A solution of 765 mg (1.17 mmol) of the above *E* ester in 30 mL of 80% aqueous acetic acid was stirred at room temperature overnight. The reaction was evaporated to dryness (high vacuum, room temperature) to give an oil, which was dissolved in 25 mL of ether. One milliliter of saturated sodium bicarbonate was added and the mixture stirred vigorously for 1 h. $MgSO_4$ was then added and the reaction mixture filtered and evaporated to give a crude residue, which was purified by flash chromatography with ethyl acetate–hexanes (3:1) to give 460 mg (80%) of **51** as a colorless oil: $[\alpha]^{25}_D$ +11.9° (*c* 0.27, $CHCl_3$); ^1H NMR (400 MHz) δ 0.99 (d, *J* = 7 Hz, 3 H), 1.15 (d, *J* = 7 Hz, 3 H), 2.23 (s, 3 H), 2.31 (t, *J* = 8 Hz, 2 H), 3.68 (s, 3 H), 4.08 (t, *J* = 8 Hz, 2 H), 5.47 (m, 2 H), 5.76 (br s, 1 H); ^{13}C NMR (50 MHz) δ 16.62 (C-17), 19.07 (C-15), 20.33 (C-14), 24.80 (C-3′), 25.91 (C-7′), 28.64 (C-8′), 29.04 (C-4′,5′,6′), 32.29 (C-9), 34.07 (C-2′), 41.86 (C-8), 43.08 (C-4), 44.67 (C-12), 51.46 (OMe), 63.78 (C-9′), 64.83 (C-16), 68.84 (C-6), 70.29 (C-7), 71.15 (C-13), 74.69 (C-5), 117.53 (C-2), 129.40 (C-10), 134.41 (C-11), 156.82 (C-3), 166.79 (C-1), 174.38 (C-1′); IR ($CHCl_3$) 3650, 3560, 1725, 1711, 1650 cm^{-1}; mass spectrum, *m/e* (relative intensity) 454 (10), 266 (75), 82 (100); UV (EtOH) λ_{max} 218 nm (ε 10620). Anal. Calcd for $C_{27}H_{46}O_8$: C, 65.03; H, 9.30. Found: C, 64.72; H, 9.20.

[2*S*-[2α(*E*),3β,4β,5α(2*E*,4*S,5*R**)]]-9-[[3-Methyl-1-oxo-4-[tetrahydro-3,4-dihydroxy-5-(5-hydroxy-4-methyl-2-hexenyl)-2*H*-pyran-2-yl]-2-butenyl]oxy]nonanoic Acid (Pseudomonic Acid C; 1c).** To a solution of 50 mg (0.1 mmol) of **51** in 1 mL of absolute ethanol and 1 mL of THF at 0 °C were added 1 mL of 1 N aqueous $NaHCO_3$ and 1 mL of 1 N aqueous KOH followed 5 min later by an additional 1 mL of 1 N KOH. After 4.5 h at 0 °C, the mixture was poured into 25 mL of rapidly stirring 1 N HCl at 0 °C, salted with solid NaCl, and extracted with 5 × 25 mL of ethyl acetate. The combined organic extracts were dried ($NaSO_4$) and evaporated to give a crude residue, which was purified by flash chromatography with methylene chloride–methanol (95:5 then 90:10) to give 37 mg (77%) of pseudomonic acid C as a colorless, viscous oil: $[\alpha]^{25}_D$ +7.64° (*c* 0.78, $CHCl_3$); ^1H NMR (200 MHz) δ 0.98 (d, *J* = 7 Hz, 3 H), 1.15 (d, *J* = 6 Hz, 3 H), 2.20 (s, 3 H), 2.29 (t, *J* = 7 Hz, 2 H), 4.08 (t, *J* = 6 Hz, 2 H), 5.45 (m, 2 H), 5.76 (br s, 1 H); ^{13}C NMR (50 MHz) δ 16.69, 19.12, 20.33, 24.62, 25.82, 28.46, 28.66, 28.75, 28.84, 32.29, 33.85, 41.83, 42.92, 44.73, 63.78, 64.83, 68.89, 70.34, 71.25, 74.75, 117.53, 129.54, 134.44, 156.77, 166.80, 178.10. Anal. Calcd for $C_{26}H_{44}O_8$: C, 64.44; H, 9.15. Found: C, 64.11; H, 9.29.

Registry No. **1c**, 71980-98-8; **11**, 49826-00-8; **12**, 54483-22-6; **13**, 115118-71-3; **14**, 107148-21-0; **19**, 107148-20-9; **16**, 115118-72-4; **16** (diol), 115183-63-6; **17**, 107148-22-1; **18**, 115118-73-5; **19** (epimer 1), 115118-74-6; **19** (epimer 2), 115118-75-7; **20a**, 115118-76-8; **20b**, 107148-23-2; **22a**, 115118-79-1; **22b**, 115118-78-0; **23a**, 115118-77-9; **24**, 115183-64-7; **25**, 115183-65-8; **26**, 115140-92-6; **27**, 107148-24-3; **27** (de-isopropylidinyl diol), 115118-80-4; **28**, 107148-25-4; **29**, 115118-81-5; **30**, 115118-82-6; (*E*)-**34**, 107148-28-7; (*Z*)-**34**, 115183-66-9; **34** (6-ol), 115118-88-2; **34** (6-iodo derivative), 115118-89-3; **34** (2-ol), 115118-90-6; **34** (2-al), 115118-91-7; **36**, 78088-28-5; **37**, 85576-58-5; **39**, 115118-83-7; **39** (1-ol), 85576-59-6; **40**, 115118-85-9; **41a**, 107148-26-5; **41b**, 107241-79-2; **44**, 115118-87-1; (12*R*,13*R*)-**46a**, 107148-27-6; (12*R*,13*S*)-**46a**, 115183-67-0; **46b**, 107148-32-3; **47**, 107148-29-8; **47** (reduced), 107148-30-1; **47** (reduced, phenylmethoxyacetate), 115140-93-7; **48**, 107148-31-2; **50**, 89726-74-9; **50** (reduced, diastereomer-1), 115118-92-8; **50** (reduced, diastereomer-2), 115183-68-1; **51**, 72042-22-9; (C-2*E*)-**51** (C-6,7-di-*O*-isopropylidene, C-13-*O*-TBDMS derivative), 89726-76-1; (C-2*Z*)-**51** (C-6,7-di-*O*-isopropylidene, C-13-*O*-TBDMS derivative), 115183-69-2; $CH_3C(OMe)_2NMe_2$, 18871-66-4; $CH_3C{\equiv}CH$, 74-99-7; $HOCH_2COOH$, 79-14-1; $HOCH_2COOCH_2Ph$, 30379-58-9; *t*-$BuMe_2SiOCH_2COOCH_2Ph$, 115118-86-0; *t*-$BuMe_2SiOCH_2COOH$, 105459-05-0; $(MeO)_2P(O)CH_2CO_2(CH_2)_8COOMe$, 92516-83-1; 3,5-hexadienoyl chloride, 108306-38-3; (*R*)-(+)-α-phenethylamine, 3886-69-9; (2*S*,3*S*)-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methyl-1-iodobutane, 115118-84-8.

Stereoselective Total Synthesis of (±)-Saframycin B

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A 20-step total synthesis of (±)-saframycin B (**2**) from (*Z*)-1-acetyl-3-arylidene-6-(arylmethyl)-2,5-piperazinedione **11** is described. Conversion of **11** to the imide **17a** was followed by 1,2-reduction with lithium tri-*tert*-butoxyaluminum hydride in a highly regioselective manner, and this was then cyclized to (*E*)-1,5-imino-3-benzazocine **19a** with isomerization of the double bond. The intermediate **19a** was efficiently converted to the *N*-methyl tricyclic lactam **26**, the structure of which was determined by X-ray crystallography. Conversion of **26** to the amine **13** and subsequent stereoselective intramolecular cyclization through its *O*,*N*-acetal **30** provided 9-*epi*-pentacyclic ester **31**. Epimerization took place in **31** at the C-9 position to the desired ester **34**, which was transformed to the pyruvamide **39** in a four-step sequence. Finally, **39** was subjected to two-step oxidative demethylation to provide (±)-saframycin B (**2**).

Saframycin B (**2**)[1a] is a novel antitumor antibiotic discovered in the culture broths of *Streptomyces lavendulae*[2] along with saframycins A (**1**),[1b] C (**3**),[1a] and D (**4**).[1c] Over the last several years the additional saframycin derivatives, namely, safracins A (**5**) and B (**6**),[3] renieramycins A (**7**) and C (**8**),[4] and saframycins MX 1 (**9**) and Mx 2 (**10**),[5] have been independently isolated from bacterial sources and marine sponges (Chart I). Saframcyins are highly active against gram-positive bacteria and exhibit antitumor activities. Among this group, saframycin A (**1**) has been shown to possess the highest antitumor activity against various tumors including P388 leukemia and Ehrlich ascites tumor.[6] The structure of **2** was elucidated by comparing its spectroscopic data with those of saframycin C

(1) (a) Arai, T.; Takahashi, K.; Kubo, A.; Nakahara, S.; Sato, S.; Aiba, K.; Tamura, C. *Tetrahedron Lett.* **1979**, 2355–2358. (b) Arai, T.; Takahashi, K.; Kubo, A.; Nakahara, S. *Experientia* **1980**, *36*, 1025–1026. (c) Kubo, A.; Saito, N.; Kitahara, Y.; Takahashi, K.; Yazawa, K.; Arai, T. *Chem. Pharm. Bull.* **1987**, *35*, 440–442. Recently, a new series of saframycins Y3, Yd-1, Yd-2, Ad-1, Y-2b, and Y2b-d was produced by directed biosynthesis employing resting cells of saframycin producer, *Streptomyces lavendulae*: Yazawa, K.; Takahashi, K.; Mikami, Y.; Arai, T.; Saito, N.; Kubo, A. *J. Antibiot.* **1986**, *39*, 1639–1650.

(2) (a) Arai, T.; Kubo, A. *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1983; Vol. 21, pp 55–100. (b) Tomson, R. H. *Naturally Occurring Quinone III*; Chapman and Hall: New York, 1987, pp 633–666, and references therein.

(3) (a) Ikeda, Y.; Matsuki, H.; Ogawa, T., Munakata, T. *J. Antibiot.* **1983**, *36*, 1284–1289. (b) Cooper, R.; Unger, S. *Ibid.* **1985**, *38*, 24–30.

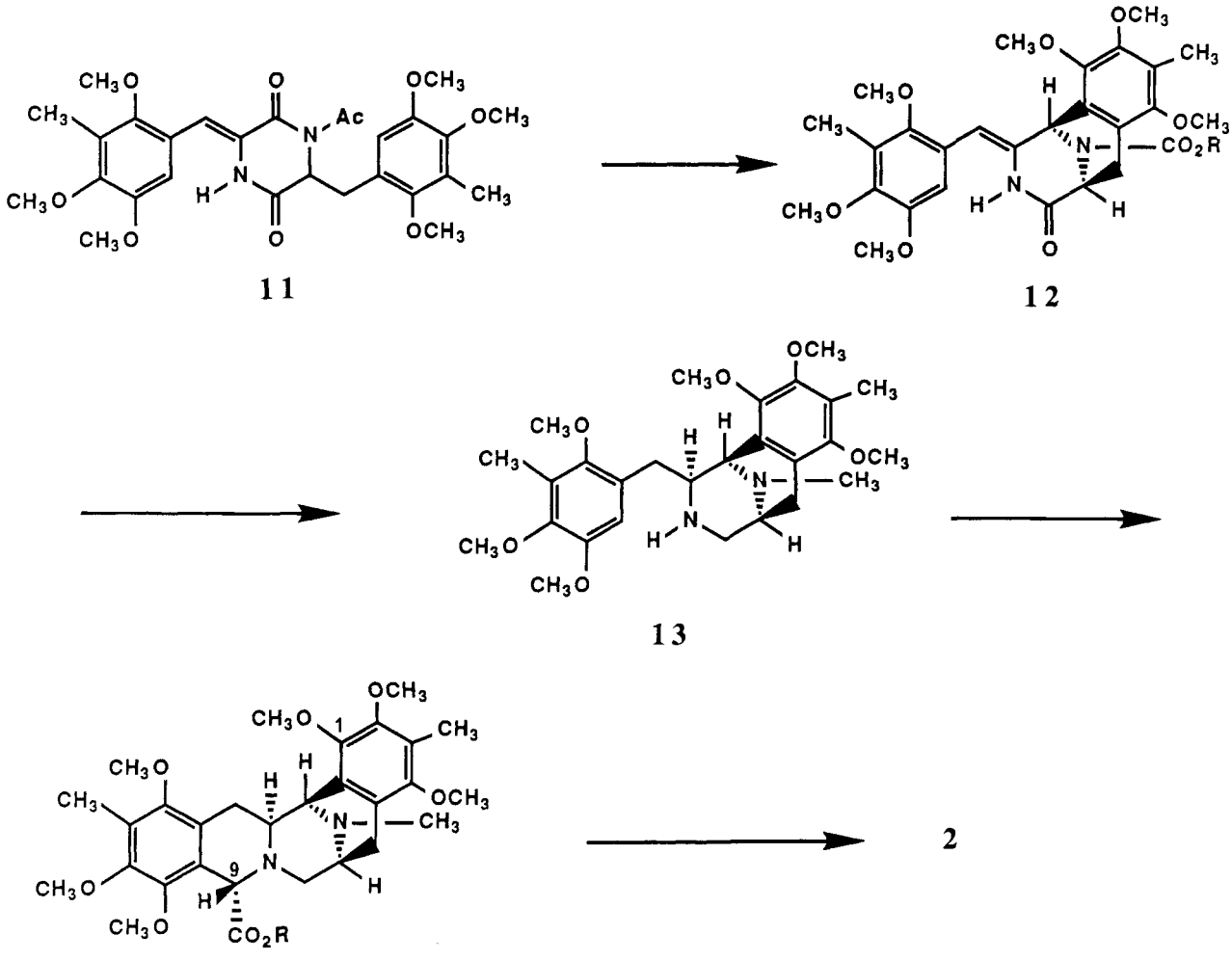
(4) Frincke, J. M.; Faulkner, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 265–269; (erratta) *Ibid.* **1982**, *104*, 5004.

(5) Trowitzsch-Kienast, W.; Irschik, H.; Reichenbach, H.; Wray, V.; Höfle, G. *Liebigs Ann. Chem.* **1988**, 475–481.

(6) Arai, T.; Takahashi, K.; Ishiguro, K.; Mikami, Y. *Gann* **1980**, *71*, 790–796.

0022-3263/88/1953-4295$01.50/0

Scheme I



11 12 13 14 2

(3), the structure of which has been determined by X-ray crystallography. The first total synthesis of (±)-2, based on the double cyclization of the dipeptide, was reported by Fukuyama and Sachleben.[7] Recently, we completed our total synthesis of (±)-2 by a different approach.[8] In this paper, the full account of our synthesis of (±)-saframycin B (2) and related compounds is reported.

The synthetic plan, which utilizes the 2,5-piperazinedione 11[9] as starting material, involves the key transformations outlined in Scheme I: (1) a highly regioselective synthesis of the 1,5-imino-3-benzazocine derivative 12; (2) transformation of 12 into the secondary amine 13 and subsequent modified Pictet–Spengler cyclization leading to the pentacyclic intermediate 14, and (3) epimerization of 14 at C-9 position and subsequent transformation to (±)-2.

Results and Discussion

Benzylation of 11 with benzyl bromide followed by hydrazine hydrate treatment afforded N-benzylated derivative 16 in 94% yield (Scheme II). This material was then converted into the imides 17a–e in 89–94% yield according to the procedure of Grieco.[10] Transformation of the imide 17 into the 1,5-imino-3-benzazocine derivative 12, which is the first key stage in our synthetic plan, began with regioselective reduction of an amide carbonyl group at C-2 position in 17. However, treatment of 17 with other reagents (e.g., sodium cyanoborohydride,[11a] 9-borabicyclo[3.3.1]nonane,[11b] diisobutylaluminum hydride,[11c] cerium chloride–sodium borohydride[11d]), which have been useful for the selective reduction of α,β-unsaturated carbonyl compounds to the corresponding allylic alcohols, did not yield 18 but restored 16 quantitatively. Obviously, an unfavorable hydride attack had occurred. It was our hope

Table I

starting material		yield[a] (%)		yield[a] (%)
17	R	18	16	19
a	$CH(CH_3)_2$	69	7	60[b] (52)[c]
b	CH_3	21	40	64 (16)
c	$CH_2CH(CH_3)_2$	45	37	60 (31)
d	Bn	29	57	58 (17)
e	$C(CH_3)_3$	69	7	

[a] Yields after separation of the crude reaction mixture with chromatography. [b] Yields based on 18. [c] Yields in parentheses were for two steps.

(7) Fukuyama, T.; Sachleben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957–4958.

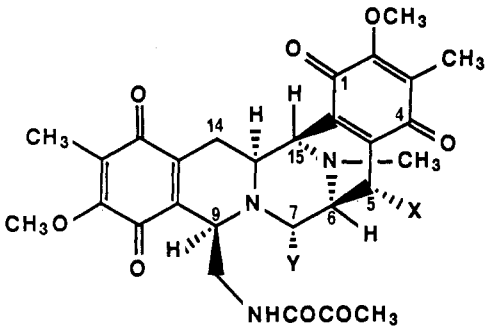
(8) (a) Kubo, A.; Saito, N.; Nakamura, M.; Ogata, K.; Sakai, S. *Heterocycles* **1987**, *26*, 1765–1770. (b) Kubo, A.; Saito, N.; Yamauchi, R.; Sakai, S. *Chem. Pharm. Bull.* **1987**, *35*, 2158–2161.

(9) Kubo, A.; Saito, N.; Yamato, H., Kawakami, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2525–2532.

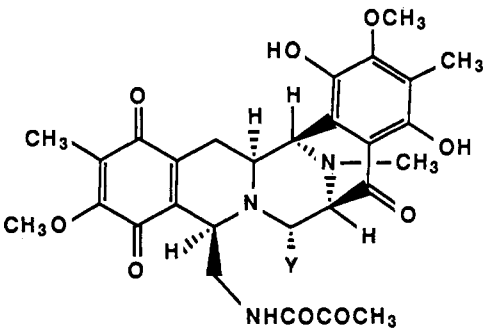
(10) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424–2426.

(11) (a) Hutchins, R. O.; Kandasamy, D. *J. Org. Chem.* **1975**, *40*, 2530–2533. (b) Krishnamurthy, S.; Brown, H. C. *Ibid.* **1977**, *42*, 1197–1201. (c) Wilson, K. E.; Seidner, R. T.; Masamune, S. *J. Chem. Soc.* **1970**, 213–214. (d) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

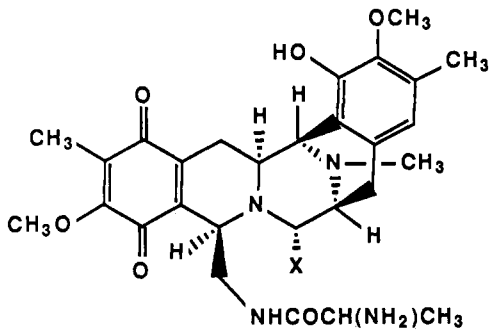
Chart I



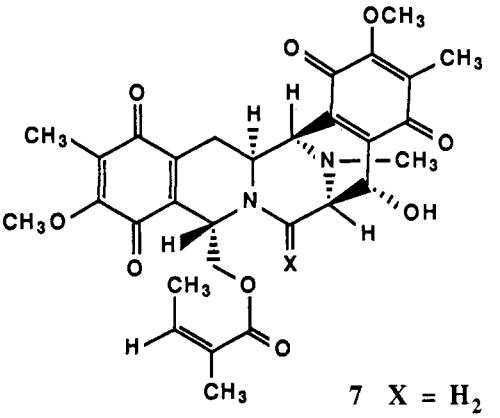
1 X = H, Y = CN
2 X = Y = H
3 X = OCH_3, Y = H



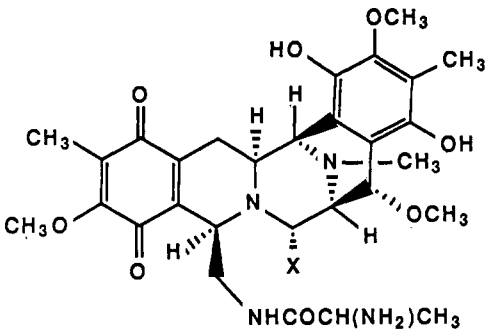
4



5 X = H
6 X = OH



7 X = H_2
8 X = O

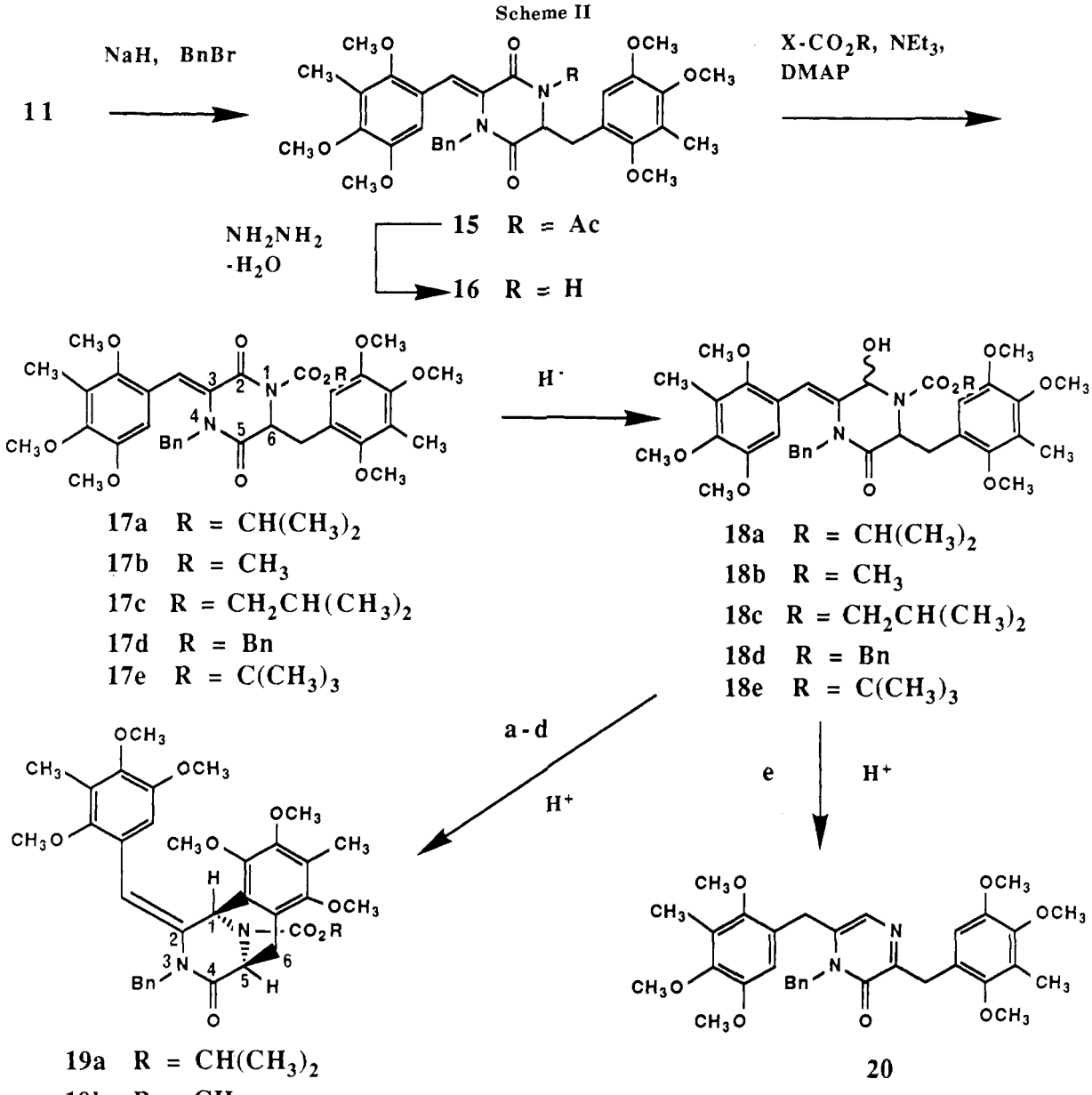


9 X = OH
10 X = H

that the bulky carbamate and the bulky reagent would exert enough steric influence on the course of reduction, thus forcing the reduction of the amide carbonyl (path A in **21**, Scheme III) to occur regioselectively. Conversion of **17** to **18** was therefore carried out by using lithium tri-*tert*-butoxyaluminum hydride[12] (Table I). Cyclization of **18a–d** was effected by treatment with formic acid at 60 °C to afford the 1,5-imino-3-benzazocine derivatives **19a–d** in 58–64% yields. However, after treatment of **18e** under the same conditions no cyclized compound could be isolated; instead, pyrazinone **20** was formed in 53% yield. Treatment of **17a** with lithium tri-*tert*-butoxyaluminum hydride thus afforded the allylic alcohol **18a** (contaminated with a small amount of **16**), which on treatment with formic acid afforded **19a** in 52% overall yield. The *E* stereochemical assignment to **19** is based on ^{1}H NMR spectral evidence. The δ value observed for the methine proton at the C-1 position of compounds **19a–d** (δ 6.77–6.79) indicates that this proton is positioned in the deshielding zone of the aromatic ring of the side chain at the C-2 position and the carbonyl group (vide infra). The probable mechanistic pathways for the formation of *E*-cyclized products **19a–d** from the *Z*-allylic alcohols **18a–d** are shown in Scheme III.

(12) It has been found that this reagent reduces exclusively the less hindered carbonyl group of 3,5-dimethoxyphthalic anhydride: Taub, D.; Girotra, N. N.; Hoffsommer, R. D.; Kuo, C. H.; Slates, H. L.; Weber, S.; Wendles, N. L. *Tetrahedron* **1968**, *24*, 2443–2461.

Scheme II

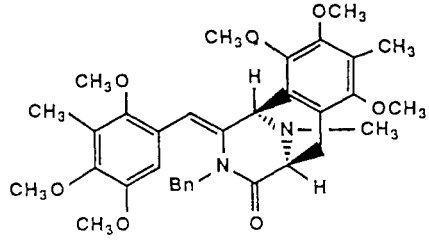


Subsequently we studied the conversion of **19a** into the secondary amine **13**. Reduction of the double bond of **19a**, accompanied by debenzylation, was not possible by using other reagents. Treatment of **19a** with platinum oxide in ethanol gave the cyclohexylmethyl compound **24** in 87% yield.[13] Furthermore, reduction of **19a** with lithium aluminum hydride in THF gave **27** with a maximum yield of only 14%. Accordingly, the sequence of reactions in Scheme IV was studied. Deprotection of **19a** with trifluoroacetic acid and H_2SO_4 gave the secondary amine **25** in quantitative yield. As yet, however, we have not been able to remove the *N*-benzyl group.[14] Methylation of **25** with formaldehyde and formic acid at 70 °C for 1 h gave the tricyclic lactam **26** in 96% yield. The stereochemical structure of **26** was confirmed by X-ray crystallographic analysis (Figure 1). This explaines why H-1 is strongly deshielded in the ^1H NMR spectra of compounds **19a–d**, **26** (δ 5.41), and **25** (δ 5.53).[15]

(13) A benzyl derivative has been used to protect a pyrrole, but hydrogenolysis of the benzyl derivative led to a cyclohexyl compound: Cleanthis, M. J.; Froussions, C.; Evans, D. A. *J. Chem. Soc., Chem. Commun.* **1976**, 472–473.

(14) Acid-catalyzed removal of the benzyl group with H_2SO_4 in trifluoroacetic acid was employed by Evans in his synthesis of porphobilinogen.[13] Surprisingly, **19a** resisted the debenzylation.

(15) The ^1H NMR spectrum of i, which was prepared from **11** in eight steps (Kubo, A.; Saito, N.; Nishioka, Y., unpublished results), showed the H-1 peak at higher filed (δ 4.55).



i

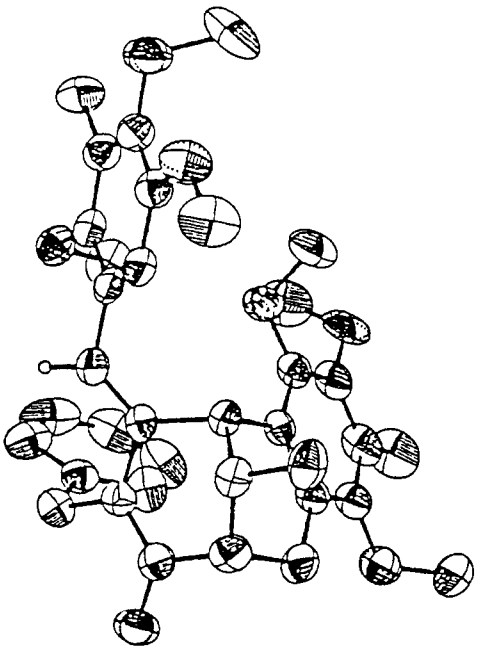


Figure 1. ORTEP drawing of compound **26**.

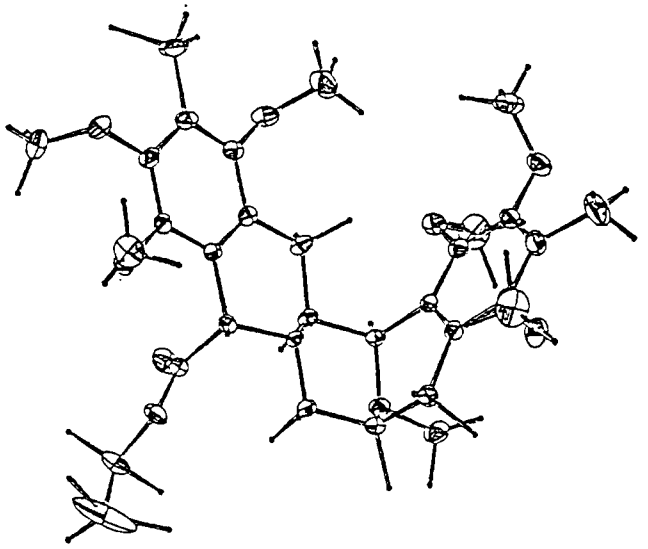
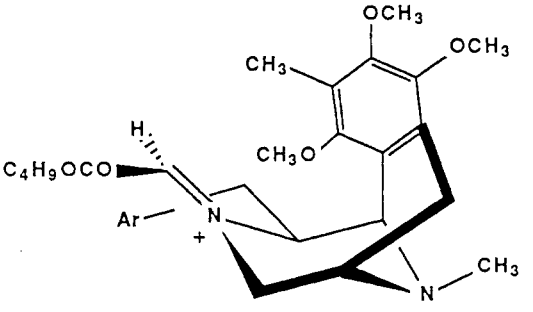


Figure 2. ORTEP drawing of compound **32**.

Reduction of **26** with aluminum hydride at 0 °C in THF for 1 h gave the unstable enamine **27** in 93% yield. Reduction of the double bond of **27** through the action of hydrogen (4 atm) on 20% palladium on carbon[16] in ethanol at 80 °C for 24 h occurred cleanly from the α face accompanied by the debenzylation to afford the secondary amine **13** in 99% yield.

The next stage of the investigation was to establish a method to construct a 1-substituted tetrahydroisoquinoline from **13**. The amine **13** was then condensed with phthalimidoacetyl chloride[17] in the presence of triethylamine in dichloromethane to give **28** in 89% yield. Bischler–Napieralski reaction of **28** gave only polar polymeric material. In addition, attempts under a variety of conditions to cyclize the amide **29**, which was readily prepared from **13** with ethyl oxalyl chloride in 74% yield, were fruitless. This problem was solved by using an amino acetal intermediate.[18] The reaction of **13** with a large



33

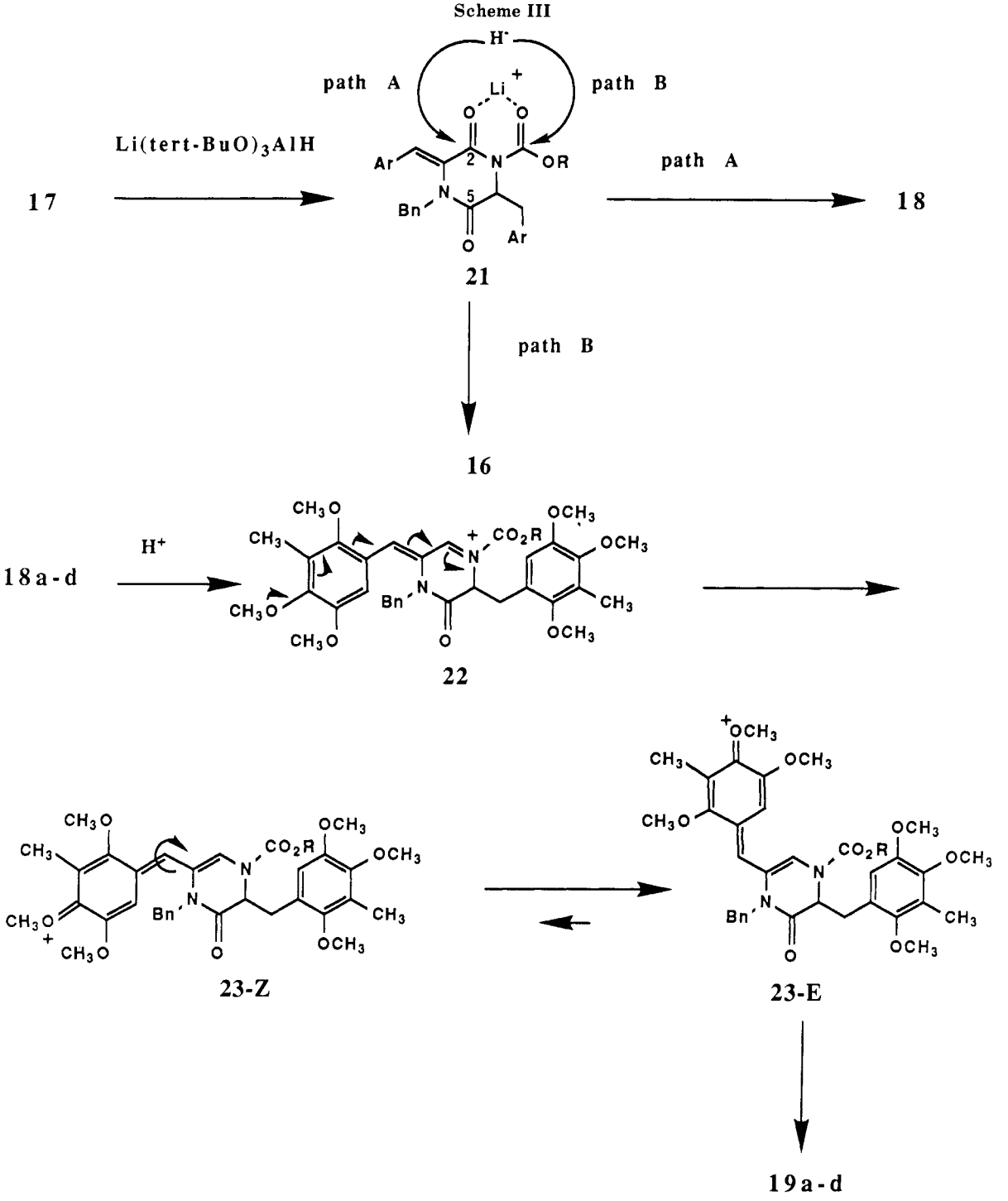
Figure 3.

(16) Similar conditions were employed by Nakatsuka in his synthesis of bicyclomycin: Nakatsuka, S.; Goto, T. *Heterocycles* **1984**, *21*, 61–73.

(17) (a) Shiotani, S.; Mitsuhashi, K. *Yakugaku Zasshi* **1966**, *86*, 169–173. (b) Sheehan, J. C.; Frank, V. S. *J. Am. Chem. Soc.* **1949**, *71*, 1856–1861.

(18) Kubo, A.; Saito, N.; Kawakami, N.; Matsuyama, Y.; Miwa, T. *Synthesis* **1987**, 824–827.

Scheme III



excess of butyl glyoxylate[19] in the presence of K_2CO_3 in butanol at 25 °C for 24 h gave the *O,N*-acetal **30**, which was subsequently treated with trifluoroacetic acid at 25 °C for 1 h to provide the desired pentacyclic product **31** in 70% overall yield (Scheme V). The stereochemistry of **31** was undetermined at this stage. *n*-Butyl ester **31** was then transformed to ethyl ester **32** (H_2SO_4, EtOH). Its structure was determined by X-ray crystallography (Figure 2) and revealed that the stereochemistry of the C-9 position was epimeric to that of natural saframycins. Comparison of the ^1H NMR and ^{13}C NMR spectra of **31** and **32** (see Experimental Section) indicated that their stereochemistries were identical. The stereochemical course of this reaction could be rationalized by proceeding through (*E*)-imminium isomer **33** (Figure 3). Thus, this stereoselective cyclization would proceed from the less hindered α face. Numerous efforts for epimerization of **31** at the C-9 position under basic conditions were totally unsuccessful. Another approach was based on the oxidation of **31** followed by reduction with sodium borohydride, which turned out to give the desired compound **34**.[20] Thus, epimerization at the C-9 position in **31** with mercury acetate (10 equiv) in 5% aqueous AcOH at 90 °C for 2 h followed by reduction with sodium borohydride (hydride attack from the less hindered α side) afforded the desired ester **34** in 70.6% yield (5.6% yield of **31** was recovered) along with the decarbobutoxylated compound **35** in 13%

(19) Kelly, T. R.; Schmidt, T. E.; Haggerty, J. G. *Synthesis* **1972**, 544–545.

(20) Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1962**, *84*, 4914–4919.

yield, which was synthesized alternatively from **13** in two steps.[18] The ^1H NMR spectrum of **34** displayed H-9 as a singlet at δ 4.09, and H-14a as a doublet of doublet of doublets at δ 2.84, whereas the ^1H NMR spectrum of **31** showed the H-9 peak (δ 4.56, s) and the H-14a (δ 3.57, ddd) at lower fields. The remarkable differences of the chemical shifts of the methine protons in **31** and **34** must arise from the stereochemical interrelationships among the side chains at C-9 and H-14a. Reduction of **34** with lithium aluminum hydride afforded the alcohol **36** in 77% yield. Although **36** could not be transformed to the corresponding amine **38** via the extremely unstable halide or tosylate of **36**,[21] this transformation was accomplished by utilizing the Mitsunobu procedure.[22] Treatment of **36** with diethyl azodicarboxylate, triphenylphosphine, and phthalimide in THF at 25 °C for 3 h to give the imide **37** was followed by cleavage of the phthaloyl group with hydrazine hydrate to afford the amine **38**, which was acylated with pyruvoyl chloride[23] to give the pyruvamide **39** in 76% overall yield.

Conversion of the polymethoxyarene **39** to a bis-*p*-quinone system, the final stage in the total synthesis, was initiated by oxidative demethylation (Scheme VI). After numerous efforts under a variety of conditions,[24] the direct oxidative demethylation of **39** with 10 M HNO_3 was achieved.[26] The reaction of **39** with 10 M HNO_3 at 25 °C for 1 h afforded (±)-saframycin B (**2**) in 1.5% yield. However, the major products were the monoquinones **40** and **41** obtained in 12% and 27% yields, respectively. The proposed structures of these quinones were established by comparison of spectral data with that of saframycin B (**2**) (vide infra). Methylation of **41** with diazomethane afforded **40** in 81% yield. The fact that yield of this process was disappointingly low and that it proved to be exceedingly troublesome prompted us to examine the oxidative demethylation of the corresponding phenols **42**[27] (54%) and **43** (16%), which were prepared from **39** via partial demethylation with boron tribromide in dichloromethane at −78 °C for 1 h. The mixture of the phenols **42** and **43** was subjected to oxidative demethylation with ceric ammonium nitrate at 0 °C for 1 h to afford (±)-saframycin B (**2**) and the monoquinone **45** in 17% and 45% yields, respectively. Assignment of the monoquinones **40**, **41**, and **45** was made by 400-MHz ^1H NMR analysis. In the ^1H NMR spectra of **40** and **41**, the diagnostic homoallylic coupling between H-9 and H-14 over five bonds was observed, together with the data of natural compounds (for example, **2**).[28,29] On the other hand, this coupling was negligible in the spectra of the pentacyclic methoxyarenes (**31**, **32**, **34–39**) and the monoquinone **45**. After extensive investigation of the reaction conditions, the following procedure was found to be best in terms of product yield and reproducibility of the reaction: Treatment of **39** in dichloromethane in the presence of 4.0 equiv of boron tribromide at −78 °C for 1 h and then with 10 N HNO_3 provided (±)-saframycin B (**2**) in 41% overall yield. The synthetic saframycin B was identical with the natural one on comparison of spectroscopic ^1H NMR, ^{13}C NMR, IR, UV, MS, and TLC data.

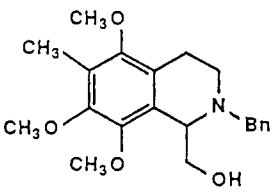
In summary, we have achieved the total synthesis of racemic saframycin B, in 20 steps from 2,5-piperazinedione **11** (ca. 5% overall yield). Efforts to refine the synthesis of **2** and to prepare analogues for biological screening and mechanism of action studies are under way.

Experimental Section

All melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. UV spectra were determined in methanol. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ at 400 and 100 MHz, respectively. All reactions were conducted under an argon atmosphere. Dry solvents and reagents were obtained by using standard procedures. Anhydrous sodium sulfate was used for drying organic solvent extracts, and removal of the solvent was performed with a rotary evaporator and finally under high vacuum. Column chromatography was performed with E. Merck silica gel 60 (70–230 mesh). Elemental analyses were obtained by using a Perkin-Elmer Model 240B elemental analyzer.

(*Z*)-4-Benzyl-6-[(2,4,5-trimethoxy-3-methylphenyl)methyl]-3-[(2,4,5-trimethoxy-3-methylphenyl)methylene]-2,5-piperazinedione (16). Sodium hydride (50% oil dispersion, washed with dry hexane three times, 1.0 g, 41.7 mmol) was added to a stirred solution of **11** (21.76 g, 40.1 mmol) in dry DMF (200 mL), and stirring was continued for 30 min at 0 °C. Benzyl bromide (4.8 mL, 40.4 mmol) in dry DMF (50 mL) was added

(21) A preliminary experiment for was carried out by employing the readily available model compound ii, which was obtained from butyl 2-benzyl-5,7,8-trimethoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate[18] ($LiAlH_4$, THF; 72%). The replacement of a hydroxy group of ii using carbon tetrachloride and triphenylphosphine failed: Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1972**, *37*, 2289–2299. Treatment of ii with mesyl chloride or tosyl chloride in pyridine caused decomposition of the starting material.

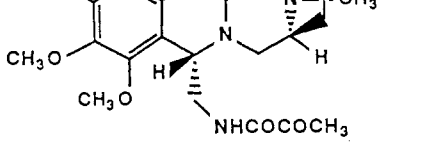


ii

(22) Mitsunobu, O. *Synthesis* **1981**, 1–28.

(23) Ottenheijm, H. C. J.; Tuhuis, de Man, J. H. M. *Synthesis* **1975**, 163–164.

(24) As preliminary experiment, the oxidative demethylation of **39** employing usual agents (e.g., ceric ammonium nitrate,[25a] argentic oxide,[25b] ceric ammonium nitrate–2,4,6-pyridine-tricarboxylic acid system,[25c] silver(II) dipicolinate,[25d] and nitric acid impregnated manganese dioxide[25e]) failed; only starting material was recovered. In contrast, the oxidative demethylation of 9-*epi*-pyruvamide iii, with the above reagent, were unsuccessful, afforded only polar polymeric material: Kubo, A.; Saito, N.; Yamauchi, R., unpublished results.



iii

(25) (a) Jacob, P., III; Callery, P. S.; Shulgin, A. T.; Castagnoli, N. *J. Org. Chem.* **1976**, *41*, 3627–3629. (b) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227–231. (c) Syper, L.; Kloc, K.; Młochowski, J. *Tetrahedron* **1980**, *36*, 123–129. (d) Kloc, K.; Młochowski, J.; Syper, L. *Chem. Lett.* **1980**, 725–728. (e) Cassis, R.; Valderrama, A. *Synth. Commun.* **1983**, *13*, 347–356.

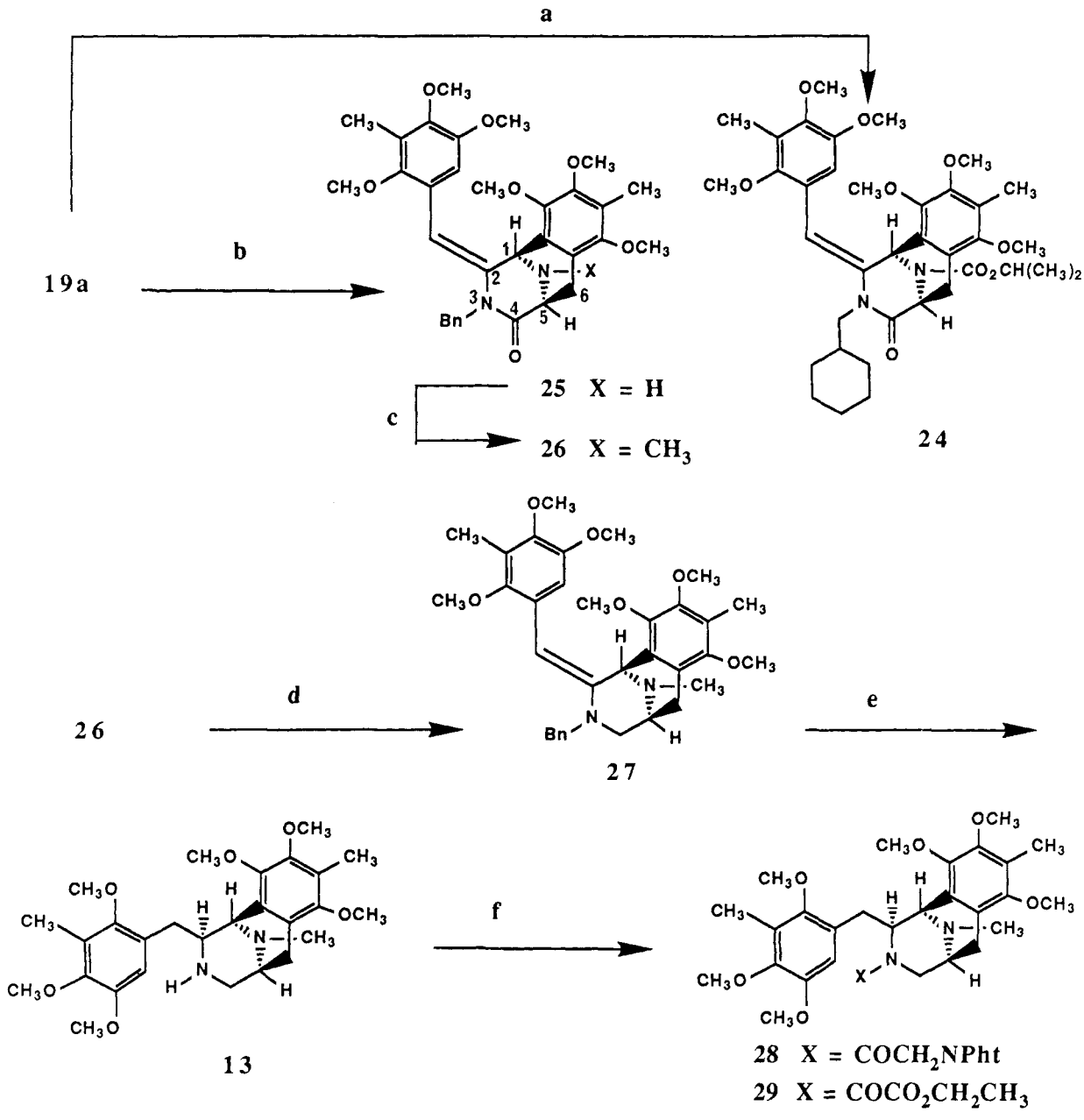
(26) Musgrave, O. C. *Chem. Rev.* **1969**, *69*, 499–531.

(27) The orientations of the methyl ether substituents in the aromatic ring of the phenol **42** was undecided yet. Acetylation of **42** with acetic anhydride in pyridine afforded the acetate **44** in 78% yield (see Experimental Section).

(28) A detailed analysis of the high-field (400 MHz) ^1H NMR spectra of saframycins A (**1**) and C (**3**) have been reported. (a) Lown, L. W.; Joshua, A. V.; Chen, H. H. *Can. J. Chem.* **1981**, *59*, 2945–2952. (b) Haruyama, H.; Kurihara, H.; Kondo, M. *Chem. Pharm. Bull.* **1985**, *33*, 905–915.

(29) The characteristic features of resulting molecular ion species and fragment ions of the quinones **40** and **45** under liquid SIMS conditions using various matrices has recently been studied: Harada, K. I.; Masuda, K.; Suzuki, M.; Saito, N.; Kubo, A., submitted to *Org. Mass Spectrom.* This result was also supported by NMR studies.

Scheme IV[a]



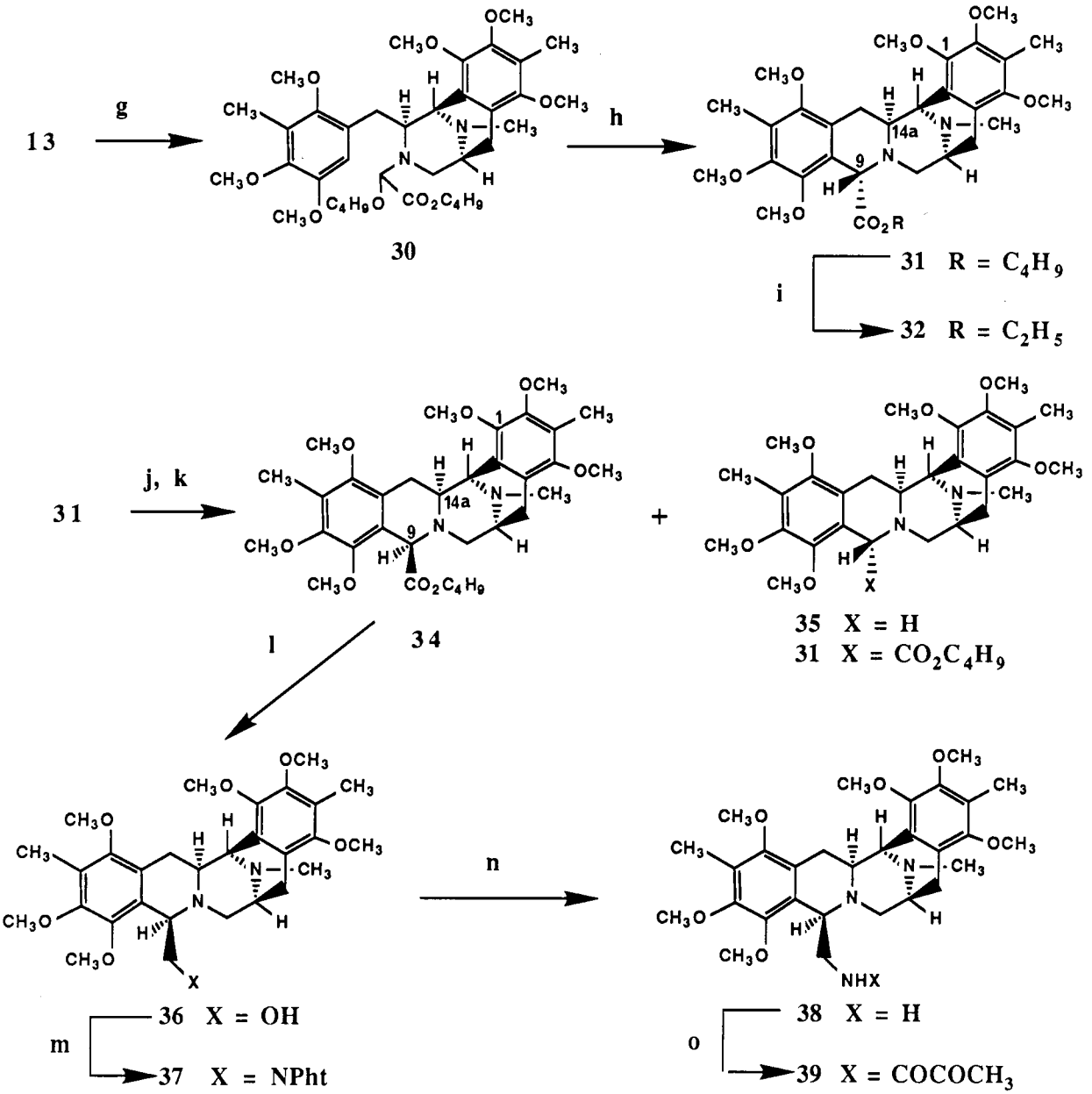
[a] (a) PtO_2, H_2, EtOH, room temperature (87%); (b) H_2SO_4, trifluoroacetic acid, room temperature (ca. 100%); (c) HCHO, HCO_2H, 70 °C (96%); (d) AlH_3, THF, 0 °C (93%); (e) 20% Pd–C, H_2 (4 atm), EtOH, 80 °C (99%); (f) X = $COCH_2NPht$: $ClCOCH_2NPht$, NEt_3, CH_2Cl_2, 0 °C (89%); X = $COCO_2Et$: $ClCOCO_2Et$, NEt_3, CH_2Cl_2, 0 °C (74%).

during 10 min, and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was concentrated in vacuo, and the residue was diluted with water (100 mL) and extracted with benzene (150 mL × 3). The combined extracts were washed with water (100 mL), dried, and concentrated in vacuo to furnish **15** (25.4 g, 100%) as a pale yellow oil, which was used for the next step without further purification. An analytical sample was obtained by column chromatography (silica gel, elution with 1:10 AcOEt–benzene) as a colorless amorphous powder whose spectra were identical with those of an authentic sample described earlier.[9]

Hydrazine monohydrate (2.1 mL, 43.3 mmol) was added to a stirred solution of the crude **15** (25.4 g, 43.5 mmol) in DMF (200 mL) and the resulting solution was stirred for 1 h at room temperature. The reaction mixture was concentrated in vacuo to give **16** as a colorless solid, recrystallization of which from acetone afforded pure **16** (22.7 g, 94% from **11**) as colorless prisms. mp 170–172 °C (lit.[9] mp 170–172 °C).

(*Z*)-4-Benzyl-1-[(isopropyloxy)carbonyl]-6-[2,4,5-trimethoxy-3-methylphenyl)methyl]-3-[(2,4,5-trimethoxy-3-methylphenyl)methylene]-2,5-piperazinedione (17a). A solution of **16** (10.84 g, 20 mmol), triethylamine (5.6 mL, 40 mmol), and 4-(dimethylamino)pyridine (4.9 g, 40 mmol) in dry dichloromethane (200 mL) was cooled with ice–water, and isopropyl chloroformate (9.11 mL, 80 mmol) was added dropwise over 10 min. The solution was stirred for 1 h at 25 °C. The organic layer was washed with 1 N HCl (30 mL × 2), dried, and concentrated in vacuo to give **17a** as a colorless solid, recrystallization of which from AcOEt–ether afforded pure **17a** (12.71 g, 94%) as colorless prisms: mp 137–138.5 °C; IR (KBr) 1780, 1730, 1690 cm^{-1}; UV λ_{max} (log ϵ) 252 (4.02), 288 (3.93), 340 (4.12) nm; ^1H NMR δ 1.21 (3 H, d, J = 7 Hz, $CHCH_3$), 1.28 (3 H, d, J = 7 Hz, $CHCH_3$), 1.98 (3 H, s, Ar CH_3), 2.16 (3 H, s, Ar CH_3), 3.21 (2 H, d, J = 7 Hz, CH_2), 3.45, 3.61, 3.61, 3.77, 3.85, 3.90 (each 3 H, s, OCH_3), 4.15 (1 H, d, J = 15 Hz, NCH), 4.95 (1 H, sep, J = 7 Hz, OCH), 5.17 (1 H, t, J = 7 Hz, H-6), 5.25 (1 H, d, J = 15 Hz, NCH), 6.49 (1 H, s), 6.76 (1 H, s), 6.76–6.96 (2 H, m), 7.06–7.20 (3 H, m), 7.26 (1 H, s); ^{13}C NMR δ 9.3 (q), 9.7 (q), 21.5 (q), 21.6 (q), 32.5 (t), 47.7 (t), 55.9 (q), 56.1 (q), 59.9 (q), 60.1 (q), 60.4 (q), 60.8 (d), 61.8 (q), 71.8 (d), 110.6 (d), 111.9 (d), 120.2 (d), 121.1 (s), 122.5 (s), 125.5

Scheme V[a]



[a] (g) $CHOCO_2Bu$, K_2CO_3, BuOH, room temperature; (h) CF_3CO_2H, room temperature (70% from **13**); (i) H_2SO_4, EtOH, reflux (72%); (j) $Hg(OAc)_2$, 5% AcOH–H_2O, 90 °C; (k) $NaBH_4$, EtOH–H_2O, room temperature (**34**, 71%; **35**, 13%, **31**, 5.6% from **31**); (l) $LiAlH_4$, THF, reflux (77%); (m) DEAD, PhtNH, PPh_3, THF, room temperature; (n) NH_2NH_2–H_2O, EtOH, reflux (o) $ClCOCOCH_3$, DMAP, NEt_3, CH_2Cl_2, room temperature (76% from **36**).

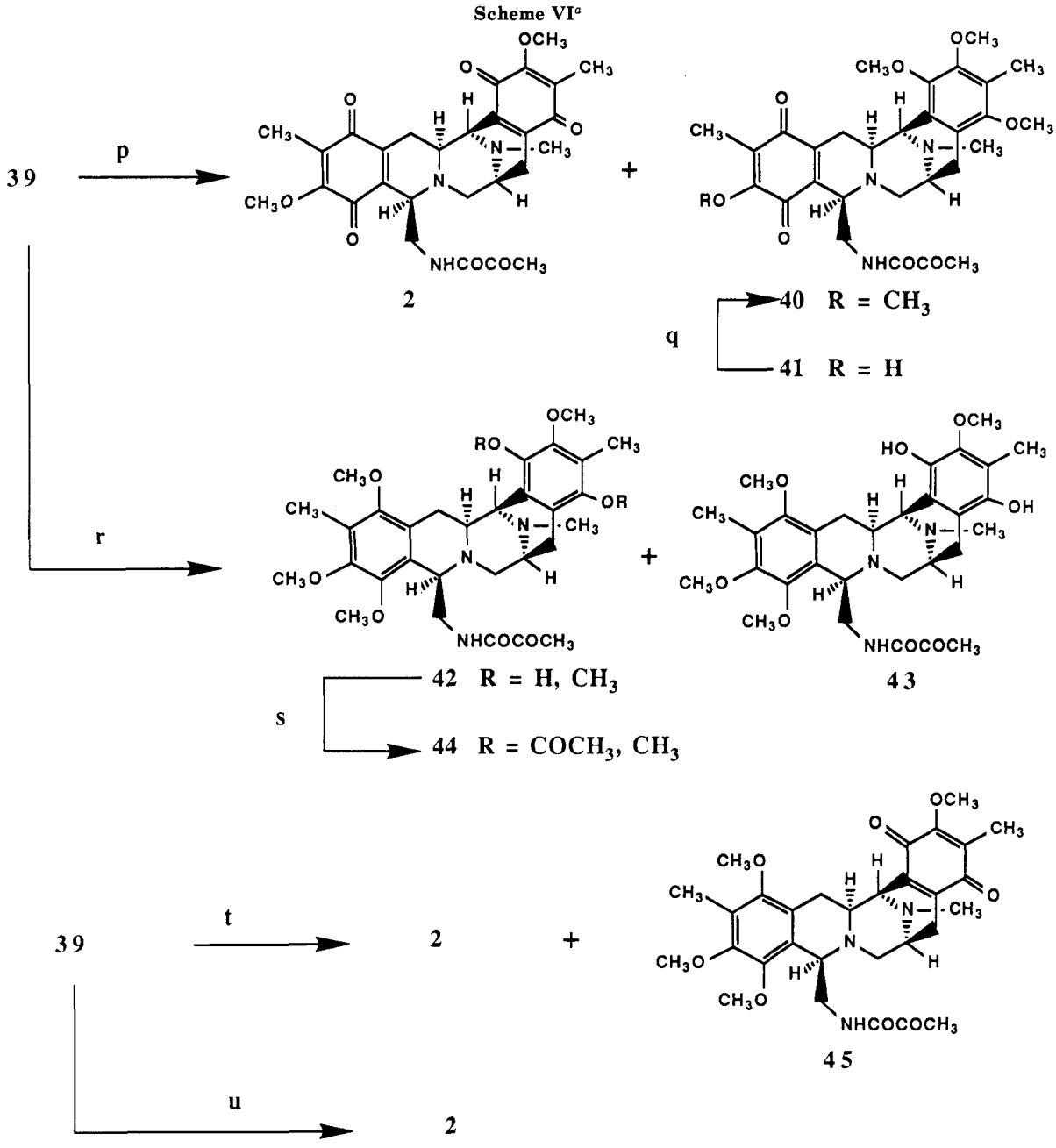
(s), 125.5 (s), 125.7 (s), 127.5 (d), 127.7 (d), 128.4 (d), 128.6 (s), 135.9 (s), 147.5 (s), 148.9 (s), 149.1 (s), 149.6 (s), 151.0 (s), 151.6 (s), 152.6 (s), 162.0 (s), 166.9 (s); MS, *m/z* (relative intensity) 676 (M^+, 15), 645 (28), 559 (28), 195 (100), 91 (19). Anal. Calcd for $C_{37}H_{44}N_2O_{10}$: C, 65.66; H, 6.55; N, 4.14. Found: C, 65.40; H, 6.60; N, 4.05.

General Procedure for the Preparation of the (*Z*)-1-(Alkoxycarbonyl)-4-benzyl-6-[(2,4,5-trimethoxy-3-methylphenyl)methyl]-3-[(2,4,5-trimethoxy-3-methylphenyl)methylene]-2,5-piperazinediones 17b–e. The same procedure as described above but using **16** (0.59 g, 1 mmol), triethylamine (0.28 mL, 2 mmol), 4-(dimethylamino)pyridine (245 mg, 2 mmol), and the acylating reagent (4 mmol) in dry dichloromethane (10 mL) afforded the residue, which was purified as indicated to afford pure **17b–e**.

(*Z*)-4-Benzyl-1-(methoxycarbonyl)-6-[(2,4,5-trimethoxy-3-methylphenyl)methyl]-3-[(2,4,5-trimethoxy-3-methylphenyl)methylene]-2,5-piperazinedione (17b) was prepared as described above but using methyl chloroformate (0.31 mL, 4 mmol). The crude reaction mixture was purified by recrystallization from AcOEt–ether to afford **17b** (594 mg, 92%) as colorless prisms: mp 153.5–155 °C; IR (KBr) 1775, 1720, 1680 cm^{-1}; UV λ_{max} (log ϵ) 252 (4.01), 288 (3.90), 342 (4.10) nm; ^1H NMR δ 1.99 (3 H, s, Ar CH_3), 2.16 (3 H, s, Ar CH_3), 3.22 (2 H, d, J = 7 Hz, CH_2), 3.44, 3.61, 3.81, 3.83, 3.85, 3.91 (each 3 H, s, OCH_3), 4.17 (1 H, d, J = 14 Hz, NCH), 5.20 (1 H, t, J = 7 Hz, H-6), 5.29 (1 H, d, J = 14 Hz, NCH), 6.51 (1 H, s), 6.79 (1 H, s), 6.78–6.94 (2 H, m), 7.04–7.22 (3 H, m), 7.23 (1 H, s); MS, *m/z* (relative intensity) 648 (M^+, 6), 617 (15), 573 (41), 196 (12), 195 (100), 165 (13), 92 (20). Anal. Calcd for $C_{35}H_{40}N_2O_{10}$: C, 64.80; H, 6.22; N, 4.32. Found: C, 64.79; H, 6.25; N, 4.26.

(*Z*)-4-Benzyl-1-(isobutoxycarbonyl)-6-[(2,4,5-trimethoxy-3-methylphenyl)methyl]-3-[(2,4,5-trimethoxy-3-methylphenyl)methylene]-2,5-piperazinedione (17c) was prepared as described above but using isobutyl chloroformate (0.52 mL, 4 mmol). The crude reaction mixture was purified by recrystallization from AcOEt–ether to afford **17c** (614 mg, 89%) as colorless prisms: mp 127.5–129 °C; IR (KBr) 1710, 1685 cm^{-1}; UV λ_{max} (log ϵ) 258 (4.33), 282 (4.13), 340 (4.03) nm; ^1H NMR δ 0.98 (6 H, d, J = 7 Hz, $CH(CH_3)_2$), 1.97 (3 H, s, Ar CH_3), 2.08 (1

Scheme VI[a]



[a] (p) 10 M HNO_3, room temperature (**2**, 1.5%; **40**, 12%; **41**, 27%); (q) CH_2N_2, ether, 0 °C (81.3%); (r) BBr_3, CH_2Cl_2, −78 °C to 0 °C (**42**, 54%; **43**, 16%); (s) Ac_2O, pyridine, room temperature (78%); (t) conditions (r), and then ceric ammonium nitrate, CH_3CN–H_2O, 0 °C (**2**, 17%; **45**, 45% from **39**); (u) conditions (r), and then 10 M HNO_3, room temperature (41% from **39**).

H, m, C*H*$(CH_3)_2$), 2 .17 (3 H, s, Ar CH_3), 3.15 (2 H, d, J = 7 Hz, CH_2), 3.43, 3.58, 3.58, 3.75, 3.83, 3.88 (each 3 H, s, OCH_3), 3.93 (2 H, d, J = 7 Hz, OCH_2), 4.14 (1 H, d, J = 14 Hz, NCH), 5.13 (1 H, t, J = 7 Hz, H-6), 5.23 (1 H, d, J = 14 Hz, NCH), 6.43 (1 H, s), 6.72 (1 H, s), 6.77 (2 H, m), 7.15 (4 H, m); MS, m/z (relative intensity) 690 (M^+, 15), 660 (16), 659 (37), 196 (13), 195 (100), 165 (12), 91 (20). Anal. Calcd for $C_{38}H_{46}N_2O_{10}$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.19; H, 6.75; N, 4.09.

(*Z*)-4-Benzyl-1-[(benzyloxy)carbonyl]-6-[(2,4,5-trimethoxy-3-methylphenyl)methyl]-3-[(2,4,5-trimethoxy-3-methylphenyl)methylene]-2,5-piperazinedione (17d) was prepared as described above but using benzyl chloroformate (0.57 mL, 4 mmol). The crude reaction mixture was purified by recrystallization from AcOEt–ether to afford **17d** (615 mg, 85%) as colorless prisms: mp 127.5–128 °C; IR (KBr) 1770, 1715, 1685 cm^{-1}; UV λ_{max} (log ϵ) 287 (3.94), 344 (4.15) nm; ^1H NMR δ 1.96 (3 H, s, Ar CH_3), 2.19 (3 H, s, Ar CH_3), 3.25 (2 H, d, J = 7 Hz, CH_2), 3.47, 3.57, 3.62, 3.69, 3.89, 3.95 (each 3 H, s, OCH_3), 4.20 (1 H, d, J = 14 Hz, NCH), 5.16 (1 H, d, J = 13 Hz, OCH), 5.21 (1 H, t, J = 7 Hz, H-6), 5.28 (1 H, d, J = 14 Hz, NCH), 5.36 (1 H, d, J = 13 Hz, OCH), 6.43 (1 H, s), 6.82 (1 H, s), 6.78–6.96 (2 H, m), 7.08–7.20 (3 H, m), 7.27 (1 H, s), 7.40 (5 H, s); MS, m/z (relative intensity) 724 (M^+, 12), 693 (10), 649 (18), 559 (12), 196 (13), 195 (100), 165 (10), 91 (35); high-resolution MS calcd for $C_{41}H_{44}N_2O_{10}$ 724.2996, found 724.2976. Anal. Calcd for $C_{41}H_{44}N_2O_{10}$·$CHCl_3$: C, 59.76; H, 5.37; N, 3.32. Found: C, 59.93; H, 5.36; N, 3.28.

(*Z*)-4-Benzyl-1-(*tert*-butoxycarbonyl)-6-[(2,4,5-trimethoxy-3-methylphenyl)methyl]-3-[(2,4,5-trimethoxy-3-methylphenyl)methylene]-2,5-piperazinedione (17e) was prepared as described above but using di-*tert*-butyl dicarbonate (0.92 mL, 4 mmol). The crude reaction mixture was purified by recrystallization from AcOEt–ether to afford **17e** (634 mg, 92%) as colorless prisms: mp 123–124.5 °C; IR (KBr) 1770, 1720, 1680 cm^{-1}; UV λ_{max} (log ϵ) 289 (4.01), 340 (4.18) nm; ^1H NMR δ 1.48 (9 H, s, $C(CH_3)_3$), 2.06 (3 H, s, Ar CH_3), 2.12 (3 H, s, Ar CH_3), 3.24 (2 H, d, J = 8 Hz, CH_2), 3.51, 3.67, 3.70, 3.84, 3.91, 3.95 (each 3 H, s, OCH_3), 4.19 (1 H, d, J = 14 Hz, NCH), 5.17 (1 H, t, J = 8 Hz, H-6), 5.27 (1 H, d, J = 14 Hz, NCH), 6.54 (1 H, s), 6.78 (1 H, s), 6.82–6.96 (2 H, m), 7.08–7.32 (3 H, m), 7.13 (1 H, s); MS,

m/z (relative intensity) 690 (M^+, 1), 590 (15), 560 (37), 559 (100), 195 (72), 165 (11), 91 (24). Anal. Calcd for $C_{38}H_{46}N_2O_{10}$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.85; H, 6.70; N, 4.07.

(*E*)-3-Benzyl-2-[(2,4,5-trimethoxy-3-methylphenyl)-methylene]-7,9,10-trimethoxy-8-methyl-4-oxo-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine-11-carboxylic Acid Isopropyl Ester (19a). A stirred solution of **17a** (12.17 g, 18 mmol) in dry THF (200 mL) was cooled with ice–water, and lithium tri-*tert*-butoxyaluminum hydride (13.7 g, 54 mmol) was added over 15 min. After continued stirring at the same temperature for 1 h, the reaction mixture was quenched by addition of water (5 mL). The reaction mixture was filtered through a Celite pad, which was then washed with chloroform (200 mL), and the combined filtrates were concentrated in vacuo. The crude diastereomeric mixture of the allylic alcohols **18a** (along with **16**) obtained were used for the next step without isolation. A solution of the above mixture (**16** and **18a**) in formic acid (150 mL) was heated at 60 °C for 1 h. The reaction mixture was diluted with water (150 mL) and extracted with chloroform (150 mL × 3). The combined organic extracts were washed with 10% NH_4OH (100 mL) and then with water (100 mL), dried, and concentrated in vacuo to give the residue. Chromatography on a silica gel (160 g) column with hexane–AcOEt (5:1–3:1) as the eluent gave **19a** as colorless solid, recrystallization of which from AcOEt–ether afforded pure **19a** (6.18 g, 52%) as colorless prisms. Further elution with AcOEt–MeOH (8:1) gave **16** (743 mg, 7%) as colorless prisms whose spectra were identical with those of an authentic sample obtained as above. Compound **19a**: mp 176.5–178 °C; IR (KBr) 1705, 1670, 1640 cm^{-1}; UV λ_{max} (log ϵ) 274 (4.22), 302 (4.04) nm; ^1H NMR δ 1.26 (3 H, d, J = 7 Hz, $CHCH_3$), 1.28 (3 H, d, J = 7 Hz, $CHCH_3$), 2.14 (3 H, s, Ar CH_3), 2.16 (3 H, s, Ar CH_3), 2.84, 2.95 (each 3 H, s, OCH_3), 3.10 (1 H, dd, J = 16, 7 Hz, H-6α), 3.29 (1 H, d, J = 16 Hz, H-6β), 3.42, 3.67, 3.87, 3.96 (each 3 H, s, OCH_3), 4.48 (1 H, d, J = 16 Hz, NCH), 5.01 (1 H, sep, J = 7 Hz, OCH), 5.20 (1 H, d, J = 7 Hz, H-5), 5.66 (1 H, d, J = 16 Hz, NCH), 6.06 (1 H, s, C=CH), 6.56 (2 H, m), 6.77 (1 H, s, H-1), 6.88–7.08 (3 H, m), 7.48 (1 H, s); ^{13}C NMR δ 9.3 (q), 9.3 (q), 22.2 (q), 22.2 (q), 28.2 (t), 43.8 (t), 45.8 (d), 53.5 (d), 56.6 (q), 59.1 (q), 59.6 (q), 59.9 (q), 60.1 (q), 60.3 (q), 69.6 (d), 107.6 (d), 110.3 (d), 121.7 (s), 124.7 (s), 125.1 (s), 125.2 (s), 125.4 (s), 126.7 (d), 126.9 (d), 128.4 (d), 134.7 (s), 136.4 (s), 146.5 (s), 146.9 (s), 149.2 (s), 150.3 (s), 150.7 (s), 152.7 (s), 152.9 (s), 168.4 (s); MS, m/z (relative intensity) 660 (M^+, 100), 278 (17), 234 (33), 204 (13), 91 (17), 43 (11). Anal. Calcd for $C_{37}H_{44}N_2O_9$: C, 67.25; H, 6.71; N, 4.24. Found: C, 67.05; H, 6.73; N, 4.19.

(*E*)-3-Benzyl-2-[(2,4,5-trimethoxy-3-methylphenyl)-methylene]-7,9,10-trimethoxy-8-methyl-4-oxo-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine-11-carboxylic Acid Methyl Ester (19b) was prepared by the two-step reaction as described above from **17b** (324 mg, 0.5 mmol). Column chromatography of the crude reaction mixture on silica gel gave **19b** and **16** in yields of 16%, and 40%, respectively. Compound **19b**: mp 156.5–158 °C (AcOEt–ether); IR (KBr) 1700, 1690, 1670, 1630 cm^{-1}; UV λ_{max} (log ϵ) 274 (4.23), 304 (4.05) nm; ^1H NMR δ 2.17 (3 H, s, Ar CH_3), 2.19 (3 H, s, Ar CH_3), 2.86, 2.98 (each 3 H, s, OCH_3), 3.09 (1 H, dd, J = 16.9, 5.4 Hz, H-6α), 3.41 (1 H, d, J = 16.9 Hz, H-6β), 3.45, 3.69, 3.80, 3.81, 4.01 (each 3 H, s, OCH_3), 4.52 (1 H, d, J = 16.2 Hz, NCH), 5.23 (1 H, d, J = 5.4 Hz, H-5), 5.68 (1 H, d, J = 16.2 Hz, NCH), 6.10 (1 H, s, C=CH), 6.58 (2 H, m), 6.77 (1 H, s, H-1), 7.02–7.04 (3 H, m), 7.56 (1 H, s); MS, m/z (relative intensity) 632 (M^+, 100), 293 (25), 292 (65), 278 (13), 234 (6), 91 (17). Anal. Calcd for $C_{35}H_{40}N_2O_9$: C, 66.44; H, 6.37; N, 4.43. Found: C, 66.47; H, 6.43; N, 4.44.

(*E*)-3-Benzyl-2-[(2,4,5-trimethoxy-3-methylphenyl)-methylene]-7,9,10-trimethoxy-8-methyl-4-oxo-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine-11-carboxylic Acid Isobutyl Ester (19c) was prepared by the two-step reaction as described above from **17c** (2.02 g, 2.93 mmol). Column chromatography of the crude reaction mixture on silica gel gave **19c** and **16** in yields of 31%, and 37%, respectively. Compound **19c**: mp 146.5–148 °C (AcOEt–ether); IR (KBr) 1700, 1685, 1640 cm^{-1}; UV λ_{max} (log ϵ) 274 (4.25), 304 (4.07) nm; ^1H NMR δ 0.99 (6 H, d, J = 6.6 Hz, $CH(CH_3)_2$), 2.00 (1 H, m, CH_2CH), 2.17 (3 H, s, Ar CH_3), 2.19 (3 H, s, Ar CH_3), 2.86, 2.98 (each 3 H, s, OCH_3), 3.10 (1 H, dd, J = 16.8, 5.6 Hz, H-6α), 3.42 (1 H, d, J = 16.8 Hz, H-6β), 3.45, 3.69, 3.79 (each 3 H, s, OCH_3), 3.97 (2 H, d, J = 6.6 Hz, OCH_2), 4.00 (3 H, s, OCH_3), 4.58 (1 H, d, J = 16.6 Hz, NCH), 5.26 (1 H, d, J = 5.6 Hz, H-5), 5.70 (1 H, d, J = 16.6 Hz, NCH), 6.10 (1 H, s, C=CH), 6.58 (2 H, m), 6.78 (1 H, s, H-1), 7.01–7.06 (3 H, m), 7.51 (1 H, s); MS, m/z (relative intensity) 674 (M^+, 100), 335 (12), 334 (18), 293 (25), 278 (15), 234 (33), 204 (13), 91 (19). Anal. Calcd for $C_{38}H_{46}N_2O_9$: C, 67.64; H, 6.87; N, 4.15. Found: C, 67.44; H, 6.95; N, 4.11.

(*E*)-3-Benzyl-2-[(2,4,5-trimethoxy-3-methylphenyl)-methylene]-7,9,10-trimethoxy-8-methyl-4-oxo-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine-11-carboxylic Acid Benzyl Ester (19d) was prepared by the two-step reaction as described above from **17d** (108.6 mg, 0.15 mmol). Column chromatography of the crude on a silica gel gave **19d** and **16** in yields of 17%, and 57%, respectively. Compound **19d** (not crystallizable): IR ($CHCl_3$) 1700, 1670, 1640 cm^{-1}; UV λ_{max} (log ϵ) 274 (4.25), 302 (4.07) nm; ^1H NMR δ 2.17 (3 H, s, Ar CH_3), 2.18 (3 H, s, Ar CH_3), 2.86, 2.98 (each 3 H, s, OCH_3), 3.08 (1 H, dd, J = 16.0, 5.4 Hz, H-6α), 3.40 (1 H, d, J = 16.0 Hz, H-6β), 3.45, 3.67, 3.80, 4.01 (each 3 H, s, OCH_3), 4.50 (1 H, d, J = 16.0 Hz, NCH), 5.20 (1 H, d, J = 14.0 Hz, OCH), 5.26 (1 H, d, J = 14.0 Hz, OCH), 5.28 (1 H, d, J = 5.4 Hz, H-5), 5.69 (1 H, d, J = 16.0 Hz, NCH), 6.10 (1 H, s, C=CH), 6.66 (2 H, m), 6.79 (1 H, s, H-1), 7.03 (3 H, m), 7.39 (5 H, m), 7.52 (1 H, s); MS, m/z (relative intensity) 708 (M^+, 100), 573 (6), 324 (17), 234 (47), 204 (15), 91 (92); high-resolution MS calcd for $C_{41}H_{44}N_2O_9$ 708.3046, found 708.3062.

Reduction of 17e. A stirred solution of **17e** (103.5 mg, 0.15 mmol) in dry THF (4 mL) was cooled with ice–water, and lithium tri-*tert*-butoxyaluminum hydride (53.4 mg, 0.21 mmol) was added over 15 min. After continued stirring at the same temperature for 1 h, the reaction mixture was subjected to standard workup to give a pale yellow oil. Chromatography of this material (silica gel, 6 g, elution with 1:5 AcOEt–hexane) afford **18e** (71.3 mg, 69%) as a white foam (ca. 9:1 diastereomeric mixture). One crystalline diastereomer was obtained by recrystallization from hexane–ether as colorless needles. Further elution with AcOEt gave **16** (6.2 mg, 7%) as colorless prisms. Compound **18e**: mp 155–159 °C; IR (KBr) 3450, intensity) 1670 cm^{-1}; UV λ_{max} (log ϵ) 274 (4.22), 304 (3.91) nm; ^1H NMR δ 1.17 (9 H, s, $C(CH_3)_3$), 2.19 (3 H, s, Ar CH_3), 2.25 (3 H, s, Ar CH_3), 3.15 (2 H, m, CH_2), 3.60, 3.65, 3.78, 3.81, 3.84, 3.88 (each 3 H, s, OCH_3), 4.06 (1 H, d, J = 16.0 Hz, NCH), 4.84 (1 H, m, OH), 4.92 (1 H, m, H-6), 5.22 (1 H, d J = 16.0 Hz, NCH), 5.64 (1 H, m, H-2), 6.71 (1 H, s), 6.79 (1 H, s), 6.84–7.04 (2 H, m), 7.14–7.27 (4 H, m); MS, m/z (relative intensity) 692 (M^+, 2), 674 (4), 575 (39), 574 (100), 544 (13), 543 (30), 394 (24), 195 (54), 91 (41). Anal. Calcd for $C_{38}H_{48}N_2O_9$: C, 65.88; H, 6.98; N, 4.04. Found: C, 65.64; H, 7.06; N, 3.96.

Reaction of 18e with Formic Acid. A solution of **18e** (64.4 mg, 0.093 mmol) in formic acid (2 mL) was heated at 60 °C for 1 h and treated as above to give a pale yellow oil. Chromatography of this material (silica gel, 2 g, elution with 1:10 AcOEt–hexane) afforded **20** (28.2 mg, 53%) as a pale yellow oil: IR ($CHCl_3$) 1640, 1590 cm^{-1}; UV λ_{max} 296, 325 nm; ^1H NMR δ 2.16 (3 H, s, Ar CH_3), 2.21 (3 H, s, Ar CH_3), 3.48, 3.70, 3.77, 3.77, 3.79, 3.79 (each 3 H, s, OCH_3), 3.81 (2 H, s, CH_2), 4.18 (2 H, s, CH_2), 5.26 (2 H, s, NCH_2), 6.34 (1 H, s), 6.72 (1 H, s), 6.99 (1 H, s), 7.08–7.32 (5 H, m); ^{13}C NMR δ 9.7 (q), 9.7 (q), 30.3 (t), 33.9 (t), 47.0 (t), 55.8 (q), 55.8 (q), 56.0 (q), 60.1 (q), 60.7 (q), 60.7 (q), 110.3 (d), 111.3 (d), 122.9 (s), 123.5 (d), 125.3 (s), 125.9 (d), 126.5 (s), 126.5 (d), 127.5 (d), 128.6 (s), 128.6 (d), 135.3 (s), 138.1 (s), 146.4 (s), 147.4 (s), 148.8 (s), 149.4 (s), 150.2 (s), 150.7 (s), 156.7 (s); MS, m/z (relative intensity) 574 (M^+, 100), 544 (11), 543 (30), 453 (11), 452 (30), 394 (21), 195 (16), 91 (40).

Hydrogenolysis of 19a. A solution of **19a** (66 mg, 0.1 mmol) in AcOEt (6 mL) was hydrogenated over platinum oxide (40 mg) at 1 atm for 34 h. The catalyst was removed by filtration and washed with ethanol (50 mL). The combined filtrates were concentrated in vacuo and the residue was subjected to chromatography (silica gel, 10 g; elution with 1:8 AcOEt–hexane) to give **24** (58 mg, 87%) as a solid, which was recrystallized from acetone–ether to give colorless prisms; mp 177.5–178 °C: IR (KBr) 1705, 1675, 1645 cm^{-1}; UV λ_{max} (log ϵ) 274 (4.29), 300 sh (4.10) nm; ^1H NMR δ 0.58–1.10 (4 H, m), 1.26 (3 H, d, J = 6.2 Hz, $CHCH_3$), 1.29 (3 H, d, J = 6.2 Hz, $CHCH_3$), 1.23–1.33 (2 H, m), 1.49–1.69 (5 H, m), 2.11 (3 H, s, Ar CH_3), 2.29 (3 H, s, Ar CH_3), 2.99 (1 H, dd, J = 16.1, 5.5 Hz, H-6α), 3.23 (1 H, d, J = 16.1 Hz,

H-6β), 3.30 (1 H, br d, NCH), 3.57, 3.62, 3.71, 3.84, 4.02 (each 3 H, s, OCH_3), 4.16 (1 H, m, NCH), 4.99 (1 H, sep, J = 7 Hz, OCH), 5.09 (1 H, d, J = 5.5 Hz, H-5), 6.18 (1 H, s, C=CH), 6.74 (1 H, s, H-1), 7.53 (1 H, s); ^{13}C NMR δ 9.4 (q), 9.6 (q), 22.2 (q), 22.2 (q), 26.2 (t), 28.3 (t), 29.4 (t), 30.8 (t), 34.9 (d), 45.6 (t), 45.8 (d), 53.4 (d), 56.5 (q), 59.3 (q), 60.0 (q), 60.1 (q), 60.3 (q), 60.4 (q), 69.5 (d), 106.8 (d), 110.7 (d), 122.0 (s), 124.9 (s), 125.0 (s), 125.4 (s), 125.9 (s), 135.6 (s), 146.3 (s), 147.0 (s), 149.4 (s), 150.3 (s), 150.8 (s), 152.7 (s), 152.9 (s), 168.0 (s); MS, m/z (relative intensity) 666 (M^+, 100), 321 (41), 320 (12), 279 (18), 278 (16), 234 (25), 204 (11), 55 (14), 43 (20). Anal. Calcd for $C_{37}H_{50}N_2O_9 \cdot {}^1/_2H_2O$: C, 66.15; H, 7.65; N, 4.17. Found: C, 66.13; H, 7.68; N, 4.18.

(*E*)-3-Benzyl-2-[(2,4,5-trimethoxy-3-methylphenyl)methylene]-7,9,10-trimethoxy-8,11-dimethyl-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (27). Lithium aluminum hydride (19 mg, 0.5 mmol) was added to a stirred solution of **19a** (33.0 mg, 0.05 mmol) in dry ether (5 mL), and the mixture was heated at reflux for 2 h. After quenching at 0 °C by addition of water, the mixture was filtered, and the filter cake was carefully washed with chloroform (50 mL). The combined filtrates were concentrated in vacuo. The residue was subjected to chromatography (silica gel, 2 g; 100:1 CH_2Cl_2–MeOH) to give **27** (3.9 mg, 14%) as a colorless amorphous powder: IR ($CHCl_3$) 1635 cm^{-1}; UV λ_{max} (log ε) 275 (4.14), 302 (4.14); ^1H NMR δ 2.15 (3 H, s, Ar CH_3), 2.21 (3 H, s, Ar CH_3), 2.61 (3 H, s, NCH_3), 2.77 (1 H, d, J = 18.1 Hz, H-6β), 2.93 (3 H, s, OCH_3), 2.96 (1 H, d, J = 10.3 Hz, H-4α), 3.07 (3 H, s, OCH_3), 3.19 (1 H, dd, J = 18.1, 7.1 Hz, H-6α), 3.37 (1 H, ddd, J = 7.1, 3.0, 0.5 Hz, H-5), 3.45 (1 H, dd, J = 10.3, 3.0 Hz, H-4β), 3.56 (3 H, s, OCH_3), 3.74 (1 H, d, J = 14.9 Hz, NCH), 3.75, 3.78, 3.89 (each 3 H, s, OCH_3), 4.23 (1 H, d, J = 14.9 Hz, NCH), 5.20 (1 H, br s, H-1), 5.54 (1 H, s, C=CH), 6.84–6.86 (2 H, m), 6.93 (1 H, s), 7.07–7.09 (3 H, m); ^{13}C NMR δ 9.3 (q), 9.4 (q), 24.4 (t), 40.9 (q), 41.0 (t), 53.3 (d), 53.9 (d), 55.4 (t), 56.3 (q), 59.3 (q), 59.4 (q), 59.4 (q), 60.0 (q), 60.3 (q), 60.3 (q), 103.8 (d), 111.0 (d), 123.0 (s), 124.6 (s), 124.6 (s), 124.6 (s), 126.6 (d), 126.7 (s), 127.0 (s), 127.1 (d), 128.1 (d), 139.0 (s), 145.9 (s), 146.5 (s), 148.3 (s), 149.5 (s), 150.7 (s), 151.5 (s); MS, m/z (relative intensity) 574 (M^+, 63), 559 (7), 544 (40), 543 (100), 483 (11), 263 (13), 262 (17), 250 (40), 249 (26), 248 (98), 234 (8), 233 (9), 218 (21), 91 (14).

(*E*)-3-Benzyl-2-[(2,4,5-trimethoxy-3-methylphenyl)methylene]-7,9,10-trimethoxy-8,11-dimethyl-4-oxo-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (26). Concentrated H_2SO_4 (5 mL) was added to a stirred solution of **19a** (5.28 g, 8 mmol) in trifluoroacetic acid (100 mL), and the resulting solution was stirred for 24 h at 25 °C. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2. The extract was washed with dilute NH_4OH, dried, and evaporated to give **25** (4.70 g) as an amorphous powder, which was used in the next step without further purification: IR ($CHCl_3$) 3300–3250, 1660, 1625 cm^{-1}; UV λ_{max} (log ε) 274 (4.30), 300 (4.14) nm; ^1H NMR δ 2.18 (3 H, s, Ar CH_3), 2.19 (3 H, s, Ar CH_3), 2.58 (1 H, br, NH), 2.94 (3 H, s, OCH_3), 3.07 (1 H, dd, J = 16.9, 5.1 Hz, H-6α), 3.08 (3 H, s, OCH_3), 3.38 (1 H, d, J = 16.9 Hz, H-6β), 3.50, 3.69, 3.78, 3.83 (each 3 H, s, OCH_3), 4.28 (1 H, d, J = 5.1 Hz, H-5), 4.62 (1 H, d, J = 16.5 Hz, NCH), 5.53 (1 H, s, H-1), 5.55 (1 H, d, J = 16.5 Hz, NCH), 5.93 (1 H, s, C=CH), 6.71 (1 H, s), 6.72–6.75 (2 H, m), 7.03–7.07 (3 H, m); ^{13}C NMR δ 9.3 (q), 9.3 (q), 27.6 (t), 44.4 (t), 46.2 (d), 51.6 (d), 56.2 (q), 58.7 (q), 59.7 (q), 59.8 (q), 59.9 (q), 60.3 (q), 110.7 (d), 112.1 (d), 120.9 (s), 123.9 (s), 125.4 (s), 126.1 (d), 126.7 (s), 126.9 (d), 128.4 (d), 131.0 (s), 135.4 (s), 146.4 (s), 147.8 (s), 149.1 (s), 150.6 (s), 150.9 (s), 152.3 (s), 165.1 (s); MS, m/z (relative intensity) 574 (M^+, 69), 559 (16), 543 (24), 393 (13), 235 (22), 234 (100), 219 (11), 204 (28), 91 (35).

Formaldehyde (37 wt % solution water, 6.4 mL) was added to a stirred solution of crude **25** (4.7 g) in formic acid (7.4 mL) at 50 °C. After being stirred for 1 h at 70 °C, the reaction mixture was poured into water (200 mL) and extracted with $CHCl_3$ (100 mL × 3). The combined extracts were washed with saturated aqueous $NaHCO_3$ and water (100 mL × 2), dried, and concentrated in vacuo to give a solid, recrystallization of which from AcOEt–ether gave **26** (4.54 g, 96% from **19a**) as colorless prisms: mp 162–163.5 °C; IR (KBr) 1665, 1635 cm^{-1}; UV λ_{max} (log ε) 272 (4.21), 301 (4.07) nm; ^1H NMR δ 2.17 (3 H, s, Ar CH_3), 2.19 (3 H, s, Ar CH_3), 2.82 (3 H, s, NCH_3), 2.94, 2.95 (each 3 H, s, OCH_3), 3.17 (1 H, dd, J = 17.2, 6.2 Hz, H-6α), 3.30 (1 H, dd, J = 17.2, 1.8 Hz, H-6β), 3.46, 3.70, 3.79, 3.85 (each 3 H, s, OCH_3), 3.86 (1 H, dd, J = 6.2, 1.8 Hz, H-5), 4.61 (1 H, d, J = 16.1 Hz, NCH), 5.41 (1 H, s, H-1), 5.65 (1 H, d, J = 16.1 Hz, NCH), 6.18 (1 H, s, C=CH), 6.70–6.72 (2 H, m), 6.89 (1 H, s), 7.03–7.05 (3 H, m); ^{13}C NMR δ 9.3 (q), 9.3 (q), 28.3 (t), 41.6 (q), 43.5 (t), 52.6 (d), 56.2 (q), 58.9 (q), 59.6 (q), 59.9 (q), 60.0 (q), 60.4 (q), 60.6 (d), 109.1 (d), 109.8 (d), 122.0 (s), 126.3 (d), 126.6 (d), 128.4 (d), 135.0 (s), 136.8 (s), 146.8 (s), 147.0 (s), 148.6 (s), 150.1 (s), 151.2 (s), 152.6 (s), 169.8 (s); MS, m/z (relative intensity) 588 (M^+, 42), 249 (24), 248 (100), 218 (15). Anal. Calcd for $C_{34}H_{40}N_2O_7$: C, 69.37; H, 6.85; N, 4.76. Found: C, 69.16; H, 6.81; N, 4.67.

X-ray Structure Determination of 26. Crystals of **26** ($C_{34}H_{40}N_2O_7$) belong to the triclinic space group $P\bar{1}$, with cell constants a = 12.911 (3) Å, b = 12.396 (3) Å, c = 10.506 (3) Å, Z = 2, d_c = 1.26 cm^{-3}. X-ray intensities were measured at 296 K with a AFC-5 (Rigaku Denki) type diffractometer using graphite-monochromated Cu Kα radiation, ω –2θ scan mode, 3° ≤ 2θ ≤ 155°, number of reflextions measured 6479, number of reflextions with $F_o > \delta(F_o)$ 3911. The structure was solved by direct methods. Refinements were done by a local block-diagonal version of UNICS III system[30] (Open program Tokyo University). Hydrogen atoms were found from difference Fourier syntheses. The final R factor was 11.5%. The drawing of the molecule was made by ORTEP.

2-[(2,4,5-Trimethoxy-3-methylphenyl)methyl]-7,9,10-trimethoxy-8,11-dimethyl-(1α,2α,5α)-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (13). A stirred solution of the lactam **26** (5.292 g, 9 mmol) in dry THF (200 mL) was cooled with ice–water, a THF solution of aluminum hydride (0.5 M, 120 mL, 60 mmol) was added dropwise over 1 h, and then stirring was continued at 0 °C for 1 h. After being quenched by addition of MeOH (4 mL), the reaction mixture was concentrated in vacuo to give **27** (4.80 g, 8.36 mmol) as an amorphous powder, which was used the next step without further purification. A solution of the crude **27** (4.80 g) in ethanol (30 mL) was shaken for 24 h at 80 °C under 4 atm of hydrogen in the presence of 20% palladium on carbon (2.0 g). The catalyst was removed by filtration and washed with ethanol (100 mL). The combined filtrates were evaporated and the residue was dissolved with benzene (100 mL) and extracted with 1 N HCl (50 mL × 3). The combined aqueous layer was made alkaline with 10% NH_4OH and extracted with chloroform (100 mL × 3). The combined organic extracts were washed with water (100 mL), dried, and concentrated in vacuo to give a solid, recrystallization of which from AcOEt–ether afforded pure **13** (4.02 g, 92% from **26**) as colorless needles: mp 121–122 °C; IR (KBr) 3400, 2950, 2920, 2820, 1485, 1460, 1405, 1375, 1335, 1305, 1240, 1230, 1190, 1130, 1120, 1110, 1085, 1075, 1050, 1015, 995, 980, 970 cm^{-1}; UV λ_{max} (log ε) 224 (4.29), 281 (3.49) nm; ^1H NMR δ 2.04 (1 H, dd, J = 14.7, 11.2 Hz, H-2a), 2.15 (3 H, s, Ar CH_3), 2.24 (3 H, s, Ar CH_3), 2.36 (3 H, s, NCH_3), 2.54 (1 H, d, J = 18.1 Hz, H-6β), 2.91 (1 H, dd, J = 12.2, 1.9 Hz, H-4α), 2.99 (1 H, dd, J = 18.1, 8.1 Hz, H-6α), 3.00 (1 H, ddd, J = 11.2, 2.4, 2.2 Hz, H-2), 3.06 (1 H, m, H-5), 3.18 (1 H, dd, J = 12.2, 2.2 Hz, H-4β), 3.49 (1 H, dd, J = 14.7, 2.4 Hz, H-2a), 3.52 (3 H, s, OCH_3), 3.65 (1 H, br s, NH), 3.74, 3.75, 3.79, 3.80, 3.82 (each, 3 H, s, OCH_3), 4.10 (1 H, dd, J = 2.2, 0.5 Hz, H-1), 6.62 (1 H, s, Ar H); ^{13}C NMR δ 9.4 (q), 9.6 (q), 21.9 (t), 32.5 (t), 41.7 (q), 51.9 (d), 53.8 (t), 55.8 (q), 58.1 (d), 59.6 (q), 60.0 (q), 60.1 (q), 60.2 (q), 60.3 (q), 60.4 (d), 110.2 (d), 123.2 (s), 123.5 (s), 124.5 (s), 125.1 (s), 127.4 (s), 145.9 (s), 147.6 (s), 149.0 (s), 149.4 (s), 150.9 (s), 151.3 (s); MS, m/z (relative intensity) 486 (M^+, 6), 292 (19), 291 (100), 263 (13), 251 (13), 250 (80), 249 (19), 248 (85), 234 (11), 218 (14); high-resolution MS calcd for $C_{27}H_{38}N_2O_6$ 486.2729, found 486.2779. Anal. Calcd for $C_{27}H_{38}N_2O_6 \cdot H_2O$: C, 64.26; H, 7.99; N, 5.55. Found: C, 64.61; H, 8.38; N, 5.18.

2-[(2,4,5-Trimethoxy-3-methylphenyl)methyl]-7,9,10-trimethoxy-8,11-dimethyl-3-(phthalimidoacetyl)-(1α,2α,5α)-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (28). To a stirred solution of the amine **13** (48.6 mg, 0.1 mmol) and triethylamine (0.04 mL) in dry dichloromethane (4 mL) was added a solution of phthalimidoacetyl chloride (44.7 mg, 0.2 mmol) in dry dichloromethane (2 mL) under ice-cooling over a period of 25 min. The reaction mixture was stirred for 30 min, then diluted with dichloromethane (20 mL), and washed successively with

(30) Sakurai, T.; Kobayashi, K. *Rika Gaku Kenkyusho Hokoku* **1979**, *55*, 69–77.

water, saturated $NaHCO_3$ solution, and brine. The organic layer was dried and concentrated in vacuo. The residue was subjected to chromatography (silica gel, 4 g; elution with 100:1 $CHCl_3$–MeOH) to give **28**[31] (60.1 mg, 89.3%) as colorless needles: mp 218–219 °C (AcOEt–ether); IR (KBr) 1770, 1715, 1655 cm^{-1}; UV λ_{max} (log ϵ) 220 (4.87), 242 sh (3.94), 282 (3.70), 302 sh (3.25) nm; MS, m/z (relative intensity) 673 (M^+, 1), 478 (5), 261 (5), 248 (100), 218 (7). Anal. Calcd for $C_{37}H_{43}N_2O_9$: C, 65.96; H, 6.43; N, 6.24. Found: C, 65.78; H, 6.38; N, 6.14.

3-[2-[(2,4,5-Trimethoxy-3-methylphenyl)methyl]-7,9,10-trimethoxy-8,11-dimethyl-3-(ethoxyoxalyl)-(1α,2α,5α)-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (29). To a stirred solution of the amine **13** (48.6 mg, 0.1 mmol) and triethylamine (0.04 mL) in dry dichloromethane (4 mL) was added a solution of ethyl oxalyl chloride (0.022 mL, 0.2 mmol) in dry dichloromethane (2 mL) under ice-cooling over a period of 25 min and treated as above to give a solid, which was subjected to chromatography (silica gel, 4 g; elution with 100:1 $CHCl_3$–MeOH) to give **29**[31] (43.6 mg, 74.4%) as colorless needles: mp 130–132 °C; IR (KBr) 1730, 1665 cm^{-1}; UV λ_{max} (log ϵ) 224 (4.38), 280 (3.59) nm; MS, m/z (relative intensity) 586 (M^+, 4), 485 (14), 248 (100), 218 (7). Anal. Calcd for $C_{31}H_{42}N_2O_9$: C, 63.46; H, 7.22; N, 4.78. found: C, 63.27; H, 7.41; N, 4.75.

Butyl 1,2,4,10,11,13-Hexamethoxy-3,12,16-trimethyl-(6α,9β,14aα,15α)-6,7,9,14,14a,15-hexahydro-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocine-9-carboxylate (31). A solution of **13** (1.944 g, 4 mmol) and anhydrous K_2CO_3 (5.22 g, 37.8 mmol) in butanol (30 mL) was stirred for 30 min. Butyl glyoxylate (5.20 g, 40 mmol) in butanol (20 mL) was then added dropwise over 30 min, and the mixture was stirred at 25 °C for 24 h and then filtered, which was washed with chloroform (100 mL). The combined filtrates were concentrated under reduced pressure. The *O,N*-acetal **30** (containing butanol) was stirred with trifluoroacetic acid (50 mL) at 25 °C for 1 h. The mixture was diluted with water (100 mL), made alkaline with $NaHCO_3$, and extracted with chloroform (100 mL × 3). The combined extracts were washed with water (100 mL), dried, and concentrated in vacuo. The residual oil was subjected to chromatography (silica gel, 160 g; elution with 2:1 AcOEt–benzene) to give **31** (1.677 g, 70% from **13**) as a solid, which was recrystallized frm AcOEt–ether to give colorless prisms: mp 111–112 °C; IR (KBr) 1720 cm^{-1}; UV λ_{max} (log ϵ) 226 sh (4.31), 272 (3.26), 279 (3.32) nm; ^1H NMR δ 0.88 (3 H, t, J = 7.3 Hz, CH_2CH_3), 1.32 (2 H, m, CH_2CH_3), 1.60 (2 H, m, $CH_2CH_2CH_3$), 2.12 (3 H, s, Ar CH_3), 2.15 (3 H, s, Ar CH_3), 2.27 (3 H, s, NCH_3), 2.29 (1 H, dd, J = 17.6, 10.7 Hz, H-14β), 2.52 (1 H, d, J = 17.6 Hz, H-5β), 2.89 (1 H, dd, J = 9.5, 2.7 Hz, H-7α), 3.00 (1 H, dd, J = 9.5, 1.2 Hz, H-7β), 3.01 (1 H, dd, J = 17.6, 9.5 Hz, H-5α), 3.05 (1 H, d, J = 17.6, 4.6 Hz, H-5α), 3.21 (1 H, m, H-6), 3.57 (1 H, ddd, J = 10.7, 4.6, 1.2 Hz, H-14a), 3.61, 3.68, 3.69, 3.73, 3.75, 3.84 (each 3 H, s, OCH_3), 4.05 (1 H, m, OCH), 4.09 (1 H, dd, J = 1.2, 0.5 Hz, H-15), 4.15 (1 H, m, OCH), 4.56 (1 H, s, H-9); ^{13}C NMR δ 9.1 (q), 9.4 (q), 13.6 (q), 19.2 (t), 22.3 (t), 25.7 (t), 30.7 (t), 41.8 (q), 52.4 (d), 53.9 (d), 57.2 (d), 59.0 (t), 59.4 (q), 59.5 (q), 59.7 (q), 59.8 (q), 59.8 (q), 60.1 (q), 62.2 (d), 64.1 (t), 123.4 (s), 123.7 (s), 124.0 (s), 124.2 (s), 124.5 (s), 124.6 (s), 145.5 (s), 147.9 (s), 148.6 (s), 148.9 (s), 151.3 (s), 151.8 (s), 171.6 (s); MS, m/z (relative intensity) 598 (M^+, 3), 498 (32), 497 (100), 263 (8), 250 (9), 249 (27), 248 (41). Anal. Calcd for $C_{33}H_{46}N_2O_8 \cdot {}^1/_5H_2O$: C, 65.80; H, 7.76; N, 4.65. Found: C, 65.84; H, 7.88; N, 4.59.

Ethyl 1,2,4,10,11,13-Hexamethoxy-3,12,16-trimethyl-(6α,9β,14aα,15α)-6,7,9,14,14a,15-hexahydro-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocine-9-carboxylate (32). A solutin of **31** (287 mg, 0.47 mmol) and concentrated H_2SO_4 (1 mL) in dry ethanol (20 mL) was heated at reflux for 4 day, and the reaction mixture was concentrated in vacuo to remove most of the EtOH. The residue was diluted with water (20 mL), made alkaline with 5% $NaHCO_3$, and extracted with chloroform (30 mL × 3). The combined extracts were washed with water (20 mL), dried, and concentrated in vacuo. The residue was subjected to chromatography (silica gel, 15 g; elution with 1:2 AcOEt–benzene) to give **32** (196.3 mg, 72%) as a pale yellow solid. Recrystallization of which from AcOEt afforded pure **32** as colorless prisms: mp 209–211 °C; IR (KBr) 1715 cm^{-1}; UV λ_{max} (log ϵ) 230 (4.12), 272 sh (3.06), 280 (4.10) nm; ^1H NMR δ 1.27 (3 H, t, J = 7.0 Hz, CH_2CH_3), 2.12 (3 H, s, Ar CH_3), 2.15 (3 H, s, Ar CH_3), 2.28 (3 H, s, NCH_3), 2.28 (1 H, dd, J = 17.1, 11.0 Hz, H-14β), 2.52 (1 H, d, J = 18.3 Hz, H-5β), 2.91 (1 H, dd, J = 10.7, 2.7 Hz, H-7α), 3.01 (1 H, dd, J = 10.7, 2.4 Hz, H-7β), 3.02 (1 H, dd, J = 18.3, 8.5 Hz, H-5α), 3.03 (1 H, dd, J = 17.1, 4.6 Hz, H-14α), 3.22 (1 H, br d, H-6), 3.60 (1 H, ddd, J = 11.0, 4.6, 3.4 Hz, H-14a), 3.61, 3.68, 3.69, 3.73, 3.75, 3.84 (each 3 H, s, OCH_3), 4.09 (1 H, dd, J = 3.4, 0.5 Hz, H-15), 4.18 (2 H, q, J = 7.0 Hz, OCH_2), 4.56 (1 H, s, H-9); ^{13}C NMR δ 9.2 (q), 9.3 (q), 14.4 (q), 22.3 (t), 25.6 (t), 41.8 (q), 52.4 (d), 53.8 (d), 57.2 (d), 58.8 (t), 59.4 (q), 59.4 (q), 59.5 (q), 59.6 (q), 59.8 (q), 60.1 (q), 60.1 (t), 62.1 (d), 123.4 (s), 123.6 (s), 124.1 (s), 124.1 (s), 124.3 (s), 124.5 (s), 145.5 (s), 147.9 (s), 148.5 (s), 149.0 (s), 151.3 (s), 151.7 (s), 171.5 (s); MS, m/z (relative intensity) 570 (M^+, 6), 499 (6), 498 (32), 497 (100), 263 (9), 249 (29), 248 (41). Anal. Calcd for $C_{31}H_{42}N_2O_8$: C, 65.24; H, 7.42; N, 4.91. Found: C, 65.12; H, 7.54; N, 4.87.

X-ray Structure Determination of 32. Crystals of **32** ($C_{31}H_{42}N_2O_8$) belong to the monoclinic space group $P2_1/C$, with cell constants a = 25.972 (6) Å, b = 12.613 (1) Å, c = 9.734 (4) Å, Z = 4, d_c = 1.27 cm^{-3}. X-ray intensities were measured at 296 K with a AFC-5 (Rigaku Denki) type diffractometer using graphite-monochromated Cu Kα radiation, ω–2θ scan mode, 3° ≤ 2θ ≤ 155°, number of reflextions measured 6530, number of reflextions with $F_o > \delta(F_o)$ 5044. The structure was solved by direct methods. Refinements were done by a local block-diagonal version of UNICS III system (Open program Tokyo University). Hydrogen atoms were found from difference Fourier syntheses. The final R factor was 8.8%. The drawing of the molecule was made by ORTEP.

Butyl 1,2,4,10,11,13-Hexamethoxy-3,12,16-trimethyl-(6α,9α,14aα,15α)-6,7,9,14,14a,15-hexahydro-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocine-9-carboxylate (34). A solution of **31** (598 mg, 1 mmol) and mercury(II) acetate (3.178 g, 10 mmol) in 5% acetic acid (50 mL) was heated at 90 °C for 2 h and treated with hydrogen sulfide for 1 h at the same temperature. After filtration of the mixture through cellulose powder and the filter cake was carefully washed with diluted acetic acid (50 mL), the combined filtrates were concentrated to dryness and the residue was again dissolved in 50% aqueous EtOH (100 mL). The pH was brought to 6–7 with solid $NaHCO_3$, to which was added sodium borohydride (815 mg, 21.5 mmol), and the mixture was left at room temperature overnight. The solution was acidified with 2 N HCl and concentrated to a small volume, the residual solution was extracted with benzene (50 mL × 3). The organic layer was washed with water (50 mL), dried, and concentrated in vacuo to give the neutral fraction (607 mg), which was subjected to chromatography (silica gel, 20 g) with 200:1 CH_2Cl_2–MeOH as the eluent to give 50 mg of crystals (fraction A), with 50:1 CH_2Cl_2–MeOH as the eluent to give 460 mg of crystals (fraction B).

The fraction A gave colorless prisms (33.6 mg, 5.6%), mp 111–112 °C, after recrystallization from AcOEt–ether and was identical with the starting material **31** by the mixture melting point test, thin layer chromatography, and IR comparison. The fraction B was recrystallized from AcOEt–ether to give **34** (422 mg, 70.6%) as colorless prisms: mp 174–176 °C; IR (KBr) 1720 cm^{-1}; UV λ_{max} (log ϵ) 226 (4.32), 272 (3.31), 279 (3.36) nm; ^1H NMR δ 0.83 (3 H, t, J = 7.0 Hz, CH_2CH_3), 1.25 (2 H, m, CH_2CH_3), 1.48 (2 H, m, $CH_2CH_2CH_3$), 2.08 (1 H, dd, J = 15.9, 11.7 Hz, H-14β), 2.15 (3 H, s, Ar CH_3), 2.17 (3 H, s, Ar CH_3), 2.30 (3 H, s, NCH_3), 2.45 (1 H, d, J = 17.8 Hz, H-5β), 2.84 (1 H, ddd, J = 11.7, 2.7, 2.7 Hz, H-14a), 2.90 (1 H, dd, J = 10.7 2.4 Hz, H-7α), 2.99 (1 H, dd, J = 17.8, 7.6 Hz, H-5α), 3.05 (1 H, dd, J = 15.9, 2.7 Hz, H-14α), 3.19 (1 H, m, H-6), 3.23 (1 H, dd, J = 10.7, 2.4 Hz, H-7β), 3.61, 3.67, 3.71, 3.71, 3.77, 3.84 (each 3 H, s, OCH_3), 3.98 (2 H, m, OCH_2), 4.08 (1 H, dd, J = 2.4, 0.5 Hz, H-15), 4.09 (1 H, s, H-9); ^{13}C NMR δ 9.2 (q), 9.2 (q), 13.6 (q), 19.7 (t), 22.5 (t), 26.3 (t), 30.5 (t), 41.4 (q), 52.7 (d), 57.5 (d), 59.5 (q), 59.6 (q), 59.8 (q), 59.9 (q), 59.9 (q), 60.2 (q), 61.5 (t), 64.7 (d), 64.1 (t), 123.2 (s), 123.7 (s), 124.6 (s), 124.6 (s), 124.7 (s), 124.7 (s), 145.7 (s), 147.6 (s), 148.8 (s), 148.9 (s), 151.2 (s), 151.2 (s), 172.4 (s); MS, m/z (relative intensity) 598 (M^+, 5), 497 (56), 263 (100), 250 (9), 249 (35), 248 (100), 233 (8), 218 (9); high-resolution MS calcd for $C_{33}H_{46}N_2O_8$ 598.3254, found 598.3217. Anal. Calcd for $C_{33}H_{46}N_2O_8 \cdot H_2O$: C, 64.26; H, 7.85;

(31) The signals in the ^1H NMR spectra of **28** and **29** were not split, which indicated that there was a mixture of two rotational isomers, respectively.

N, 4.54. Found: C, 64.37; H, 7.49; N, 4.65.

The acidic aqueous layer was made alkaline with diluted NH_4OH and extracted with chloroform (50 mL × 3). The combined extracts were washed with water (50 mL), dried, and concentrated in vacuo. The residue was subjected to chromatography (silica gel, 6 g; elution with 80:1 CH_2Cl_2–MeOH) to give **35** (65.4 mg, 13%) as a pale yellow solid. Recrystallization of which from AcOEt–ether afforded pure **35** as colorless prisms, mp 158.5–160 °C, whose spectra were identical with those of an authentic sample obtained earlier.[18]

1,2,4,10,11,13-Hexamethoxy-3,12,16-trimethyl-(6α,9α,14aα,15α)-6,7,9,14,14a,15-hexahydro-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocine-9-methanol (36). Lithium aluminum hydride (325 mg, 8.58 mmol) was added to a stirred solution of **34** (854.4 mg, 1.43 mmol) in dry THF (50 mL), and the mixture was heated at reflux for 2 h. After being quenched at 0 °C by addition of water, the mixture was filtered and the filter cake was carefully washed with chloroform (100 mL). The combined filtrates were concentrated in vacuo. The residue was subjected to chromatography (silica gel, 40 g, elution with 100:1 CH_2Cl_2–MeOH) to give **36** (579.5 mg, 77%) as colorless amorphous powder. An analytical sample was obtained by crystallization from ether: mp 152.5–154 °C; IR (KBr) 3420 cm^{-1}; UV λ_{max} (log ε) 226 sh (4.34), 272 (3.20), 278 (3.25) nm; ^1H NMR δ 1.82 (1 H, dd, *J* = 15.7, 11.8 Hz, H-14β), 2.14 (3 H, s, Ar CH_3), 2.19 (3 H, s, Ar CH_3), 2.36 (3 H, s, NCH_3), 2.55 (1 H, d, *J* = 18.3 Hz, H-5β), 2.68 (1 H, m, OH), 2.95 (1 H, ddd, *J* = 11.8, 2.7, 2.2 Hz, H-14a), 3.03–3.04 (3 H, m, H_2-7 and H-5α), 3.08 (1 H, dd, *J* =15.7, 2.7 Hz, H-14α), 3.21 (1 H, m, H-6), 3.34 (1 H, dd, *J* = 10.0, 4.3 Hz, C*H*OH), 3.61 (3 H, s, OCH_3), 3.69 (1 H, dd, *J* = 10.0, 4.3 Hz, C*H*OH), 3.72 (1 H, dd, *J* = 4.3, 1.5 Hz, H-9), 3.74, 3.74, 3.76, 3.81, 3.85 (each 3 H, s, OCH_3), 4.12 (1 H, dd, *J* = 2.2, 0.5 Hz, H-15); ^{13}C NMR δ 9.2 (q), 9.3 (q), 22.7 (t), 26.5 (t), 41.4 (q), 52.6 (d), 57.6 (d), 59.2 (d), 59.9 (q), 59.9 (q), 59.9 (q), 60.0 (q), 60.2 (q), 60.3, (q), 60.3 (t), 64.2 (t), 123.3 (s), 123.7 (s), 124.0 (s), 124.1 (s), 125.2 (s), 126.7 (s), 145.7 (s), 147.6 (s), 149.2 (s), 149.3 (s), 150.9 (s), 151.4 (s); MS, *m/z* (relative intensity) 528 (M^+, 0.5), 510 (2), 497 (100), 263 (6), 248 (56), 234 (7), 233 (7), 218 (11); high-resolution MS calcd for $C_{29}H_{40}N_2O_7$ 528.2835, found 528.2806. Anal. Calcd for $C_{29}H_{40}N_2O_7$: C, 65.89; H, 7.63; N, 5.30. Found: C, 65.76; H, 7.84; N, 5.19.

***N*-[(1,2,4,10,11,13-Hexamethoxy-3,12,16-trimethyl-(6α,9α,14aα,15α)-6,7,9,14,14a,15-hexahydro-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-yl)methyl]-2-oxopropanamide (39).** A solution of diethyl azodicarboxylate (0.83 mL, 5.25 mmol) in THF (5 mL) was added dropwise to a solution of **36** (554.4 mg, 1.05 mmol), phthalimide (772 mg, 5.25 mmol), and triphenylphosphine (1.377 g, 5.25 mmol) in THF (20 mL) at room temperature. After the solution was stirred at room temperature for 3 h, the solvent was removed in vacuo. The residue was diluted with water (50 mL) and extracted with chloroform (50 mL × 3). The combined extracts were washed with water (50 mL), dried, and concentrated in vacuo to furnished **37** (690 mg, 100%) as a colorless amorphous powder, which was used for the next step without further purification. An analytical sample was obtained by column chromatography (elution with 50:1 CH_2Cl_2–MeOH): IR ($CHCl_3$) 1770, 1710 cm^{-1}; UV λ_{max} 278, 302 nm; ^1H NMR δ 1.75 (1 H, dd, *J* = 15.4, 11.7 Hz, H-14β), 2.10 (3 H, s, Ar CH_3), 2.23 (3 H, s, Ar CH_3), 2.33 (3 H, s, NCH_3), 2.71 (1 H, d, *J* = 18.1 Hz, H-5β), 2.78 (1 H, dt, *J* = 11.7, 1.7 Hz, H-14a), 3.03 (1 H, dd, *J* = 18.1, 7.6 Hz, H-5α), 3.10 (1 H, dd, *J* = 15.4, 1.7 Hz, H-14α), 3.10 (1 H, dd, *J* = 10.5, 1.0 Hz, H-7α), 3.21 (1 H, m, H-6), 3.24 (1 H, dd, *J* = 10.5, 2.2 Hz, H-7β), 3.29 (3 H, s, OCH_3), 3.39 (1 H, dd, *J* = 13.7, 3.7 Hz, CHNPht), 3.50 (3 H, s, OCH_3), 3.57 (1 H, dd, *J* = 13.7, 9.0 Hz, CHNPht), 3.60 (3 H, s, OCH_3), 3.74, 3.74, 3.85 (each 3 H, s, OCH_3), 4.02 (1 H, dd, *J* = 1.7, 0.5 Hz, H-15), 4.03 (1 H, dd, *J* = 9.0 3.7 Hz, H-9), 7.60–7.63 (2 H, m), 7.64–7.67 (2 H, m); ^{13}C NMR δ 9.2 (q), 9.4 (q), 22.7 (t), 27.1 (t), 41.4 (q), 43.6 (t), 53.1 (d), 57.7 (d), 59.5 (q), 59.6 (d), 59.6 (d), 59.8 (q), 59.9 (q), 60.2 (q), 60.3 (q), 60.5 (q), 61.1 (t), 122.5 (s), 122.6 (s), 122.9 (s), 123.3 (s), 125.1 (s), 125.7 (s), 126.5 (s), 132.5 (d), 133.2 (d), 146.1 (s), 147.3 (s), 148.8 (s), 149.3 (s), 151.0 (s), 151.6 (s), 168.1 (s); MS, *m/z* (relative intensity) 656 (M^+ – 1, 0.6), 497 (100), 248 (37), 233 (7), 218 (8); high-resolution MS calcd for $C_{37}H_{42}N_3O_8$ 656.2971 (M^+ – 1), found 656.2993; calcd for $C_{28}H_{37}N_2O_6$ 497.2651 (base peak), found 497.2629.

Hydrazine monohydrate (2.0 mL) was added to a stirred solution of crude **37** (690 mg, 1.05 mmol) in EtOH (20 mL), the resulting solution was heated under reflux for 2 h, and the reaction mixture was concentrated in vacuo. The residue was dissolved in benzene (20 mL) and extracted with 1 N HCl (20 mL × 3). The acidic aqueous layer was made alkaline with diluted NH_4OH and extracted with chloroform (30 mL × 3). The combined extracts were washed with water (30 mL), dried, and concentrated in vacuo to give **38** (498 mg, 90%) as a colorless amorphous powder, which was used for the next step without further purification: IR ($CHCl_3$) 3400–3000, 1455, 1410 cm^{-1}; UV λ_{max} 230, 272, 278 nm; ^1H NMR δ 1.77 (1 H, dd, *J* = 15.6, 11.7 Hz, H-14β), 1.94 (2 H, br s, NH_2), 2.15 (3 H, s, Ar CH_3), 2.19 (3 H, s, Ar CH_3), 2.34 (3 H, s, NCH_3), 2.54 (1 H, d, *J* = 18.1 Hz, H-5β), 2.67 (1 H, dd, *J* = 13.2, 2.4 Hz, C*H*NH_2), 2.76 (1 H, dd, *J* = 13.2, 3.7 Hz, C*H*NH_2), 2.86 (1 H, ddd, *J* = 11.7, 2.7, 2.4 Hz, H-14a), 2.97 (1 H, dd, *J* = 10.7, 2.2 Hz, H-7α), 3.01 (1 H, dd, *J* = 10.7, 2.4 Hz, H-7β), 3.04 (1 H, dd, *J* = 18.1, 7.6 Hz, H-5α), 3.06 (1 H, dd, *J* = 15.6, 2.4 Hz, H-14α), 3.19 (1 H, m, H-6), 3.62 (3 H, s, OCH_3), 3.68 (1 H, dd, *J* = 3.7, 2.4 Hz, H-9), 3.73, 3.75, 3.78, 3.80, 3.85 (each 3 H, s, OCH_3), 4.09 (1 H, dd, *J* = 2.7, 0.5 Hz, H-15); MS, *m/z* (relative intensity) 527 (M^+, 0.1), 497 (100), 248 (29), 218 (9).

A solution of the crude **38** (498 mg, 0.944 mmol), triethylamine (0.27 mL, 1.9 mmol), and 4-(dimethylamino)pyridine (232 mg, 1.9 mmol) in dry dichloromethane (15 mL) was cooled with ice–water, and a carbon tetrachloride solution of pyruvoyl chloride (1.0 M, 3.8 mL) was added dropwise over 10 min. The solution was stirred for 1 h at 25 °C, and the reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (20 mL × 3). The combined extracts were washed with water (20 mL), dried, and concentrated in vacuo. The residue was subjected to chromatography (silica gel, 40 g; elution with 50:1 CH_2Cl_2–MeOH) to give **39** (475 mg, 76% from **36**) as a solid, which was recrystallized from AcOEt–ether to give colorless prisms: mp 135.5–137 °C; IR (KBr) 3350, 1715, 1690 cm^{-1}; UV λ_{max} (log ε) 209 (4.80), 230sh (4.24), 272 (3.32), 278 (3.33) nm; ^1H NMR δ 1.82 (1 H, dd, *J* = 16.1, 11.7 Hz, H-14β), 2.13 (3 H, s, Ar CH_3), 2.13 (3 H, s, $COCH_3$), 2.20 (3 H, s, Ar CH_3), 2.37 (3 H, s, NCH_3), 2.52 (1 H, d, *J* = 18.1 Hz, H-5β), 2.82 (1 H, ddd, *J* = 11.7, 2.7, 2.5 Hz, H-14a), 2.95 (1 H, dd, *J* = 10.5, 2.7 Hz, H-7α), 3.01 (1 H, dd, *J* = 10.5, 2.5 Hz, H-7β), 3.02 (1 H, dd, *J* = 18.1, 7.8 Hz, H-5α), 3.06 (1 H, dd, *J* = 16.1, 2.5 Hz, H-14α), 3.19 (1 H, m, H-6), 3.20 (1 H, ddd, *J* = 12.9, 3.7, 3.4 Hz, C*H*NH), 3.59 (3 H, s, OCH_3), 3.60 (1 H, ddd, *J* = 12.9, 8.1, 2.0 Hz, C*H*NH), 3.72, 3.73, 3.78 (each 3 H, s, OCH_3), 3.82 (1 H, dd, *J* = 3.4, 2.0 Hz, H-9), 3.86 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 4.05 (1 H, dd, *J* = 2.7, 0.5 Hz, H-15), 6.56 (1 H, dd, *J* = 8.1, 3.7 Hz, NH); ^{13}C NMR δ 9.1 (q), 9.3 (q), 22.6 (t), 24.3 (q), 26.6 (t), 41.5 (q), 43.0 (t), 52.8 (d), 57.6 (d), 58.4 (d), 59.1 (d), 59.4 (q), 59.7 (q), 59.9 (q), 60.1 (q), 60.1 (q), 60.3 (q), 60.4 (t), 123.6 (s), 123.7 (s), 123.8 (s), 124.2 (s), 125.1 (s), 125.5 (s), 145.8 (s), 147.7 (s), 149.2 (s), 150.9 (s), 151.0 (s), 159.9 (s), 195.9 (s); MS, *m/z* (relative intensity) 597 (M^+, 0.3), 554 (1), 497 (100), 248 (41), 234 (5), 233 (6), 218 (9). Anal. Calcd for $C_{32}H_{43}N_3O_8$: C, 64.30; H, 7.25; N, 7.03. Found: C, 64.36; H, 7.44; N, 7.03.

***N*-[(2,11-Dimethoxy-3,12,16-trimethyl-1,4,10,13-tetraoxo-(6α,9α,14aα,15α)-1,5,6,7,9,10,13,14,14a,15-decahydro-6,15-imino-4*H*-isoquino[3,2-*b*][3]benzazocin-9-yl)methyl]-2-oxopropanamide (Saframycin B, 2). (A) Oxidative Demethylation of 39 with 10 M HNO_3.** A solution of **39** (29.8 mg, 0.05 mmol) in 10 M HNO_3 (2 mL) was stirred at 25 °C for 1 h. The reaction mixture was diluted with water (5 mL) and extracted with chloroform (20 mL × 3). The combined extracts were washed with water (10 mL), dried, and concentrated in vacuo. The residue (11.6 mg), which showed two major spots on TLC (R_f 0.43 and 0.22, 4:5 acetone–$CHCl_3$), was subjected to chromatography on preparative layer silica gel plates (Merck 5715, solvent 4:5 acetone–$CHCl_3$) to afford **2** (0.4 mg, 1.5%) and **40** (3.4 mg, 12%). The acidic aqueous layer was made alkaline with saturated aqueous $NaHCO_3$ and extracted with chloroform (20 mL × 3). The combined extracts were washed with water (10 mL), dried, and concentrated in vacuo. The residue (8.4 mg) was subjected to chromatography on preparative layer silica gel plates (Merck 5715, solvent 4:5 acetone–$CHCl_3$) to give **41** (7.4 mg, 27%) as colorless powder.

Compound 40: pale yellow needles from acetone, mp 203–205 °C dec; IR (KBr) 3370, 1720, 1670, 1650, 1640 cm^{-1}; UV λ_{max} (log

ϵ) 268 (3.79), 370 (2.71) nm; ^{1}H NMR δ 1.44 (1 H, ddd, J = 18.1, 11.0, 3.0 Hz, H-14β), 1.89 (3 H, s, Ar CH_3), 2.14 (3 H, s, Ar CH_3), 2.25 (3 H, s, $COCH_3$), 2.33 (3 H, s, NCH_3), 2.47 (1 H, d, J = 18.1 Hz, H-5β), 2.73 (1 H, ddd, J = 11.0, 2.8, 2.4 Hz, H-14a), 2.88 (1 H, dd, J = 18.1, 2.8 Hz, H-14α), 2.88 (1 H, dd, J = 10.7, 2.0 Hz, H-7α), 3.03 (1 H, dd, J = 10.7, 2.0 Hz, H-7β), 3.03 (1 H, dd, J = 18.1, 7.6 Hz, H-5α), 3.11 (1 H, ddd, J = 13.7, 3.2, 3.2 Hz, C*H*NH), 3.19 (1 H, dddd, J = 7.6, 2.0, 2.0, 0.5 Hz, H-6), 3.61 (1 H, ddd, J = 3.2, 3.0, 1.2 Hz, H-9), 3.66 (3 H, s, OCH_3), 3.77 (1 H, ddd, J = 13.7, 10.1, 1.2 Hz, C*H*NH), 3.82, 3.82, 4.00 (each 3 H, s, OCH_3), 4.02 (1 H, dd, J = 2.4, 0.5 Hz, H-15), 6.43 (1 H, dd, J = 10.1, 1.2 Hz, NH); ^{13}C NMR δ 8.5 (q), 9.4 (q), 22.6 (t), 24.2 (q), 25.0 (t), 41.0 (t), 41.4 (q), 52.5 (d), 57.0 (d), 57.8 (d), 58.0 (d), 59.5 (q), 59.8 (t), 59.9 (q), 60.3 (q), 60.9 (q), 122.8 (s), 123.7 (s), 124.5 (s), 127.6 (s), 136.5 (s), 142.4 (s), 147.6 (s), 149.5 (s), 151.0 (s), 156.2 (s), 160.4 (s), 181.4 (s), 186.2 (s), 195.4 (s); MS, m/z (relative intensity) 567 (M^+, 6), 469 (52), 467 (41), 248 (100), 218 (19). Anal. Calcd for $C_{30}H_{37}N_3O_8$: C, 63.22; H, 6.72; N, 7.25. Found: C, 63.48; H, 6.57; N, 7.40.

Compound 41 (not crystallizable): IR ($CHCl_3$) 3420–3380, 1725, 1685, 1645 cm^{-1}; UV λ_{max} (log ϵ) 271 (4.39), 278 sh (4.37), 391 (3.71) nm; ^{1}H NMR δ δ 1.50 (1 H, ddd, J = 18.6, 11.0, 2.9 Hz, H-14β), 1.88 (3 H, s, Ar CH_3), 2.15 (3 H, s, Ar CH_3), 2.25 (3 H, s, $COCH_3$), 2.35 (3 H, s, NCH_3), 2.50 (1 H, d, J = 18.1 Hz, H-5β), 2.79 (1 H, ddd, J = 11.0, 2.4, 2.4 Hz, H-14a), 2.92 (1 H, dd, J = 11.0, 2.4 Hz, H-7α), 2.95 (1 H, dd, J = 18.6, 1.7 Hz, H-14α), 3.04 (1 H, dd, J = 11.0, 1.0 Hz, H-7β), 3.04 (1 H, dd, J = 18.1, 7.8 Hz, H-5α), 3.15 (1 H, ddd, J = 13.9, 3.4, 2.9 Hz, C*H*NH), 3.25 (1 H, dddd, J = 7.8, 2.4, 1.0, 0.5 Hz, H-6), 3.59 (1 H, ddd, J = 2.9, 2.9, 1.5 Hz, H-9), 3.65 (3 H, s, OCH_3), 3.80 (1 H, ddd, J = 13.9, 10.0, 1.5 Hz, C*H*NH), 3.82, 3.84 (each 3 H, s, OCH_3), 4.09 (1 H, dd, J = 2.4, 0.5 Hz, H-15), 4.47–5.62 (1 H, br, OH), 6.46 (1 H, dd, J = 10.0, 3.4 Hz, NH); MS, m/z (relative intensity) 553 (M^+, 5), 551 (9), 511 (39), 455 (72), 453 (19), 451 (22), 281 (26), 248 (100), 218 (28).

(B) Oxidative Demethylation of 39 in Two Steps Using Ceric Ammonium Nitrate. To a stirred solution of **39** (29.8 mg, 0.05 mmol) in dichloromethane (3 mL) at −78 °C was added a dichloromethane solution of boron tribromide (1.0 M, 0.2 mL, 0.2 mmol). After being kept at the same temperature for 1 h, and then at 0 °C for 1 h, the reaction mixture was poured onto ice–water and the phase separated. The aqueous layer was extracted with chloroform (20 mL × 2). The combined extracts were washed with brine (10 mL) and concentrated in vacuo. To a stirred solution of the residue (37 mg) in acetonitrile (2 mL) was added an aqueous solution (2 mL) containing ceric ammonium nitrate[25a] (82.6 mg) and then at 0 °C for 1 h. The reaction mixture was diluted with water (10 mL) and extracted with chloroform (20 mL × 3). The combined extracts were washed with water (10 mL × 2), dried, and concentrated in vacuo. The residue (29.8 mg), which showed two major spots on TLC (R_f 0.49 and 0.42, 1:3 acetone–CH_2Cl_2), was subjected to chromatography on preparative layer silica gel plates (Merck 5715, solvent 1:2 acetone–CH_2Cl_2) to afford **2** (4.6 mg, 17%) and **45** (12.7 mg, 45%).

Compound 45 (not crystallizable): IR ($CHCl_3$) 3380, 1715, 1680, 1650 cm^{-1}; UV λ_{max} (log ϵ) 268 (3.79), 370 (2.71) nm; ^{1}H NMR δ 1.67 (1 H, dd, J = 15.1, 11.7 Hz, H-14β), 1.98 (3 H, s, Ar CH_3), 2.13 (3 H, s, Ar CH_3), 2.22 (3 H, s, $COCH_3$), 2.27 (1 H, d, J = 20.8 Hz, H-5β), 2.27 (3 H, s, NCH_3), 2.76 (1 H, dd, J = 20.8, 7.1 Hz, H-5α), 2.81 (1 H, ddd, J = 12.0, 2.4, 2.4 Hz, H-14a), 2.88 (1 H, dd, J = 10.7, 2.2 Hz, H-7α), 2.88 (1 H, dd, J = 15.4, 2.2 Hz, H-14α), 2.94 (1 H, dd, J = 10.7, 2.2 Hz, H-7β), 3.15 (1 H, dddd, J = 7.1, 2.2, 2.2, 0.5 Hz, H-6), 3.29 (1 H, ddd, J = 13.4, 4.2, 3.9 Hz, C*H*NH), 3.52 (3 H, s, OCH_3), 3.62 (1 H, ddd, J = 13.4, 8.1, 2.0 Hz, C*H*NH), 3.74 (3 H, s, OCH_3), 3.86 (1 H, dd, J = 3.9, 2.0 Hz, H-9), 3.87, 4.02 (each 3 H, s, OCH_3), 4.02 (1 H, dd, J = 2.4, 0.5 Hz, H-15), 6.98 (1 H, dd, J = 8.1, 4.2 Hz, NH); ^{13}C NMR δ 8.7 (q), 9.2 (q), 22.8 (t), 24.3 (q), 27.8 (t), 41.2 (q), 42.9 (t), 52.6 (d), 55.5 (d), 58.3 (d), 58.3 (d), 59.4 (t), 59.9 (q), 60.1 (q), 60.2 (q), 60.6 (q), 124.1 (s), 124.8 (s), 125.1 (s), 129.1 (s), 136.8 (s), 142.8 (s), 147.8 (s), 149.8 (s), 150.9 (s), 155.8 (s), 159.8 (s), 183.0 (s), 187.1 (s), 197.1 (s); MS, m/z (relative intensity) 567 (M^+, 1), 469 (100), 234 (18), 220 (29).

(C) Oxidative Demethylation of 39 in Two Steps Using 10 M HNO_3. Partial O-demethylation of **39** (59.7 mg, 0.1 mmol) with boron tribromide as described above afforded the residue (74.4 mg). A solution of this residue in 10 M HNO_3 (2 mL) was stirred at 25 °C for 45 min. The reaction mixture was diluted with water (10 mL) and extracted with chloroform (20 mL × 3). The combined extracts were washed with water (10 mL), dried, and concentrated in vacuo. The residue (34.5 mg) was subjected to chromatography (silica gel, 6 g; elution with 1:200 MeOH–$CHCl_3$) to give **2** (22.0 mg, 41%) as a solid, which was recrystallized from AcOEt–ether to give pale yellow prisms: mp 175–180 °C dec [lit.[7] mp 175–180 °C dec]; IR (KBr) 3380, 1715, 1685, 1655, 1640, 1610, cm^{-1}; UV λ_{max} (log ϵ) 268 (4.33), 368 (3.00) nm; ^{1}H NMR δ 1.27 (1 H, ddd, J = 16.7, 10.1, 2.9 Hz, H-14β), 1.90 (3 H, s, Ar CH_3), 2.00 (3 H, s, Ar CH_3), 2.24 (3 H, s, $COCH_3$), 2.24 (1 H, d, J = 20.8 Hz, H-5β), 2.28 (3 H, s, NCH_3), 2.74 (1 H, ddd, J = 10.1, 3.5, 2.4 Hz, H-14a), 2.76 (1 H, dd, J = 16.7, 3.5 Hz, H-14α), 2.78 (1 H, dd, J = 20.8, 7.8 Hz, H-5α), 2.82 (1 H, dd, J = 10.7, 2.0 Hz, H-7β), 2.98 (1 H, dd, J = 10.7, 2.4 Hz, H-7α), 3.17 (1 H, dddd, J = 7.8, 2.4, 2.0, 0.5 Hz, H-6), 3.20 (1 H, ddd, J = 13.9, 4.2, 3.5 Hz, C*H*NH), 3.66 (1 H, ddd, J = 4.2, 2.9, 1.3 Hz, H-9), 3.75 (1 H, ddd, J = 13.9, 9.8, 1.3 Hz, C*H*NH), 4.00 (each 3 H, s, OCH_3), 4.01 (1 H, dd, J = 2.4, 0.5 Hz, H-15), 6.90 (1 H, dd, J = 9.8, 3.5 Hz, NH); ^{13}C NMR δ 8.6 (q), 8.9 (q), 22.8 (t), 24.4 (q), 25.8 (t), 40.6 (t), 41.3 (q), 52.3 (d), 54.9 (d), 57.1 (d), 57.6 (d), 58.8 (t), 61.0 (q), 61.0 (q), 128.4 (s), 129.4 (s), 136.4 (s), 136.7 (s), 141.8 (s), 142.9 (s), 155.7 (s), 156.2 (s), 160.2 (s), 181.5 (s), 183.0 (s), 185.8 (s), 187.2 (s), 196.6 (s); MS, m/z (relative intensity) 537 (M^+, 5), 441 (74), 439 (100), 437 (44), 234 (33), 231 (11), 220 (97), 218 (30). Anal. Calcd for $C_{28}H_{31}N_3O_8$: C, 62.56; H, 5.81; N, 7.82. Found: C, 62.25; H, 5.79; N, 7.65.

Partial Demethylation of 39 (Isolation of the Phenols 42 and 43). Partial O-demethylation of **39** (88 mg, 0.147 mmol) with boron tribromide as described above afforded the residue (72 mg). This material was subjected to chromatography (silica gel, 8 g; elution with 1:20 MeOH–CH_2Cl_2) to give the phenols **42** (46.4 mg, 54%) and **43** (13.3 mg, 16%).

Compound 42 (not crystallizable): IR ($CHCl_3$) 3390, 1710, 1675 cm^{-1}; ^{1}H NMR δ 1.76 (1 H, dd, J = 15.9, 11.7 Hz, H-14β), 2.15 (3 H, s, Ar CH_3), 2.16 (3 H, s, Ar CH_3), 2.23 (3 H, s, $COCH_3$), 2.30 (3 H, s, NCH_3), 2.48 (1 H, d, J = 17.3 Hz, H-5β), 2.78 (1 H, br, OH), 2.78 (1 H, ddd, J = 11.7, 2.9, 2.2 Hz, H-14a), 2.82 (1 H, dd, J = 17.3, 7.8 Hz, H-5α), 2.94 (1 H, dd, J = 10.7, 2.2 Hz, H-7α), 3.00 (1 H, dd, J = 10.7, 2.4 Hz, H-7β), 3.05 (1 H, dd, J = 15.9, 2.2 Hz, H-14α), 3.13 (1 H, ddd, J = 13.2, 4.2, 2.7 Hz, C*H*NH), 3.22 (1 H, dddd, J = 7.8, 2.4, 2.2, 0.5 Hz, H-6), 3.61 (3 H, s, OCH_3), 3.67 (1 H, ddd, J = 13.2, 8.3, 3.7 Hz, C*H*NH), 3.72 (1 H, dd, J = 3.7, 2.7 Hz, H-9), 3.76, 3.80, 3.81, 3.84 (each 3 H, s, OCH_3), 4.03 (1 H, dd, J = 2.9, 0.5 Hz, H-15), 6.36 (1 H, dd, J = 8.3, 4.2 Hz, NH); ^{13}C NMR δ 9.1 (q), 9.2 (q), 22.0 (t), 24.5 (q), 26.6 (t), 41.4 (q), 42.5 (t), 52.8 (d), 57.3 (d), 58.6 (d), 59.1 (d), 59.9 (q), 59.9 (q), 60.2 (q), 60.2 (q), 60.4 (q), 60.5 (t), 117.2 (s), 118.1 (s), 123.3 (s), 123.9 (s), 125.0 (s), 125.9 (s), 145.3 (s), 145.6 (s), 146.1 (s), 149.0 (s), 149.4 (s), 151.3 (s), 160.2 (s), 196.5 (s); MS, m/z (relative intensity) 583 (M^+, 0.3), 483 (100), 241 (13), 234 (35), 219 (6).

Compound 43 (not crystallizable): IR ($CHCl_3$) 3390, 1715, 1685 cm^{-1}; ^{1}H NMR δ 1.72 (1 H, dd, J = 15.4, 11.7 Hz, H-14β), 2.13 (3 H, s, Ar CH_3), 2.16 (3 H, s, Ar CH_3), 2.25 (3 H, s, $COCH_3$), 2.32 (3 H, s, NCH_3), 2.51 (1 H, d, J = 17.1 Hz, H-5β), 2.72 (1 H, ddd, J = 11.7, 2.7, 2.2 Hz, H-14a), 2.84 (1 H, dd, J = 17.1, 7.1 Hz, H-5α), 2.87 (1 H, dd, J = 15.4, 2.2 Hz, H-14α), 2.94 (1 H, dd, J = 10.8, 2.4 Hz, H-7α), 2.98 (1 H, dd, J = 10.8, 2.2 Hz, H-7β), 3.09 (1 H, ddd, J = 13.2, 4.4, 2.9 Hz, C*H*NH), 3.22 (1 H, dddd, J = 7.1, 2.4, 2.2, 0.5 Hz, H-6), 3.63 (1 H, ddd, J = 13.2, 7.6, 3.9 Hz, C*H*NH), 3.71 (1 H, dd, J = 3.9, 2.9 Hz, H-9), 3.74, 3.77, 3.80, 3.83 (each 3 H, s, OCH_3), 4.04 (1 H, dd, J = 2.7, 0.5 Hz, H-15), 6.43 (1 H, dd, J = 7.6, 4.4 Hz, NH); MS, m/z (relative intensity) 569 (M^+, 0.4), 469 (100), 234 (50).

Acetylation of 42. To a solution of **42** (21.2 mg, 0.036 mmol) in dry pyridine (0.4 mL) was added acetic anhydride (0.2 mL), and the mixture was kept at room temperature for 12 h. After dilution with water (10 mL), the mixture was extracted with chloroform (20 mL × 3). The combined extracts were washed with water (10 mL), dried, and concentrated in vacuo. The residue (35 mg) was subjected to chromatography (silica gel, 5 g, 1:50 MeOH–CH_2Cl_2) to give **44** (17.7 mg, 78%) as a colorless amorphous powder: IR ($CHCl_3$) 3380, 1755, 1720, 1685 cm^{-1}; ^{1}H NMR δ 1.85 (1 H, dd, J = 15.9, 11.7 Hz, H-14β), 2.06 (3 H, s, $COCH_3$), 2.13 (3 H, s, Ar CH3), 2.17 (3 H, s, Ar CH_3), 2.27 (1 H, d, J = 18.1 Hz, H-5β), 2.32 (3 H, s, $COCH_3$), 2.32 (3 H, s, NCH_3), 2.82 (1 H, ddd, J = 11.7, 2.4, 2.2 Hz, H-14a), 2.82 (1 H, dd, J = 18.1, 7.8 Hz,

H-5α), 2.94 (1 H, dd, J = 10.5, 2.2 Hz, H-7α), 3.00 (1 H, dd, J = 10.5, 2.4 Hz, H-7β), 3.07 (1 H, dd, J = 15.9, 2.2 Hz, H-14α), 3.14 (1 H, dddd, J = 7.8, 2.4, 2.2, 0.5 Hz, H-6), 3.21 (1 H, ddd, J = 13.2, 3.7, 2.7 Hz, CHNH), 3.43 (1 H, ddd, J = 13.2, 7.8, 2.9 Hz, CHNH), 3.54 (3 H, s, OCH_3), 3.74 (3 H, s, OCH_3), 3.84 (1 H, dd, J = 2.9, 2.9 Hz, H-9), 3.88, 3.88, 3.89 (each 3 H, s, OCH_3), 4.08 (1 H, dd, J = 2.4, 0.5 Hz, H-15), 6.67 (1 H, dd, J = 7.8, 3.7 Hz, NH); MS, m/z (relative intensity) 625 (M^+, 0.2), 525 (100), 276 (12), 234 (10).

Methylation of 41. Etheral diazomethane solution (0.5 mL) was added dropwise to a cooled (0 °C) solution of **41** (5.9 mg, 0.016 mmol) in dry ether (0.5 mL), and the reaction mixture was kept at the same temperature for 1 h. The reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (20 mL × 3). The combined extracts were washed with water, dried, and concentrated in vacuo to obtain **40** (4.9 mg, 81.3%) as pale yellow needles, mp 203–205 °C dec, which were identical in all respects with **40** prepared as above.

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Supplementary Material Available: Tables of X-ray structural data of **26** and **32** (46 pages). Ordering information is given on any current masthead page.

Naphtho[2,1-*b*]thiophene-Linked 1,2-Dithia-5,8-diazacyclodecanes and Imidazolidino[1,2-*d*]dithiazepines: Synthesis, Structure Proof by X-ray Diffraction Analysis, and DNA Binding Properties

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Coupling of the metal-sequestering ligand 3,3,10,10-tetramethyl-6-(hydroxymethyl)-1,2-dithia-5,8-diazacyclodecane with naphtho[2,1-*b*]thiophene-3-carboxylic acid in the presence of carbonyldiimidazole affords the ester and the 5,6-cyclic carbamate. The structure of the latter was secured and the conformation deduced from single-crystal X-ray diffraction. Similar reaction of 1,1,4,4-tetramethyl-8-(hydroxymethyl)imidazolidino[1,2-*d*]dithiazepine with the intercalative chromophore naphtho[2,1-*b*]thiophene affords the desired ester in addition to the 8,9-cyclic carbamate of the bicyclic disulfide compound. Both 7- and 8-substituted imidazolidino[1,2-*d*]dithiazepines react with tetrahydrofuran in the presence of the ether peroxide to afford the 9-(2-tetrahydrofuranyl) derivatives in a reaction that is analogous to recent anodic oxidation studies of amidyl anions in THF. The structure of a THF adduct was confirmed by X-ray diffraction analysis. The prototype sulfur ligand structures linked to the naphtho[2,1-*b*]thiophene chromophore **2** and **5** bind to double-helical DNA with binding constants of 4.3×10^6 and 3.6×10^6 M^{-1}, respectively.

The glycopeptide antitumor antibiotic bleomycin appears to act by a unique mechanism involving the site-selective binding to double-stranded DNA and oxygen-mediated scission of the strands catalyzed by the hexacoordinated iron binding domain thus brought into proximity with sensitive sites.[1,2,4-6]

Functional bleomycin models, in which the operational properties of the natural product are retained, were designed, synthesized, and tested.[7-10] Prototype structures, i.e., hemin–spermine–chromophores, reproduce many of the essential features of the natural glycopeptide in producing oxygen-mediated DNA scission in the presence of a thiol reducing agent, e.g., dithiothreitol or 2-mercaptoethanol, and at concentrations comparable with those employed with bleomycin itself.[7,8,10] The intercalative chromophores employed in the prototype structures (acridine, acodazole, naphtho[1,2-*b*]thiophene, and stilbene) resulted, as expected, in smooth and base-neutral cleavage at every base pair of test DNA sequences such as a 139 base pair HindIII/NciI fragment of pBR322.[10]

We are now exploring alternative metal-sequestering groups in addition to the porphyrins. Accordingly, we report the synthesis of structures in which both 1,2-dithia-5,8-diazacyclodecanes[11-14] and related imidazolidino-[1,2-*d*]dithiazepines[15] are linked to DNA intercalative naphtho[2,1-*b*]thiophene chromophores and initial exploration of their properties, including facile reversible aminol formation in the presence of tetrahydropyranyl hydroperoxide. We also describe the structural verification of key derivatives by X-ray diffraction and DNA binding studies of the final agents.

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