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 μL, 0.2 mmol), 30% aqueous H_2O_2 (80 μL), and 0.2 M aqueous NaOH (20 μL). 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° (*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, COO*Me*), 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 ($M^{+\cdot}$, 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° (*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, COO*Me*), 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 μL) 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 μL). 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° (*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° (*c* 0.6, $CHCl_3$). For the same derivative prepared from authentic sinefungin: $[\alpha]^{25}_D$ +22° (*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 (±)-Elwesine, (±)-Epielwesine, and (±)-Oxocrinine

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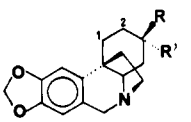
Abstract: A highly efficient total synthesis of the *Amaryllidaceae* alkaloid (±)-elwesine (**1**) and of (±)-3-epielwesine (**2**) and (±)-oxocrinine (**3**) is described. The method consists of the initial formation of the 5-formyltetrahydro-1*H*-2-benzazepine **11** by means of a modified two-step Tscherniac-Einhorn aromatic amidoalkylation followed by Robinson annulation. Cleavage of the *N*-carbobenzoxy 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 (±)-elwesine (**1**), (±)-3-epielwesine[2] (**2**), and (±)-oxocrinine (**3**).



1, R = H, R' = OH
2, R = OH, R' = H
3, R = R' = O, $\Delta^{1,2}$

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

(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.

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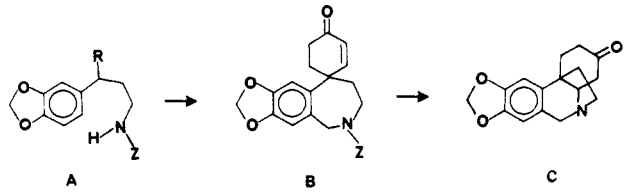
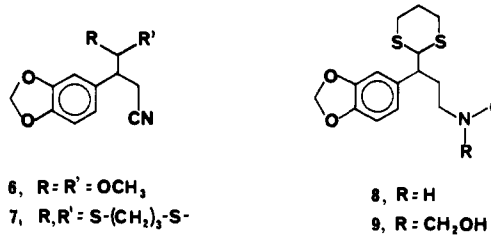
like[3] aromatic amidoalkylation with subsequent elaboration of the complete tetracyclic skeleton by intramolecular 1,4-addition of the azepine nitrogen to a spirocyclic enone system (e.g., A → B → C).[4,5]



A B C

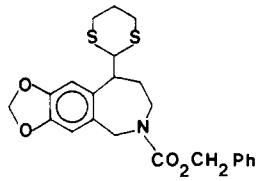
Therefore, (*E*)-3,4-(methylenedioxy)cinnamonitrile[6] (**4**) was reacted with nitromethane under Triton B catalysis to afford in 90% yield the nitromethyl derivative **5**, which was further hydrolyzed to acetal **6** (93% yield) under Jacobson's conditions.[7] After some preliminary experimentation, it soon became apparent that **6** was too labile to withstand the somewhat vigorous conditions required to carry out the next transformations, and it was thus quantitatively converted to the corresponding dithioacetal **7** by treatment with 1,3-propanedithiol and boron trifluoride etherate. Subsequent reduction of **7** with the 1:1 lithium aluminum hydride–aluminum trichloride reagent[8] and reaction of the resulting (crude) primary amine with benzyl chloroformate provided the oily urethane **8** (IR 1705 cm^{-1}) in 87% overall yield. In order to complete the construction of the required hydrobenzazepine nucleus,[9] **8** was submitted to our modification of the Tschernac–Einhorn reaction,[3] namely, initial base-catalyzed condensation with aqueous formaldehyde followed by heating the *N*-(hydroxymethyl) derivative **9** with *p*-toluenesulfonic acid in benzene. The hydrobenzazepine **10** thus obtained (95% yield) was deprotected under Vedejs' conditions[10] to generate the free aldehyde **11a** (IR 1708 cm^{-1}) in 85% yield.

4 5

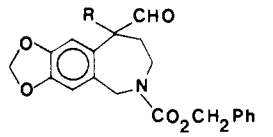


6, R = R' = OCH_3
7, R,R' = S-$(CH_2)_3$-S-

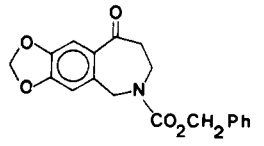
8, R = H
9, R = CH_2OH



10

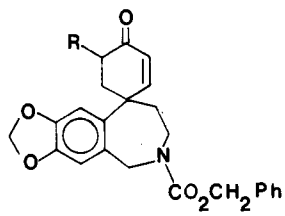


11a, R = H
11b, R = $CH_2CH_2COCH_3$

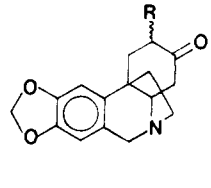


11c

The next step of our synthetic strategy required the formation of spirocyclic enone **12**. Therefore, aldehyde **11a** was first condensed with methyl vinyl ketone (MVK) under 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) catalysis.[11] The resulting keto aldehyde intermediate **11b** underwent facile base-catalyzed (0.03 N ethanolic sodium ethoxide) cycloaldolization and dehydration to give **12** (UV λ_{max} 238, 294 nm) in 85% overall yield. Hydrobenzazepinone **11c**, arising from a base-catalyzed oxydative decarbonylation of the starting aldehyde **11a**, was isolated as the minor (ca. 5%) byproduct.[12]



12, R = H
14, R = Br



13, R = H
15, R = α-Br
16, R = β-Br

The crucial formation of the complete 5,10b-ethanophenanthridine skeleton was envisaged next as occurring via removal of the *N*-(carbobenzoxy) protecting group with concomitant (acid- or base-catalyzed) intramolecular 1,4-addition of the liberated secondary amine to the spiro enone system. To our delight, the whole process was cleanly carried out *in one single operation* and in 92% overall yield by the boron trifluoride catalyzed treatment with dimethyl sulfide[13] to furnish directly (±)-di-

(2) For previous total syntheses of elwesine and its epimer, see: (a) Irie, H.; Uyeo, S.; Yoshitake, A. *J. Chem. Soc. C* **1968**, 1802–1804. (b) Stevens, R. V.; DuPree, L. E. *J. Chem. Soc., Chem. Commun.* **1970**, 1585–1586. (c) Stevens, R. V.; DuPree, L. E., Jr.; Loewenstein, P. L. *J. Org. Chem.* **1972**, *37*, 977–982. (d) Fushimi, T.; Ikuta, H.; Irie, H.; Nakadachi, K.; Uyeo, S. *Heterocycles* **1979**, *12*, 1311–1313; Sánchez, I. H.; Lõpez, F. J.; Flores, H. J.; Larraza, M. I. *Ibid.* **1983**, *20*, 247–254.

(3) For a recent review of the aromatic amidoalkylation reaction, see: Zaugg, H. E.; Martin, W. B. *Org. React. (N.Y.)* **1965**, *14*, 52–269 and references cited therein. For a related process, see: Wittekind, R. R.; Lazarus, S. *J. Heterocycl. Chem.* **1971**, *8*, 495–501. For recent examples of the closely related Ben-Ishai's intramolecular aromatic amidoalkylation reaction, see: (a) Ben-Ishai, D.; Peled, N.; Sataty, I. *Tetrahedron Lett.* **1980**, *21*, 569–572. (b) Danishefsky, S.; Berman, E.; Cvetovich, R.; Minamikawa, J. I. *Ibid.* **1980**, *21*, 4819–4822.

(4) The use of spirocyclic tetrahydrobenzazepines as potential synthetic precursors of the 5,10b-ethanophenanthridine ring system was suggested from their occurrence as biosynthetic precursors. For recent reviews summarizing the biosynthesis of the *Amaryllidaceae* alkaloids, see: (a) Sainsbury, M. In "Rodd's Chemistry of Carbon Compounds", 2nd ed.; Coffey, S., Ed.; Elsevier: Amsterdam, 1977; Vol. IV, Part B, Chapter 10, pp 178–183. (b) Cordell, G. A. "Introduction to Alkaloids-A Biogenetic Approach"; Wiley-Interscience: New York, 1981; Chapter 8, pp 545–551.

(5) We have recently shown in our total synthesis of (±)-lycoramine that intermediate A-type compounds can be readily prepared from the corresponding cinnamonitriles, e.g.: Sánchez, I. H.; Soria, J. J.; Lõpez, F. J.; Flores, H. J.; Larraza, M. I. *J. Org. Chem.*, submitted for publication.

(6) DiBiase, S. A.; Lipisko, B. A.; Haag, A.; Wolak, R. A.; Gokel, G. W. *J. Org. Chem.* **1979**, *44*, 4640–4649. Contrary to the literature report, we have observed than an 84:14 mixture (^1H NMR) of the (*E*)- and (*Z*)-3,4-(methylenedioxy)cinnamonitrile, respectively, is actually obtained under the reported conditions. Recrystallization (Et_2O–hexane) of this crude mixture furnished the pure *E* isomer **4**, mp 91–92 °C. However, the crude mixture can be used in the described sequence without detriment in yield.

(7) Jacobson, R. M. *Tetrahedron Lett.* **1974**, 3215–3216.

(8) Nystrom, R. F. *J. Am. Chem. Soc.* **1955**, *77*, 2544–2545.

(9) For a comprehensive review of the chemistry of benzazepines, see: Kasparek, S. *Adv. Heterocycl. Chem.* **1974**, *17*, 45–98.

(10) Vedejs, E.; Fuchs, P. L. *J. Org. Chem.* **1971**, *36*, 366–367.

(11) Sánchez, I. H.; Tallabs, F. R. *Chem. Lett.* **1981**, 891–894.

(12) Similar oxidative decarbonylations and decyanations are often encountered if thorough exclusion of atmospheric oxygen is not observed while heating benzylic aldehydes or nitriles under basic conditions, see: Sánchez, I. H.; Lemini, C.; Hernández, C.; Larraza, M. I.; Flores, H. J.; García, R.; Machin, G. *Synth. Commun.* **1983**, *13*, 43–51.

(13) For the use of the thiol or dialkyl sulfide–Lewis acid system for the cleavage of ethers and esters, see: (a) Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull.* **1980**, *28*, 3662–3664. (b) Node, M.; Nishide, K.; Sai, M.; Ichikawa, K.; Fuji, K.; Fujita, E. *Chem. Lett.* **1979**, 97–98. (c) Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1980**, *45*, 4275–4277.

hydrooxocrinine[14] (**13**), mp 171–173 °C (lit.[2a] mp 171–173 °C).

It is known[15] that hydride reduction of **13** proceeds in a highly stereoselective manner to yield the equatorially oriented hydroxyl grouping, as in 3-epielwesine (**2**), whereas Meerwein–Ponndorf reduction[2a] is supposed to give elwesine (**1**) itself. In our hands, however, the latter conditions or even treatment with bulky hydride reagents (e.g., Dibal,[16] toluene, −78 °C) produced difficult to separate mixtures of these two isomers. Therefore, it was found best to initially reduce **13** with sodium borohydride to afford (±)-3-epielwesine[14] (**2**), mp 182–184 °C (lit.[2c] mp 184–188 °C) in 81% yield and then invert the troublesome C-3 hydroxyl by using Bose's method[17] (diethyl azodicarboxylate–triphenylphosphine–formic acid) to furnish pure (±)-elwesine[14] (**1**), mp 227–230 °C (lit.[2a] mp 221–223 °C), in 82% yield.[18]

On the one hand, enone **12** is perfectly suited for the introduction of the functional handle that will eventually allow the generation of the $\Delta^{1,2}$-unsaturation characteristic of most members of the series.[1,4a] Therefore, reaction with excess 5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane[19] produced bromo enone **14** in 87% yield. As before, the required dimethyl sulfide assisted[13] cleavage of the urethane moiety ensued with concomitant intramolecular Michael-type addition to afford a mixture of (±)-2α-**15** and (±)-2β-bromodihydrooxocrinine (**16**) in 65% and 22% yield, respectively.

On the other hand, dehydrohalogenation[20] of **15** furnished the well-known[21] (±)-oxocrinine[14] (**3**), mp 170–172 °C (lit.[2a] mp 171–173 °C), in 66% yield.

However, treatment of **16** under similar conditions resulted instead in a net dehalogenation reaction to give back ketone **13** in 55% yield.

Experimental Section

(±)-3-(3,4-(Methylenedioxy)phenyl)-4-nitrobutanenitrile (5). (*E*)-3,4-(Methylenedioxy)cinnamonitrile[6] (**4**) (17.27 g, 0.1 mol) in dry acetonitrile (158 mL) was treated with nitromethane (63.3 mL, 1.17 mol) and Triton B (1.6 mL) and heated to reflux under nitrogen for 24 h. The reaction mixture was diluted with water (100 mL) and 10% aqueous HCl (15 mL) and extracted with EtOAc (3 × 100 mL). Drying (Na_2SO_4) and concentration gave a brown residue (23 g). Purification by column chromatography (900 g of SiO_2, 8:2 hexane–EtOAc) gave the pure nitromethyl derivative **5** (21.05 g, 0.09 mol, 90%) as colorless crystals, mp 67–69 °C (EtOAc–hexane): IR (KBr) 2800, 2255, 1550, 1395, 940 cm^{-1}; ^{1}H NMR δ 6.90–6.63 (m, Ar H), 5.98 (s, OCH_2O), 4.66 (d, J = 7 Hz, CH_2NO_2), 3.73 (q, J = 7 Hz, Ar CH), 2.74 (d, J = 7 Hz, CH_2CN). Anal. ($C_{11}H_{10}N_2O_4$) C, H, N.

(±)-4,4-Dimethoxy-3-(3,4-(methylenedioxy)phenyl)butanenitrile (6). A solution of **5** (8.062 g, 0.0344 mol) in 0.5 N methanolic sodium methoxide (82.75 mL) was added dropwise to a cold (−35 °C) and stirred solution of concentrated H_2SO_4 (82.75 mL) in dry MeOH (311 mL). After 20 min the reaction mixture was poured into $CHCl_3$ (1.5 L) and water (300 mL). The extract was washed (H_2O, 3 × 1 N NaOH), dried (K_2CO_3), and evaporated to a yellow oil (8.7 g). Purification by column chromatography (450 g of SiO_2, 8:2 hexane–EtOAc) furnished pure acetal **6** (7.97 g, 0.032 mol, 93%) as a colorless oil: IR (neat) 2830, 2780, 2240, 933 cm^{-1}; ^{1}H NMR δ 6.86–6.53 (m, Ar H), 6.88 (s, OCH_2O), 4.38 (d, J = 6 Hz, $CH(OCH_3)_2$), 3.35 and 3.27 (2s, 2 OCH_3), 3.03 (dt, J = 8.5, 6 Hz, Ar CH), 2.64 (dd, J = 16.5, 6 Hz, CHCN), 2.52 (dd, J = 16.5, 8.5 Hz, CHCN). Anal. ($C_{13}H_{15}NO_4$) C, H, N.

(±)-3-(1,3-Dithian-2-yl)-3-(3,4-(methylenedioxy)phenyl)propanenitrile (7). A solution of acetal **6** (7.72 g, 0.031 mol) in dry CH_2Cl_2 (250 mL) was cooled to 0 °C and treated with 1,3-propanedithiol (5.07 mL, 0.051 mol) and boron trifluoride etherate (0.17 mL). The reaction mixture was stirred at room temperature overnight and then poured into cold 1 N NaOH (100 mL). Extraction with $CHCl_3$ (2x), washing (0.5 N NaOH, H_2O, brine), drying (Na_2SO_4), and concentration afforded a colorless oil (9.4 g). Purification by column chromatography (200 g of SiO_2, 8:2 hexane–EtOAc) gave **7** as a viscous oil (9.08 g, 0.031 mol, 100%): IR (neat) 2245, 929, 750 cm^{-1}; ^{1}H NMR δ 6.79 (s, Ar H), 5.97 (s, OCH_2O), 4.28 (d, J = 7.5 Hz, SCHS), 3.39–3.07 (m, Ar CH), 3.03–2.69 (m, 2 CH_2S, CH_2CN), 2.21–1.57 (m, CH_2). Anal. ($C_{14}H_{15}NO_2S_2$) C, H, N.

(±)-*N*-Carbobenzoxy-3-(1,3-dithian-2-yl)-3-(3,4-(methylenedioxy)-phenyl)propylamine (8). A solution of aluminum trichloride (8.36 g, 0.0627 mol) in dry tetrahydrofuran (THF, 130 mL) was rapidly added to a suspension of lithium aluminum hydride (2.40 g, 0.0632 mol) in dry THF (50 mL). After 5 min of stirring a solution of **7** (9.2 g, 0.0314 mol) in THF (50 mL) was added dropwise, and the resulting mixture was heated at 40 °C (oil bath) for 2 h. After cooling and careful addition of H_2O (15 mL) and 2 N NaOH (30 mL), the suspension was extracted with Et_2O (5x). The combined extracts were washed (H_2O, brine), dried (Na_2SO_4), and evaporated to give a nearly colorless oil (8.6 g) which was dissolved in dry dichloromethane (CH_2Cl_2, 200 mL), cooled to 5 °C, and treated with triethylamine (8.6 mL) and benzyl chloroformate (40.8 mL of a 10 wt % solution in toluene, 0.0408 mol). After 20 min at room temperature the reaction mixture was diluted with water (75 mL) and saturated NH_4Cl solution (45 mL) and extracted with $CHCl_3$ (3x). The extract was washed (brine), dried (Na_2SO_4), and concentrated to give a yellow oil (12.25 g). Purification by column chromatography (600 g of SiO_2, 7:3 hexane–EtOAc) gave the pure oily urethane **8** (11.75 g, 0.027 mol, 87%): IR (neat) 3345, 1718, 937 cm^{-1}; ^{1}H NMR δ 7.22 (s, C_6H_5), 6.73–6.47 (m, Ar H), 5.82 (s, OCH_2O), 4.94 (s, CH_2Ph), 5.07–4.78 (br, NH), 4.04 (d, J = 7 Hz, SCHS), 3.07–2.44 (m, 2 SCH_2, Ar CH, CH_2N), 2.33–1.48 (m, 2 CH_2). Anal. ($C_{22}H_{25}NO_4S_2$) C, H, N.

(±)-*N*-Carbobenzoxy-3-(1,3-dithian-2-yl)-1-(hydroxymethyl)-3-(3,4-(methylenedioxy)phenyl)propylamine (9). A solution of urethane **8** (2.55 g, 5.92 mmol) in dioxane (20 mL) was treated with aqueous formaldehyde (37 wt % solution, 32 mL) and 0.625 NaOH (3 mL) and stirred overnight at room temperature. The mixture was diluted with H_2O (20 mL) and saturated NH_4Cl solution (10 mL) and thoroughly extracted with EtOAc (5x). The combined extracts were washed (brine), dried (Na_2SO_4), and concentrated to an oily residue (3.015 g). Column chromatography (120 g of SiO_2, 6:4 hexane–EtOAc) afforded pure **9** (2.715 g, 5.89 mmol, 99.5%) as a colorless foam: IR ($CHCl_3$) 3440, 1700, 937 cm^{-1}; ^{1}H NMR δ 7.36 (s, C_6H_5), 6.81–6.54 (m, Ar H), 5.91 (s, OCH_2O), 5.11 (s, CH_2Ph), 4.69 (d, J = 7 Hz; NCH_2O), 3.47–3.04 (br, OH), 4.14 (d, J = 7 Hz, SCHS), 3.18 (t, J = 7 Hz, CH_2N), 3.0–2.63 (m, 2 SCH_2, Ar CH), 2.43–1.55 (m, 2 CH_2).

(±)-2-Carbobenzoxy-5-(1,3-dithian-2-yl)-7,8-(methylenedioxy)-2,3,4,5-tetrahydro-1*H*-2-benzazepine (10). A solution of **9** (87 mg, 0.189 mmol) in dry benzene (20 mL) was treated with *p*-toluenesulfonic acid (4 mg) and heated to reflux for 20 min using a water separator (Dean Stark). The mixture was cooled, washed (water, saturated $NaHCO_3$, brine), dried (Na_2SO_4), and evaporated to a colorless oil (82.5 mg). Preparative layer chromatography (SiO_2, 8:2 hexane–EtOAc) afforded pure **10** (79.2 mg, 0.179 mmol, 95%) as a colorless foam: IR ($CHCl_3$) 1701, 938 cm^{-1}; ^{1}H NMR δ 7.34 (s, C_6H_5), 6.80 (s, H_6), 6.75 and 6.53 (brs, 0.375 H_9, 0.625 H_9), 5.92 (s, OCH_2O), 5.09 (s, CH_2Ph), 4.61 (d, J = 9.5 Hz; SCHS), 4.4 (brs, 2 H_1), 4.0–3.36 (m, 2 H_3), 3.13 (ddd, J = 9.5, 5.5, 4 Hz, H_5), 2.98–2.68 (m, 2 SCH_2), 2.24–1.6 (m, CH_2CH_2S, and 2 H_4). Anal. ($C_{23}H_{25}NO_4S_2$) C, H, N.

(±)-2-Carbobenzoxy-5-formyl-7,8-(methylenedioxy)-2,3,4,5-tetrahydro-1*H*-2-benzazepine (11a). A solution of thioacetal **10** (887 mg, 2.0 mmol) in the minimum amount of THF (1 mL) was added dropwise under nitrogen to a stirred suspension of red mercuric oxide (867.9 mg, 4.0 mmol) and boron trifluoride etherate (0.492 mL, 4.0 mmol) in 15% v/v aqueous THF (8.9 mL). After 20 min the reaction was diluted with Et_2O (20 mL), filtered through sintered glass, washed (saturated Na_2CO_3, brine), dried (Na_2SO_4), and evaporated to give a yellow residue (692 mg). Purification by preparative layer chromatography (SiO_2, 8:2 hexane–EtOAc) furnished the pure oily aldehyde **11a** (601 mg, 1.7 mmol, 85%): IR (neat) 2717, 1708, 930 cm^{-1}; ^{1}H NMR δ 9.8 (s, CHO), 7.3

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(18) Our total synthesis of (±)-elwesine (**1**) thus proceeds in an overall 30% yield from **4**.

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(s, C_6H_5), 6.53 (s, H_6), 6.84 and 6.49 (br, 0.66 H_9, 0.34 H_9), 5.91 (s, OCH_2O), 5.06 (s, CH_2Ph), 4.44 (d, J = 16; $H_{1\alpha}$ or $H_{1\beta}$), 4.03 (d, J = 16 Hz; $H_{1\alpha}$ or $H_{1\beta}$), 3.89–3.31 (m, H_5, and 2 H_3), 2.49–1.7 (m, 2 H_4). Anal. ($C_{20}H_{19}NO_5$) C, H, N.

(±)-2-Carbobenzoxy-7,8-(methylenedioxy)-2,3,4,5-tetrahydrospiro-[1*H*-2-benzazepine-5,4′-cyclohexenone] (12) and (±)-2-Carbobenzoxy-7,8-(methylenedioxy)-2,3,4,5-tetrahydro-1*H*-2-benzazepin-5-one (11c). The aldehyde **11a** (149.2 mg, 0.423 mmol) was dissolved in dry THF (5 mL), cooled to 0 °C, and treated, under nitrogen atmosphere, with freshly distilled methyl vinyl ketone (MVK, 0.071 mL, 0.845 mmol) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, 1 drop). After 45 min the mixture was diluted with water (3 mL) and 10% v/v aqueous HCl (1 mL) and extracted with EtOAc. The combined extracts were washed (H_2O, brine), dried (Na_2SO_4), and evaporated. The residue was taken up in dry THF (0.4 mL), diluted with EtOH (10 mL), and treated with 0.03 N ethanolic sodium ethoxide (10 mL). The resulting mixture was heated to reflux under nitrogen for 40 min, diluted with water (10 mL), treated with saturated NH_4Cl (5 mL), and concentrated to a small volume. Extraction with EtOAc furnished a yellow-brown residue (161 mg) which upon preparative layer chromatography (SiO_2, 7:3 hexane-EtOAc) afforded the pure enone **12** (146 mg, 0.36 mmol, 85%) as a colorless foam: IR ($CHCl_3$) 1705, 1686, 1631, 937 cm^{-1}; ^1H NMR δ 7.37 (s, C_6H_5), 6.37 (d, J = 10.5 Hz; $H_{3'}$), 6.70 (brs, H_6), 6.60 (brs, H_9), 6.04 (d, J = 10.5 Hz, $H_{2'}$), 5.92 (s, OCH_2O), 5.08 (s, CH_2Ph), 4.48 (brs, 2 H_1), 3.75 (dd, J = 8.5, 3.5 Hz, 2 H_3), 2.49–1.97 (m, 2 $H_{5'}$, 2 $H_{6'}$, H_{4ax}), 1.86 (dt, J = 15, 3.5 Hz, H_{4ec}); UV λ_{max} (log ϵ) 238 (4.05), 294 nm (3.49); MS (EI), m/e (relative intensity) 405 (5), 315 (11), 314 (53), 270 (9), 242 (8), 241 (9), 185 (7), 91 (100), 77 (6), 65 (13). Anal. ($C_{24}H_{23}NO_5$) C, H, N. A minor less polar product ketone **11c** (8.25 mg, 0.021 mmol, 5%) was isolated as a colorless oil: IR (neat) 1710, 1680, 1625, 930 cm^{-1}; ^1H NMR δ 7.30 (s, C_6H_5), 6.83 (br, H_6), 6.66 (br, H_9), 6.0 (s, OCH_2O), 5.09 (s, CH_2Ph), 4.66 (brs, 2 H_1), 3.69 (t, J = 7 Hz, 2 H_3), 2.94 (t, J = 7 Hz, 2 H_4); MS (EI), m/e (intensity) 339 (30), 248 (40), 177 (4), 176 (13), 175 (16), 91 (100), 65 (13). On one run, the (unstable) keto aldehyde **11b** was isolated by preparative layer chromatography (SiO_2, 7:3 hexane-EtOAc) for characterization purposes: IR (neat) 2820, 2708, 1707, 930 cm^{-1}; ^1H NMR δ 9.39 (s, CHO), 7.32 (s, C_6H_5), 6.60 (s, H_6), 6.92–6.5 (br, H_9), 5.93 (s, OCH_2O), 5.09 (s, CH_2Ph), 4.36 (brs, 2 H_1), 4.04–3.04 (m, 2 H_3), 2.59–1.86 (m, CH_2CH_2CO, H_{4ax}), 2.06 (s, $COCH_3$), 1.66 (dt, J = 14.6, 4.7 Hz, H_{4ec}).

(±)-Dihydrooxocrinine (13). Spiro enone **12** (124.4 mg, 0.31 mmol) was dissolved in dry CH_2Cl_2 (6 mL), treated with distilled dimethyl sulfide (0.61 mL, 8.41 mmol) and boron trifluoride etherate (0.369 mL, 3 mmol), and stirred at room temperature for 1.5 h. After a second addition of dimethyl sulfide (0.5 mL, 6.89 mmol), the reaction was allowed to proceed for another 2 h. The mixture was then poured into water (5 mL) and 10% aqueous NH_4OH (10 mL) and extracted with $CHCl_3$ (3x). The combined extracts were washed (H_2O, brine), dried (Na_2SO_4), and evaporated to a brown gum (92 mg). Preparative layer chromatography (SiO_2, 95:5 $CHCl_3$–25% v/v methanolic trimethylamine) afforded pure **13** (76.5 mg, 0.282 mmol, 92%) as colorless prisms (benzene–Et_2O), mp 171–173 °C (lit.[2a] mp 171–173 °C): IR ($CHCl_3$) 1727, 938 cm^{-1}; ^1H NMR δ 6.7 (s, H_{10}), 6.46 (s, H_7), 5.88 (s, OCH_2O), 4.32 and 3.77 (AB, J = 17 Hz, 2 H_6), 3.65–1.76 (m, 11 H); MS (EI), m/e (intensity) 271 (63), 242 (15), 215 (45), 214 (49), 201 (100), 187 (30), 185 (51), 174 (38), 128 (35), 115 (65), 77 (19). Anal. ($C_{16}H_{17}NO_3$) C, H, N.

(±)-3-Epielwesine (2). Ketone **13** (206.3 mg, 0.76 mmol) was dissolved in MeOH (10 mL), cooled to 0 °C (ice bath), and treated with excess sodium borohydride (23 mg, 0.608 mmol) for 0.5 h. The reaction mixture was diluted with water (10 mL) containing NH_4OH (3 drops) and concentrated to a small volume. Extraction with $CHCl_3$ (4x) afforded a pale-brown residue (179.5 mg) which upon preparative layer chromatography (SiO_2, 95:5 $CHCl_3$–25% v/v methanolic trimethylamine) furnished pure **2** (166 mg, 0.608 mmol, 81%) as colorless prisms from acetone, mp 182–184 °C (lit.[2c] mp 184–188 °C). Our synthetic material proved identical with authentic comparison spectra.[14]

(±)-Elwesine (1). A solution of diethyl azodicarboxylate (DEAD, 124 mg, 0.714 mmol) in dry THF (0.7 mL) was slowly added at room temperature to a magnetically stirred mixture of **2** (97.4 mg, 0.357 mmol), triphenylphosphine (TPP, 187 mg, 0.714 mmol), and 98% formic acid (0.04 mL, 1.07 mmol) in dry THF (5 mL). The reaction was allowed to proceed under nitrogen for 3 days, while adding every 24 h extra portions of DEAD (124 mg), TPP (187 mg), and formic acid (0.027 mL, 0.714 mmol). The reaction mixture was then quenched with H_2O (1 mL), treated with 2 N NaOH (8 mL), and stirred at room temperature for 1.5 h. Extraction with $CHCl_3$ (4x) afforded a yellow oily residue. Initial percolation through basic aluminum oxide (10 g, $CHCl_3$) and further preparative layer chromatography (SiO_2, 85:15 $CHCl_3$–25% v/v methanolic trimethylamine) furnished as a more polar material pure **1** (58 mg, 0.212 mmol, 82% based on recovered starting material) as colorless prisms from acetone, mp 227–230 °C (lit.[2a] mp 221–223 °C), together with recovered **2** (26.5 mg, 0.097 mmol). The synthetic sample of **1** proved identical in all respects with authentic comparison spectra.[14]

(±)-6′-Bromo-2-carbobenzoxy-7,8-(methylenedioxy)-2,3,4,5-tetrahydrospiro[1*H*-2-benzazepine-5,4′-cyclohexenone] (14). A mixture of spiro enone **12** (284.5 mg, 0.702 mmol) and 5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane[18] (211.9 mg, 0.702 mmol) in carbon tetrachloride (20 mL) was heated to reflux for 14 h under nitrogen. The resulting light orange solution was diluted with saturated $NaHCO_3$ (10 mL) and extracted with $CHCl_3$. Upon concentration and preparative layer chromatography (SiO_2, 7:3 hexane–EtOAc) bromo enone **14** (295.7 mg, 0.611 mmol, 87%) was isolated as colorless prisms from EtOAc–hexane, mp 214–216 °C dec: IR ($CHCl_3$) 1702, 1688, 1624, 928, 598 cm^{-1}; ^1H NMR δ 7.29 (s, C_6H_5), 6.72 (d, J = 10 Hz, $H_{3'}$), 6.95–6.51 (m, H_6, H_9), 6.22 (d, J = 10 Hz, $H_{2'}$), 6.92 (s, OCH_2O), 5.07 (s, CH_2Ph), 4.57 (b, $W_{1/2}$ = 6.5 Hz, $H_{6'}$), 4.49 (brs, 2 H_1), 3.8–3.29 (m, 2 H_3), 3.12–2.04 (m, 2 $H_{5'}$, H_{4ax}), 1.87 (dt, J = 14, 4 Hz, H_{4ec}); MS (EI), m/e (intensity) 483/485 (1/1), 473 (5), 471 (5), 394 (30), 392 (30), 314 (16), 91 (100), 65 (9). Anal. ($C_{24}H_{22}BrNO_5$) C, H, N.

(±)-2α- (15) and (±)-2β-Bromodihydrooxocrinine (16). By following a similar technique as before (**12** → **13**), bromo enone **14** (57.82 mg, 0.119 mmol) furnished the pure 2α-bromo isomer **15** (27.07 mg, 0.0773 mmol, 65%) as colorless prisms (EtOAc–hexane) mp 198 °C dec: IR ($CHCl_3$) 1727, 927, 560 cm^{-1}; ^1H NMR δ 6.64 (s, H_{10}), 6.45 (s, H_7), 5.89 (s, OCH_2O), 4.93 (dd, J = 13, 6.5 Hz; $H_{2\beta}$), 4.33 and 3.79 (AB, J = 17 Hz; 2 H_1), 3.58–2.87 (m, 9 H); MS (EI), m/e (intensity) 349/351 (1/1), 270 (21), 242 (20), 228 (20), 214 (15), 201 (100), 174 (22), 128 (30). Anal. ($C_{16}H_{16}BrNO_3$) C, H, N. The minor 2β-bromo isomer **16** (9.3 mg, 0.0266 mmol, 22%) was isolated as a colorless oil: IR (neat) 1711, 928 cm^{-1}; ^1H NMR δ 6.69 (s, H_{10}), 6.47 (s, H_7), 5.9 (s, OCH_2O), 4.44 and 3.86 (AB, J = 16 Hz, 2 H_6), 4.12–1.46 (m, 10 H); MS (EI), m/e (intensity) 349/351 (1/1), 271 (100), 242 (20), 214 (32), 201 (78), 185 (30), 174 (22), 128 (22), 115 (30).

(±)-Oxocrinine (3). A solution of 2α-bromo ketone **15** (15.77 mg, 0.045 mmol) in dry dimethylformamide (DMF, 0.5 mL) was added in one portion to a suspension of anhydrous lithium bromide (6 mg, 0.072 mmol) and lithium carbonate (8.2 mg, 0.124 mmol) in dry DMF (2 mL). The reaction mixture was heated for 1.25 h at 120–125 °C (oil bath temperature) under nitrogen and then poured into cold water (5 mL). Extraction with $CHCl_3$ afforded a dark brown residue (15 mg) which upon preparative layer chromatography (SiO_2, 95:5 $CHCl_3$–25% v/v methanolic trimethylamine) furnished pure **3** (8 mg, 0.03 mmol, 66%) as a colorless powder, mp 170–172 °C (EtOAc) (lit.[2a] mp 171–173 °C). Our synthetic sample proved identical with (±)-oxocrinine obtained by activated MnO_2 oxidation[22] of natural (±)-3-epicrinine[14] (**2**, $\Delta^{1,2}$).

(±)-Dihydrooxocrinine (13) from (±)-2β-Bromodihydrooxocrinine (16). Attempted dehydrohalogenation of the 2β-bromo ketone **16** (10 mg, 0.029 mmol) under the previous conditions (**15** → **3**) afforded instead pure **13** (4 mg, 0.015 mmol, 52%).

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Registry No. (±)-**1**, 33531-72-5; (±)-**2**, 32209-87-3; (±)-**3**, 7700-86-9; **4**, 49711-07-1; (±)-**5**, 87697-84-5; (±)-**6**, 87697-85-6; (±)-**7**, 87697-86-7; (±)-**8**, 87697-87-8; (±)-**9**, 87697-88-9; (±)-**10**, 87697-89-0; (±)-**11a**, 87697-90-3; (±)-**11b**, 87697-91-4; **11c**, 87697-92-5; (±)-**12**, 87697-93-6; (±)-**13**, 10305-81-4; **14**, 87697-94-7; (±)-**15**, 87697-95-8; (±)-**16**, 87697-96-9; (±)-A (Z = H, R = $S(CH_2)_3S$), 87697-97-0; nitromethane, 75-52-5; 1,3-propanedithiol, 109-80-8; benzyl chloroformate, 501-53-1; methyl vinyl ketone, 78-94-4.

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