was evaporated under reduced pressure. The residue thus obtained was chromatographed on silica gel using gradient elution. Elution with ethyl acetate–methanol (9.5:0.5) gave the *coupled derivative* **15** (45%) as well as the *rearrangement product* **16** (20%). Derivative **15** was a mixture of two isomers that had *m/z* (FAB) 887 (MH^+); (Found: C, 61.05; H, 5.45; N, 12.25; S, 3.6. $C_{46}H_{46}N_8O_9S{\cdot}H_2O$ requires C, 61.05; H, 5.3; N, 12.4; S, 3.55%).

The product **16** had m.p. 100–105 °C, $[\alpha]_D^{20}$ +167° (*c* 0.5 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1710, 1610, 1580 and 1080; *m/z* (CI) 491 (MH^+), 240 (base + H^+) and 112 (Spy + H^+).

Amides **17a** *and* **17b**.—The mixture of isomers **15** (1.329 g, 1.5 mmol) in anhydrous benzene (10 cm^3) was treated under reflux with tributyltin hydride (1.21 cm^3, 4.5 mmol) and α,α′-azoisobutyronitrile (0.024 g, 0.15 mmol) for 3 h under argon. TLC (ethyl acetate–*tert*-butyl alcohol, 9:1) showed the presence of 2-compounds isomeric at position 6′. The solvent was removed under reduced pressure. The residue was chromatographed on a column of silica gel (ethyl acetate–*tert*-butyl alcohol, 9:1). In this way **17a** (38%) and **17b** (36%) could be separated.

Isomer **17a** had m.p. (from CH_2Cl_2–pentane) 95–96 °C, $[\alpha]_D^{20}$ +14° (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 1610, 1580 and 1070; *m/z* (FAB) 778 (MH^+), 540 (MH^+ − base) and 240 (base + H^+); δ_H(400 MHz; $CDCl_3$) 8.76 (1 H, s, 2-H), 8.11 (1 H, s, 8-H), 8.03, 7.58, 7.30 (15 H, m, 3 × Ph), 6.06 (1 H, d, 1′-H, $J_{1',2'}$ 1.5), 5.83 (2 H, m, $CONH_2$), 5.60 (1 H, m, N*H*CO_2CH_2Ph), 5.55 (1 H, br s, 2′-H), 5.08 (2 H, s, OCH_2Ph), 5.05 (2 H, s, OCH_2Ph), 4.83 (1 H, m, 3′-H), 4.26 (2 H, m, 4′-H, 9′-H), 2.16–1.69 (7 H, m, 5′-H_2, 6′-H, 7′-H_2, 8′-H_2), 1.58 and 1.37 (6 H, 2 × s, CMe_2) (Found: C, 62.7; H, 5.6; N, 12.15. $C_{41}H_{43}N_7O_9{\cdot}0.5H_2O$ requires C, 62.6; H, 5.6; N, 12.45%).

Isomer **17b** had m.p. (from CH_2Cl_2–pentane) 92–95 °C, $[\alpha]_D^{20}$ +6.5° (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 1710, 1610, 1580 and 1070; *m/z* (FAB) 778 (MH^+), 540 (MH^+ − base)$^+$ and 240 (base + H)$^+$; δ_H(400 MHz; $CDCl_3$) 8.76 (1 H, s, 2-H), 8.10 (1 H, s, 8-H), 8.01, 7.56, 7.50 (5 H, m, COPh), 7.31 (10 H, m, 2 × Ph), 6.03 (1 H, s, 1′-H), 5.98 (1 H, s, $CONH_2$), 5.63 (1 H, d, N*H*CO_2CH_2Ph), 5.58 (1 H, s, $CONH_2$), 5.41 (1 H, d, 2′-H, $J_{2',3'}$ 6), 5.15 (2 H, s, OCH_2Ph), 5.06 (2 H, s, OCH_2Ph), 4.81 (1 H, dd, 3′-H, $J_{3',2'}$ 6, $J_{3',4'}$ 4), 4.36 (1 H, m, 9′-H), 4.18 (1 H, m, 4′-H, $J_{4',3'}$ 4), 2.3 (1 H, br s, 6′-H), 2.08, 1.83, 1.60, 1.53 (6 H, m, 5′-H_2, 7′-H_2, 8′-H_2), 1.53 and 1.36 (6 H, 2 × s, CMe_2) (Found: C, 61.8; H, 5.68; N, 12.32. $C_{41}H_{43}N_7O_9H_2O$ requires C, 61.88; H, 5.66; N, 12.32%).

Sinefungin Derivatives **18a** *and* **18b**.—To the amide **17a** (0.195 g, 0.25 mmol) in a mixture of dimethylformamide (2.0 cm^3) and water (2.0 cm^3) was added iodobenzene bis(trifluoroacetate) (0.162 g, 0.375 mmol). The mixture was stirred at room temperature for 30 min, pyridine (41 mm^3, 2 equiv.) was added and the stirring was continued for 2 h at room temperature. The solvent was removed under reduced pressure and then the residue was treated with toluene which was again removed under reduced pressure to eliminate the last traces of pyridine. The amine obtained was treated at 0 °C with di-*tert*-butyl dicarbonate (0.066 g, 0.3 mmol) in dimethylformamide (2 cm^3) with addition of triethylamine (35 mm^3). After being stirred for 2 h at room temperature, the solution was again evaporated under reduced pressure. The residue was purified on silica gel (ethyl acetate–hexane, 8:2). This afforded the crystalline *sinefungin derivative* **18a** (66%), m.p. (from CH_2Cl_2–pentane) 94–97 °C, $[\alpha]_D^{20}$ +11° (*c* 0.5 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1710, 1610, 1580 and 1070; *m/z* (FAB) 850 (MH^+), 511 (MH^+ − base − Boc) and 240 (base + H^+); δ_H(400 MHz; $CDCl_3$) 8.88 (1 H, s, 2-H), 8.08 (1 H, s, 8-H), 8.03, 7.6, 7.5 (5 H, m, COPh), 7.3 (10 H, s, 2 × Ph), 6.06 (1 H, s, 1′-H), 5.51 (1 H, d, NH, J_{NH} 7), 5.41 (1 H, m, 2′-H), 5.08 (4 H, s, 2 × CH_2Ph), 4.88 (1 H, m, 3′-H), 4.36 (1 H, d, N*H*Boc), 4.28 (2 H, m, 4′-H, 9′-H), 3.6 (1 H, m, 6′-H), 1.73–1.60 (6 H, m, 5′-H_2, 7′-H_2, 8′-H_2), 1.60 (3 H, s, Me of CMe_2) and 1.38 (12 H, s, Me of CMe_2 + Boc); (Found: C, 63.05; H, 6.3; N, 11.25. $C_{45}H_{51}N_7O_{10}{\cdot}0.5H_2O$ requires C, 62.95; H, 6.05; N, 11.4%).

In exactly the same way, the amide **17b** (0.195 g) gave the 6′-*isosinefungin derivative* **18b** (68%), m.p. (from CH_2Cl_2–pentane) 90–93 °C, $[\alpha]_D^{20}$ +2° (*c* 0.5 in $CHCl_3$); ν_{max}/cm^{-1} 1710, 1610, 1580 and 1070; *m/z* (FAB) 850 (MH^+), 511 (MH^+ − base − Boc) and 240 (base + H^+); δ_H(400 MHz; $CDCl_3$) 8.81 (1 H, s, 2-H), 8.15 (1 H, s, 8-H), 8.05, 7.6, 7.53 (5 H, m, COPh), 7.35 (10 H, s, 2 × Ph), 6.05 (1 H, s, 1′-H), 5.51 (1 H, d, NH), 5.45 (2 H, m, 2′-H, N*H*Z), 5.13 (2 H, d, OCH_2Ph), 5.1 (2 H, s, OCH_2Ph), 4.85 (1 H, dd, 3′-H, $J_{3',2'}$ 4.5, $J_{3',4'}$ 2.5), 4.40 (2 H, m, 4′-H, N*H*Boc), 4.25 (1 H, m, 9′-H), 3.61 (1 H, m, 6′-H), 1.90–1.76 (6 H, m, 5′-H_2, 7′-H_2, 8′-H_2), 1.6 (3 H, s, Me of CMe_2) and 1.38 (12 H, s, Me of CMe_2 + Boc); (Found: C, 62.55; H, 6.1; N, 11.5. $C_{45}H_{51}N_7O_{10}{\cdot}H_2O$ requires C, 62.3; H, 6.1; N, 11.3%).

Sinefungin **1a** *and* 6′-epi-*Sinefungin*.—The derivative **18a** (68 mg, 0.08 mmol) was hydrogenolysed in ethanol using 10% palladium on charcoal (70 mg) at 2 atm pressure overnight. After filtration through Celite, the solvent was removed and the residue was washed with ether. The benzoyl group was removed with methanol saturated with ammonia gas at room temperature for 16 h and again, the solvent was removed under reduced pressure. Finally, the Boc protection was removed with 80% trifluoroacetic acid at room temperature for 1 h. After evaporation under reduced pressure, the residue was purified by HPLC (RP8) eluting with 0.03 mol dm^{-3} ammonium acetate in water–acetonitrile. The retention time for sinefungin **1a** was 5.2 min. After removal of solvents, sinefungin (80%) was obtained $[\alpha]_D^{20}$ +11° (*c* 0.18 in H_2O) [lit.,[1,2,3,7] +12° (natural), + 10.6° (synthetic)]; *m/z* (FAB) 382 (MH^+); δ_H(400 MHz; D_2O) 8.24 (1 H, s, 2-H), 8.17 (1 H, s, 8-H), 6.01 (1 H, d, 1′-H, $J_{1',2'}$ 4), 4.76 (1 H, dd, 2′-H, $J_{2',1'}$ 4, $J_{2',3'}$ 6), 4.34 (1 H, t, 3′-H, $J_{3',2'}$ 6, $J_{3',4'}$ 6), 4.31 (1 H, t, 4′-H, $J_{4',3'}$ 6, $J_{4',5'}$ 6), 3.79 (1 H, m, 9′-H), 3.56 (1 H, m, 6′-H), 2.23 (2 H, t, 5′-H_2, $J_{5',4'}$ 6), 1.96 and 1.82 (4 H, m, 7′-H_2, 8′-H_2).

In exactly the same way, the epimeric derivative **18b** (76.4 mg) gave 6′-epi-*sinefungin* (75%); $[\alpha]_D^{20}$ −6° (*c* 0.65 in H_2O); δ_H(400 MHz; D_2O) 8.11 (1 H, s, 2-H), 8.05 (1 H, s, 8-H), 5.86 (1 H, d, 1′-H, $J_{1',2'}$ 3.5), 4.53 (1 H, m, 2′-H), 4.08 (2 H, m, 3′-H, 4′-H), 3.58 (1 H, s, 9′-H), 3.36 (1 H, br s, 6′-H), 2.08–1.71 (6 H, m, 5′-H_2, 7′-H_2, 8′-H_2); (Found: M^+, 382.1838. $C_{15}H_{24}N_7O_5$ requires *M*, 382.1827).

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