

Synthesis of Sinefungin and Its C-6' Epimer

M. Geze, P. Blanchard, J. L. Fourrey,* and M. Robert-Géro

Contribution from the Institute de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France. Received April 18, 1983

Abstract: A synthesis of the nucleoside antibiotic sinefungin (**1**) and of its C-6' epimer is described. It was accomplished by coupling a functionized adenosine derivative, **2**, with an aldehyde synthon, **3**, derived from an L-amino acid to give the sinefungin precursor **4**. The construction of the skeleton of the glycosyl moiety of sinefungin (**1**) could be achieved starting from methyl riboside. The adopted sequence was probed further by synthesizing the sinefungin analogue **9b** (two C-6' epimers). This synthesis established that the Hoffmann rearrangement of both amides **8b** took place with complete retention of configuration at C-6'. Finally, sinefungin derivatives **9c** were obtained, and one of these was found to be identical with the same derivative prepared from authentic sinefungin (**1**). It was easily converted to sinefungin (**1**).

Sinefungin (**1**) is an antifungal antibiotic isolated from cultures of *Streptomyces griseolus* at Lilly Research Laboratories in 1971.¹ Considering its structural similarity to *S*-adenosylhomocysteine (SAH) and *S*-adenosylmethionine (SAM), the inhibitory effect of sinefungin was studied on several *S*-adenosylmethionine-mediated transmethylation reactions in cell culture and in vivo.² The compound was shown to inhibit the growth of various fungi,³ virus replication,⁴ and cell transformation⁵ and has interesting antiparasitic effects in vivo and in vitro.^{6,7} Despite these significant biological activities sinefungin cannot be considered for clinical use because it is nephrotoxic and causes bone marrow depression, in laboratory animals.⁸

Our goal was to synthesize closely related molecules which—hopefully—would be as active as the natural compound but less toxic. The first step toward this aim was the development of a general method for the synthesis of sinefungin and analogues.

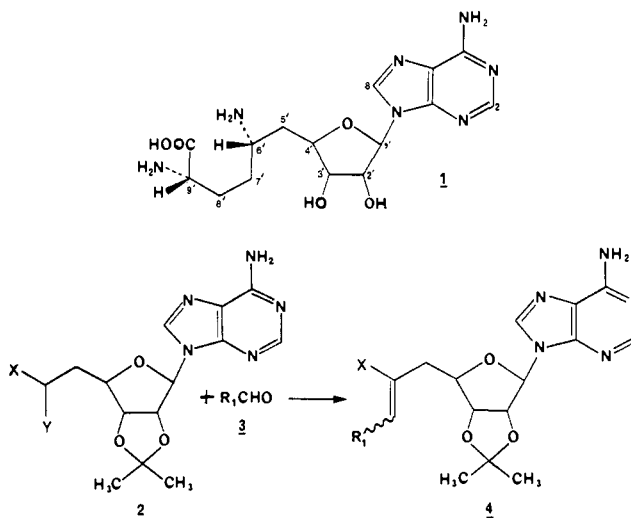
After completion of this work Moffatt et al.⁹ published the first synthesis of sinefungin by a different method: they could not, however, separate it from its C-6' epimer.¹⁰

Our approach is based on the coupling of a suitably functionized adenosine derivative **2** with an aldehyde synthon **3** derived from an L-amino acid to give the sinefungin precursor **4** as outlined in Scheme I.

It is expected that the appropriate choice of the X, Y, and R functionalities of **2** and **3** will provide a practical access to a variety of sinefungin analogues.

We first attempted to construct the glycosyl moiety of sinefungin **1** starting from methyl riboside. Thus, the (*dl*)-aldehyde **3a** (Scheme II) was readily prepared from glycine through allylation of its *N*-benzylidene methyl ester¹¹ followed by acidic treatment, *N*-(*tert*-butyloxy)carbonylation, and ozonization. Condensation of (*dl*)-**3a** with the known cyanophosphonate **5a**¹² (Mg(OMe)₂,

Scheme I



MeOH) led to the unsaturated nitrile **6a** (71%),¹³ the ¹H NMR spectrum of which showed the H-7 signal as a triplet centered at 6.36 ppm. Reduction¹⁴ of **6a** gave a mixture of nitriles **7a** (90%), which were hydrolyzed to the corresponding amides **8a** (41%). In the presence of [bis(trifluoroacetoxy)iodo]benzene¹⁵ **8a** underwent a Hoffmann rearrangement providing the expected amines which were isolated after acetylation as a mixture of *N*-acetates **9a** in 68% overall yield for the two final steps.

The scheme was further probed by starting from the adenosine-derived phosphonate **5b**¹² which upon condensation with isobutyraldehyde **3b** (NaOMe, MeOH) gave the unsaturated nitrile **6b** ([α]_D²⁵ +40° (c 1.12, CHCl₃)) in 73% yield.¹⁶ The ¹H NMR spectrum of **6b** showed the H-7' proton signal at 6.36 ppm. **6b** was reduced to a mixture of nitriles **7b** (82%), which gave two amides **8b** after reaction with alkaline hydrogen peroxide in 71% yield. The C-6' epimers **8b** could be separated by medium-pressure column chromatography¹⁷ and fully characterized. Each amide **8b** was oxidatively rearranged as above to a single amine. In both cases the amines were isolated as their (*tert*-butyloxy)carbonyl derivatives **9b** (80%), which differ only by the configuration at C-6'. This result is of particular importance since

(1) Hamill, R. L.; Hoehn, M. M. *Abstr. 11th Interscience Conf. Antimicrob. Agents Chemother.* 1971, p 21.

(2) Robert-Géro, M.; Pierré, A.; Vedel, M.; Enouf, J.; Lawrence, F.; Lederer, E. "Enzyme Inhibitors"; Verlag Chemie: Weinheim/Bergstr., Germany, 1980; p 61.

(3) Gordee, R. S.; Butter, T. F. *J. Antibiot.* 1973, 26, 466.

(4) Pugh, C. S. G.; Borchardt, R. T.; Stone, H. O. *J. Biol. Chem.* 1978, 253, 4075.

(5) Vedel, M.; Lawrence, F.; Robert-Géro, M.; Lederer, E. *Biochem. Biophys. Res. Commun.* 1978, 85, 371.

(6) Duke, D. K.; Mpimbaza, G.; Allison, A. C.; Lederer, E.; Rovis, L. unpublished results.

(7) Bachrach, U.; Schuur, L. E.; El-On, Y.; Greenblatt, C. L.; Pearlman, E.; Robert-Géro, M.; Lederer, E. *FEBS Lett.* 1980, 121, 287.

(8) Gordee, R. S., personal communication.

(9) Mock, G. A.; Moffatt, J. G. *Nucleic Acids Res.* 1982, 10, 6223.

(10) For related approaches based on reaction of nitroalkanes with nucleoside-5'-aldehydes, see: Mizuno, Y.; Tsuchida, K.; Tampo, H. *Nucleic Acids Res., Symp. Ser.* 1982, No. 11, 45. Moorman, A. R.; Martin, T.; Borchardt, R. T. *Carbohydr. Res.* 1983, 113, 233.

(11) Stork, G.; Leory, A. Y. W.; Touzin, A. M. *J. Org. Chem.* 1976, 41, 3491. Donnel, M. J.; Boniece, J. M.; Earp, S. E. *Tetrahedron Lett.* 1978, 30, 2641.

(12) Hampton, A.; Sasaki, T.; Paul, B. *J. Am. Chem. Soc.* 1973, 95, 4404.

(13) Satisfactory spectroscopic (¹H NMR, ¹³C NMR, and mass spectra) and exact mass data were obtained for all new compounds.

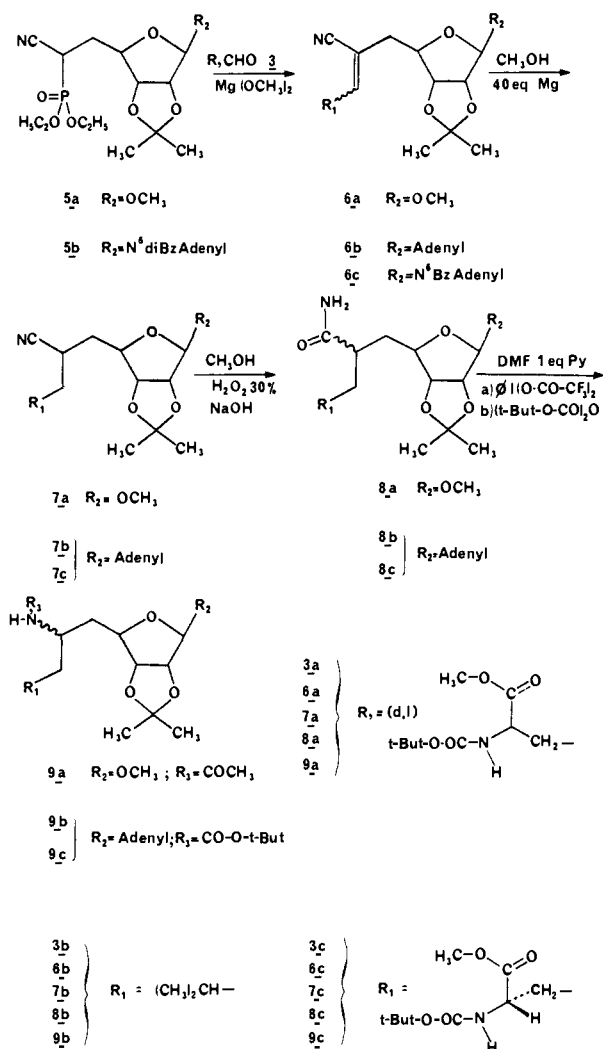
(14) Proffitt, J. A.; Watt, D. S.; Corey, E. J. *J. Org. Chem.* 1975, 40, 127.

(15) Radhakrishna, A. S.; Parhan, E.; Riggs, R. M.; London, G. M. *J. Org. Chem.* 1979, 44, 1746.

(16) Under these basic conditions the adenine moiety is totally debenzoylated at N⁶.

(17) Silica 60 "230-400 mesh" AcOEt/EtOH gradient 4-20%: less polar amide [α]_D²⁵ +24° (c 0.88, CHCl₃), more polar amide [α]_D²⁵ -6° (c 0.92, CHCl₃).

Scheme II



it establishes that under the adopted reaction conditions the Hoffmann rearrangement of both amides **8b** took place with complete retention of the configuration at C-6'.

Finally, the (L)-aldehyde **3c** was conveniently prepared in three steps from the commercially available L-allylglycine¹⁸ in 76% overall yield. The Horner–Emmons condensation of this compound **3c** with phosphonate **5b**¹² gave a 50:50 mixture of unsaturated nitriles **6c** (72%), the ¹H NMR spectrum of which showed two signals, each integrating for 0.5 proton at 6.29 and 5.94 ppm, respectively. They were attributed to the H-7' protons of the two geometric isomers **6c**; these were reduced to a mixture of nitriles **7c** in 84% yield. Unfortunately, hydration of the pair of nitriles to give the corresponding amides **8c** proceeded in poor yield (22%). However, it was rewarding to find that the two C-6' epimers (*R*)- and (*S*)-**8c** could be easily separated by high-performance liquid chromatography. Hoffmann oxidative rearrangement of each amide **8c** provided a single amine, which was isolated as its *N*-(*tert*-butyloxy)carbonyl derivative (*R*)- and (*S*)-**9c**.¹⁹ It was evident from their spectral data that both compounds were C-6' epimers. In particular, comparison of the chemical shifts and signal patterns due to OMe, H-2, H-8, H-4', and H-9' resonances of their 400-MHz ¹H NMR spectra strongly supported that both derivatives **9c** were enantiomerically pure at positions C-6' and C-9'.

This interpretation could be confirmed in the following manner. Authentic sinefungin (**1**)²⁰ was successively treated with di-

tert-butyl dicarbonate, 2,2-dimethoxypropane in the presence of boron trifluoride etherate,²¹ and diazomethane to give a derivative the spectral and analytical data of which were identical with those of the synthetic derivative (*S*)-**9c** obtained from the less polar amide **8c** on HPLC.²²

Deprotection of (*S*)-**9c** to sinefungin (**1**) was accomplished in two steps. Saponification of the methyl ester (CO₂K₂, aqueous MeOH) and acidic treatment (CF₃COOH, 1 mn, 0 °C) to remove the (*tert*-butyloxy)carbonyl, followed by formic acid (80%, overnight, room temperature) cleavage of the isopropylidene protecting group, provided sinefungin (**1**), which was identical with authentic material by FAB mass spectrometry and TLC. It had the same inhibitory effect on the growth of *Leishmania donovani* promastigotes. Growth was arrested by a concentration as low as 10 ng/mL.²³

Experimental Section

¹H NMR spectra were recorded on a Bruker 400-MHz spectrometer in CDCl₃/Me₄Si and are reported in values from Me₄Si. Standard abbreviations are used to report NMR multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. Electron impact (EI) and high-resolution mass spectra (HRMS) were obtained with an AEI MS 50 spectrometer. For chemical ionization (CI) an AEI MS 9 instrument was used. Yields refer to chromatographically and spectroscopically pure compounds. Optical rotations were measured on a Roussel Jouan "Quick" polarimeter at the sodium D line and ambient temperature. The compounds described in this section are named according to the IUPAC carbohydrate nomenclature. However, for the sake of clarity the numbering adopted for the figures and the description of the NMR spectra follows the convention normally used in the nucleoside series.

9-[Methyl 9(S)-[[(*tert*-butyloxy)carbonyl]amino]-6-cyano-5,6,7,8,9-pentadeoxy-2,3-O-isopropylidene-β-D-ribo-deca-6-enofuranosyluronate]adenine (6c). A solution of phosphonate **5c** (575 mg, 1 mmol) in methanol (1 mL) was added under argon to a stirred molar solution of magnesium methoxide in methanol (1 mL) maintained at 0 °C. Then a methanol solution (1 mL) of aldehyde **3c** (460 mg, 2 mmol) was introduced with a syringe into the above mixture in four portions each at 15-min intervals. After 4 h the reaction was quenched with a solution of oxalic acid in methanol at 0 °C. The reaction mixture was concentrated to give a solid residue which was rinsed 3 times with 20 mL of methylene chloride. The organic phase was washed with water, dried, and evaporated. The resulting gum (510 mg) was purified by medium-pressure chromatography on a column of silica gel. Elution with ethyl acetate/methylene chloride 9/1 and a methanol gradient (0–10%) gave **6c** (300 mg) and its *N*⁶-debenzoylated derivative (140 mg) (total yield 72%).

6c: NMR showed the presence of two geometrical isomers A and B in ratio of 1:1 δ 8.81 (s, 1 H, H-2), 8.07 (2 s, 1 H, H-8_A and H-8_B), 8.02 (d, 2 H), 7.50 (m, 3 H), 6.29 (t, H-7'_A), 6.10 (d, 1 H, H-1'), 5.94 (t, H-7'_B), 5.61 and 5.52 (2 dd, 1 H, H-2'), 5.08 (dd, H-3'_A), 5.02 (dd, H-3'_B), 4.47 (b, H-4' and H-9'_B), 4.25 (b, H-9'_A), 3.71 and 3.65 (2 s, 3 H, COOMe_A and COOMe_B), 2.89–2.19 (b, 4 H, 2H-5' and 2H-8'), 1.66 (s, 3 H, CH₃), 1.45 (2 s, 9 H, *t*-Bu), 1.41 (s, 3 H, CH₃); mass spectrum (EI), *m/z* (relative intensity) 647 (M⁺, 9), 632 (6), 460 (100), 432 (31), 322 (47), 268 (17), 240 (45), 136 (45); HRMS calcd for C₃₂H₃₇N₇O₈ 647.2703, found 647.2771.

9-[Methyl 9(S)-[[(*tert*-butyloxy)carbonyl]amino]-6-cyano-5,6,7,8,9-pentadeoxy-2,3-O-isopropylidene-β-D-ribo-decafuranosyluronate]adenine (7c). To a methanol solution (4.6 mL) of unsaturated nitrile **6c** (300 mg, 0.46 mmol) was added magnesium turnings (446 mg, 18.4 mmol). As soon as an exothermal reaction ensued the solution was cooled to 0 °C and stirred 1 h at this temperature. The reaction mixture was neutralized with a solution of oxalic acid in methanol. The crude reaction product was extracted as above and purified by medium-pressure column chromatography over silica gel (elution with ethyl acetate/ethanol 98/2) to give **7c** (240 mg) in 84% yield as two epimers, A and B.

7c: NMR δ 8.31 (2 s, 1 H, H-2), 7.84 (2 s, 1 H, H-8), 6.02 (d, 1 H, H-1'), 5.48 (dd, 1 H, H-2'), 4.97 (dd, 1 H, H-3'), 4.48–4.28 (b, 2 H, H-4' and H-9'), 3.73 (2 s, 3 H, COOMe), 2.65–1.55 (b, 7 H, H-6', 2H-5', 2H-8', and 2H-7'), 1.63 and 1.39 (2 s, 6 H, CH₃), 1.45 and 1.43 (2 s, 9 H, *t*-Bu); mass spectrum (EI), *m/z* (relative intensity) 545 (M⁺, 62), 530 (30), 487 (37), 486 (48), 472 (81), 445 (58), 299 (100), 218 (77),

(18) Fourrey, J. L.; Henry, G.; Jouin, P. *J. Chem. Res., Synop.* **1979**, 213.

(21) The absolute stereochemistry at C-9' and C-6' of sinefungin has been shown to be 9'(S),6'(S) on the basis of NMR data: Nagarajan, R.; personal communication.

(23) This paper is dedicated to Professor E. Lederer on the occasion of his 75th birthday.

(18) Purchased from Sigma Chemical Co.

(19) The symbols *S* and *R* refer to the absolute configuration of C-6'.

(20) We are indebted to Dr R. Nagarajan, Lilly Research laboratories, for the generous gift of sinefungin.

164 (99), 136 (100), 135 (98); HRMS calcd for $C_{25}H_{35}N_7O_7$ 545.2598, found 545.2588.

9-[Methyl 9(S)-[[(*tert*-butyloxy)carbonyl]amino]-6-carboxamido-5,6,7,8,9-pentadeoxy-2,3-O-isopropylidene- β -D-ribo-decafuranosyluronate]adenine (8c). To a methanol solution (0.4 mL) of nitriles **7c** (82 mg, 0.17 mmol) was added Me_2SO (15 μ L, 0.2 mmol), 30% aqueous H_2O_2 (80 μ L), and 0.2 M aqueous NaOH (20 μ L). The reaction mixture was maintained at 50 °C for 3 h; it was extracted with chloroform to give a mixture of two products as shown by HPTLC (ethyl acetate/methylene chloride/methanol 35/25/20). The two spots whose R_f were 0.17 and 0.12 corresponded to the two C_6' epimers A and B of **8c**, respectively. They could be separated by HPLC (Lichrosorb Si 60-10) by using the following solvent system: solvent I, ethyl acetate/methylene chloride/methanol 70/25/5; solvent II, ethyl acetate/methylene chloride 35/25; flow 7 mL/min; $t = 0$; 15% I in II; gradient 1% I in II per min. yield, 9.8 mg of amide **8c(A)** and 8.7 mg of amide **8c(B)** (yield of amides **8c** 22%).

8c(A): $[\alpha]^{25}_D +11^\circ$ (c 0.98, $CHCl_3$); NMR δ 8.35 (s, 1 H, H-2), 7.90 (s, 1 H, H-8), 6.01 (d, 1 H, H-1'), 4.85 (dd, 1 H, H-3'), 4.23 (b, 2 H, H-4' and H-9'), 3.70 (s, 3 H, COOMe), 2.23 (b, 1 H, H-6'), 2.01-1.65 (b, 6 H, 2 H-5', 2 H-7', and 2 H-8'), 1.59 and 1.37 (2 s, 6 H, CH_3), 1.42 (s, 9 H, *t*-Bu); mass spectrum (EI), m/z (relative intensity) 563 (M^+ , 22), 548 (5), 504 (20), 490 (14), 463 (20), 317 (75), 290 (25), 218 (83), 164 (100), 136 (100), 135 (98); HRMS calcd for $C_{25}H_{37}N_7O_8$ 563.2703, found 563.2715. **8c(B):** $[\alpha]^{25}_D 0^\circ$ (c 0.87, $CHCl_3$); NMR δ 8.33 (s, 1 H, H-2), 7.90 (s, 1 H, H-8), 5.97 (d, 1 H, H-1'), 5.46 (dd, 1 H, H-2'), 4.90 (dd, 1 H, H-3'), 4.29 (m, 1 H, H-9'), 4.24 (m, 1 H, H-4'), 3.73 (s, 3 H, COOMe), 2.46 (b, 1 H, H-6'), 2.19-1.8 (b, 6 H, 2 H-5', H-7', and 2 H-8'), 1.60 and 1.38 (2 s, 6 H, CH_3), 1.50 (b, 1 H, H-7'), 1.44 (s, 9 H, *t*-Bu); mass spectrum compounds **8c(A)** and **8c(B)** have identical mass spectra; HRMS calcd for $C_{25}H_{37}N_7O_8$ 563.2703, found 563.2717.

9-[Methyl 6,9(S)-bis[[(*tert*-butyloxy)carbonyl]amino]-5,6,7,8,9-pentadeoxy-2,3-O-isopropylidene- β -D-ribo-decafuranosyluronate]adenine (9c). To a water/DMF 1/1 solution (0.1 mL) of amide **8c(B)** (7.2 mg, 0.019 mmol) was added [bis(trifluoroacetoxy)iodo]benzene (8 mg, 0.019 mmol). After 15 min 2 equiv of pyridine (2 μ L) were added to this solution, which was stirred for 2 h at room temperature. The solvent was evaporated under reduced pressure and the residue treated with a DMF solution (0.25 mL) containing di-*tert*-butyl dicarbonate (4 mg, 0.0145 mmol) and triethylamine (2 μ L). The temperature was slowly raised to 25 °C. After one hour the reaction product was isolated and purified by

HPLC (Lichrosorb Si 60-10) by using the following conditions: solvent I, ethyl acetate/methanol 9/1; solvent II methylene chloride; flow 6 mL/min; $t = 0$; 30% I in II, gradient 1% I in II per min. Yield, 9'-(S),6'(R)-**9c** (5.1 mg, 63%): $[\alpha]^{25}_D -6^\circ$ (c 0.48, $CHCl_3$); NMR δ 8.36 (s, 1 H, H-2), 7.94 (s, 1 H, H-8), 6.00 (d, 1 H, H-1'), 5.44 (m, 1 H, H-2'), 4.88 (t, 1 H, H-3'), 4.26 (m, 2 H, H-4' and H-9'), 3.72 (s, 3 H, COOMe), 3.67 (b, 1 H, H-6'), 2-1.45 (b, 6 H, 2 H-5', 2 H-7', and 2 H-8'), 1.61 and 1.38 (2 s, 6 H, CH_3), 1.44 and 1.40 (2 s, 18 H, *t*-Bu); mass spectra (EI), m/z (relative intensity) 635 (M^+ , 78), 620 (8), 562 (24), 574 (18), 218 (23), 164 (46), 136 (100), 135 (32), (CI) isobutane, m/z 636 (MH^+ , 100); HRMS calcd for $C_{29}H_{45}N_7O_9$ 635.3279, found 635.3297. According to the same reaction procedure amide **8c(A)** (8.7 mg, 0.015 mmol) yielded 9'(S),6'(S)-**9c** (6.2 mg, 66%).

9'(S),6'(S)-9c: $[\alpha]^{25}_D +21^\circ$ (c 0.6, $CHCl_3$). For the same derivative prepared from authentic sinefungin: $[\alpha]^{25}_D +22^\circ$ (c 1.19, $CHCl_3$); NMR δ 8.35 (s, 1 H, H-2), 7.89 (s, 1 H, H-8), 6.03 (1 s, H, H-1'), 5.51 (m, H, H-2'), 4.91 (dd, 1 H, H-3'), 4.32 (m, 1 H, H-4'), 4.24 (m, 1 H, H-9'), 3.70 (s, 3 H, COOMe), 3.63 (m, 1 H, H-6'), 2-1.45 (b, 6 H, 2 H-5', 2 H-7', and 2 H-8'), 1.60 and 1.38 (s, 6 H, CH_3), 1.43 and 1.38 (s, 18 H, *t*-Bu); mass spectra EI (m/z) were identical for both C-6' **9c** epimers; HRMS calcd for $C_{29}H_{45}N_7O_9$ 635.3279, found 635.3304.

Acknowledgment. We are grateful to Professor E. Lederer for helpful discussions. This work was supported in part by grants from DGRST No. 50.8345, by INSERM No. 50.8224, by the Ligue Nationale Française Contre le Cancer, and by the Fondation de la Recherche Médicale.

Registry No. **1**, 58944-73-3; *epi-1*, 84799-71-3; **3a**, 87884-22-8; **3b**, 78-84-2; **3c**, 87884-14-8; **5a**, 50466-83-6; **5b**, 50466-88-1; (*Z*)-**6a**, 87884-23-9; (*E*)-**6a**, 87935-93-1; (*Z*)-**6b**, 87884-27-3; (*E*)-**6b**, 87935-94-2; (*Z*)-**6c**, 87884-15-9; (*E*)-**6c**, 87935-91-9; (*Z*)-**6c** debenzoate, 87884-16-0; (*E*)-**6c** debenzoate, 87935-92-0; **7a**, 87884-24-0; *talo-7b*, 87884-28-4; *allo-7b*, 87935-95-3; *talo-7c*, 87884-17-1; *allo-7c*, 87884-18-2; **8a**, 87884-25-1; *talo-8b*, 87884-29-5; *allo-8b*, 87935-96-4; *talo-8c*, 87884-19-3; *allo-8c*, 87884-20-6; **9a**, 87884-26-2; *talo-9b*, 87884-31-9; *allo-9b*, 87884-30-8; *allo-9c*, 87884-21-7; *talo-9c*, 87884-32-0.

Supplementary Material Available: NMR spectra of compounds **9a-c** and **8c** (12 pages). Ordering information is given on any current masthead page.

Total Synthesis of (\pm)-Elwesine, (\pm)-Epielwesine, and (\pm)-Oxocrinine

Ignacio H. Sánchez,* Francisco J. López, José J. Soria, María Isabel Larraza, and Humberto J. Flores

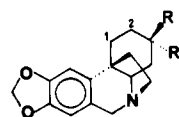
Contribution from the Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán 04510, México, D.F.

Received January 25, 1983

Abstract: A highly efficient total synthesis of the *Amaryllidaceae* alkaloid (\pm)-elwesine (**1**) and of (\pm)-3-epielwesine (**2**) and (\pm)-oxocrinine (**3**) is described. The method consists of the initial formation of the 5-formyltetrahydro-1*H*-2-benzazepine **11** by means of a modified two-step Tscherniac-Einhorn aromatic amidalkylation followed by Robinson annulation. Cleavage of the *N*-carbobenzyloxy protecting group with dimethyl sulfide-boron trifluoride ensued with concomitant 1,4-addition of the liberated azepine nitrogen to the spiro enone system to afford the complete 5,10b-ethanophenanthridine skeleton. The method can be easily modified to encompass the unsaturated members of the series, such as **3**, as well. In this manner **1** was prepared in 30% overall yield from **4**.

Elwesine (**1**) is one of the 5,10b-ethanophenanthridine-type alkaloids found in plants of the *Amaryllidaceae*.¹ We report herein a highly efficient total synthesis of (\pm)-elwesine (**1**), (\pm)-3-epielwesine² (**2**), and (\pm)-oxocrinine (**3**).

(1) For an excellent review of the chemistry of *Amaryllidaceae* alkaloids, see: Fuganti, C. *Alkaloids (N.Y.)* **1975**, *15*, 83-164 and references cited therein.



- 1**, R = H, R' = OH
2, R = OH, R' = H
3, R = R' = O, Δ^4 ,²

The synthesis of **1** features a new tetrahydrobenzazepine ring construction based on a modified two-step Tscherniac-Einhorn-