Pergamon

Tetrahedron Vol. 51, No. 30, pp. 8231-8246, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00436-X

Synthesis of Saframycins. XII.[1] Total Synthesis of (-)-*N*-Acetylsaframycin Mx 2 and Its *epi*-(+)-Enantiomer.†

Naoki Saito,[a] Shunji Harada,[a] Izumi Inouye,[a] Kentaro Yamaguchi,[b] Akinori Kubo[a]*

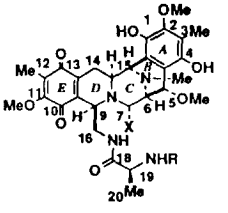
Meiji College of Pharmacy, 1-35-23 Nozawa, Setagaya-ku, Tokyo 154, Japan[a] and Department of Chemical Analysis Center, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263, Japan[b]

Abstract: *The first total synthesis of (-)-N-acetylsaframycin Mx 2 (**1c**) from (±)-pentacyclic amine **10b** is described. The reaction of **10b** with Cbz-L-alanine gave an inseparable mixture of amides **11b** and **14b**. Deprotection of the Cbz group to amines **11b** and **14b** followed by treatment with acetic anhydride in pyridine produced amides **13b** and **16b**. The structure of **16b** was determined by X-ray crystallography. The conversion of **13b** to the bisquinone **20** and subsequent stereoselective and regioselective introduction of the methoxyl group at position 5 provided **22**. Finally, **22** was subjected to catalytic reduction and regioselective oxidation to give **1c**. On the other hand, the epi-emantiomer **16b** was transformed to **27** in a same four-step sequence. The specific optical rotation and the CD spectra of **1c** and **27** were of opposite sign. The assignment of the absolute configuration of saframycins Mx as 5S,6R,9R,14aS,15R,19S is also discussed.*

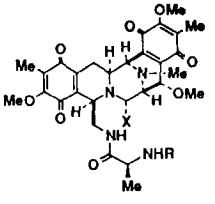
† *This paper is dedicated to Earl Blough Professor Paul A. Grieco (Indiana University) on the occasion of his 50th birthday.*

Saframycins Mx 1 (**1a**) and Mx 2 (**1b**) were discovered in the culture broth of the myxobacterium, *Myxococcus xanthus* strain Mx x48 in 1988.[2] They were active against the mouse tumor line, mouse fibroblast L929 cell line, the Vero kidney green monkey cell line, and human MBA9812 lung carcinoma. The structure of saframycin Mxs were elucidated by a detailed analysis of the high-field ^{1}H NMR spectra in CD_3OD solution. They belong to a family of novel isoquinolinequinone antibiotics such as saframycin A-F (**2a-f**)[3] and safracins A-B (**3a-b**) (Fig. 1).[4] Saframycins Mx 1 (**1a**) and Mx 2 (**1b**) are very sensitive to light and to oxygen, and above pH 7 are quickly oxidized to afford the corresponding bisquinones **1d** and **1e**, respectively. The acetylation of **1a** with acetic anhydride in buffer solution proceeds with air oxidation of the A-ring to afford the bisquinone **1f** in excellent yield. Because the acid hydrolysis of **1a** and **1b** yields *L*-alanine and by comparing the optical rotations with those of safracins A (**3a**) and B (**3b**), the relative and absolute configurations of the saframycin Mxs are probably the same as that of the safracins.[2b] We became interested in the saframycin Mxs, with an E-ring a quinone moiety and an A-ring hydroquinone, because the only successful total synthesis within the saframycin family has been of the bisquinone series.[5] Recently, we succeeded in the transformation of bisquinone **4** to the corresponding quinone-hydroquinone **2e** *via*

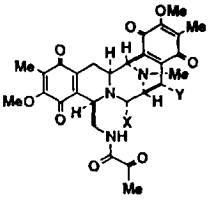
bishydroquinone **5** (Scheme 1).[6] Since then we have focused our attention on the synthetic studies of the quinones **17** and **1c** which have an alanyl amide side chain. We present here the first total synthesis of optically active *N*-acetylsaframycin Mx 2 (**1c**) from the amine (**10b**), which was a key intermediate of our saframycin B synthesis, in order to prove unambiguously the absolute configuration of the original assignment.



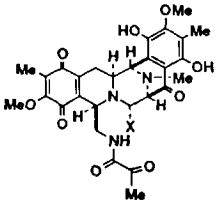
saframycins:
Mx 1 (1a): X = OH, R = H
Mx 2 (1b): X = R = H
1c: X = H, R = Ac



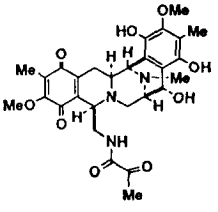
1d: X = OH, R = H
1e: X = H, R = H
1f: X = OH, R = Ac



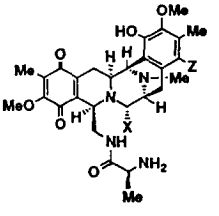
saframycins:
A (2a): X = CN, Y = H
B (2b): X = Y = H
C (2c): X = H, Y = OMe



saframycins:
D (2d): X = H
F (2f): X = CN

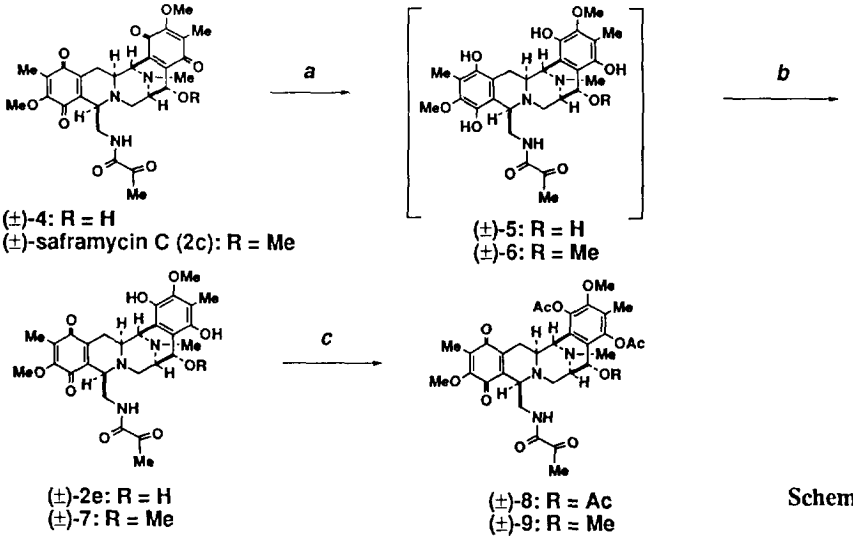


saframycin E (2e)



safracins:
A (3a): X = Z = H
B (3b): X = OH, Z = H
3c: X = H, Z = Br

Fig. 1



(±)-4: R = H
(±)-saframycin C (2c): R = Me

(±)-5: R = H
(±)-6: R = Me

(±)-2e: R = H
(±)-7: R = Me

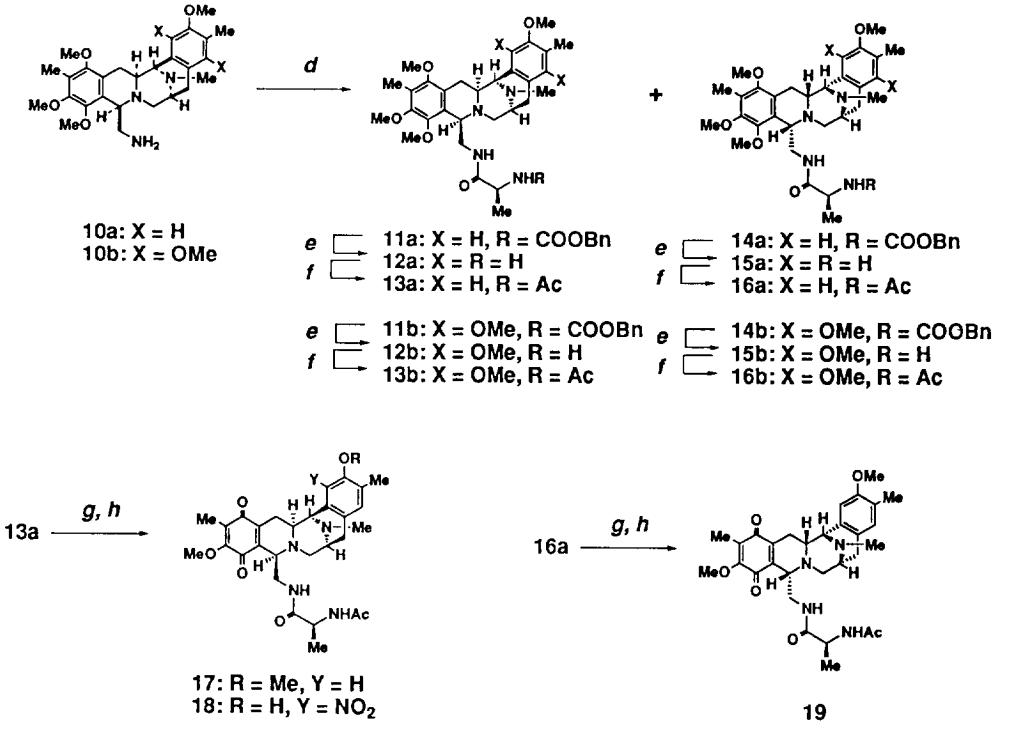
(±)-8: R = Ac
(±)-9: R = Me

Scheme 1

reagents and conditions: a) H_2, 10% Pd/C, EtOAc, room temperature, 1.5 h; b) O_2, SiO_2, EtOAc, room temperature, 40 h, 58% (2 steps); c) Ac_2O, pyridine 40%.

Results and Discussion

The stability of the A-ring hydroquinone in saframycin Mxs (**1a-b**) is believed to be due to hydrogen bonding between the C-5 methoxy group and the C-4 phenol. To test this hypothesis, we first studied the reduction of (±)-saframycin C (**2c**) to the bishydroquinone **6** (Scheme 1). Hydrogenation of (±)-**2c**[7] with 10% Pd/C in ethyl acetate for 1.5 h gave the leuco compound **6**. It was difficult to isolate this compound and upon standing in organic solvent at 0°C for several hours, it afforded a 1:2 mixture of **7** and **6**. Further treatment of this mixture with SiO_2 in ethyl acetate in the presence of oxygen for 40 h afforded only (±)-**7** in 58% overall yield. The assignment of **7** was made by ^1H NMR analysis. Diagnostic homoallylic coupling (3.0 Hz) between H-9 (δ 3.54) and H-14β (δ 1.60) through five bonds was observed.[3] Acetylation of **7** with acetic anhydride in pyridine gave the diacetate **9** in 40% yield. Thus, we achieved a useful transformation of (±)-**2c** to (±)-**7**.



Scheme 2

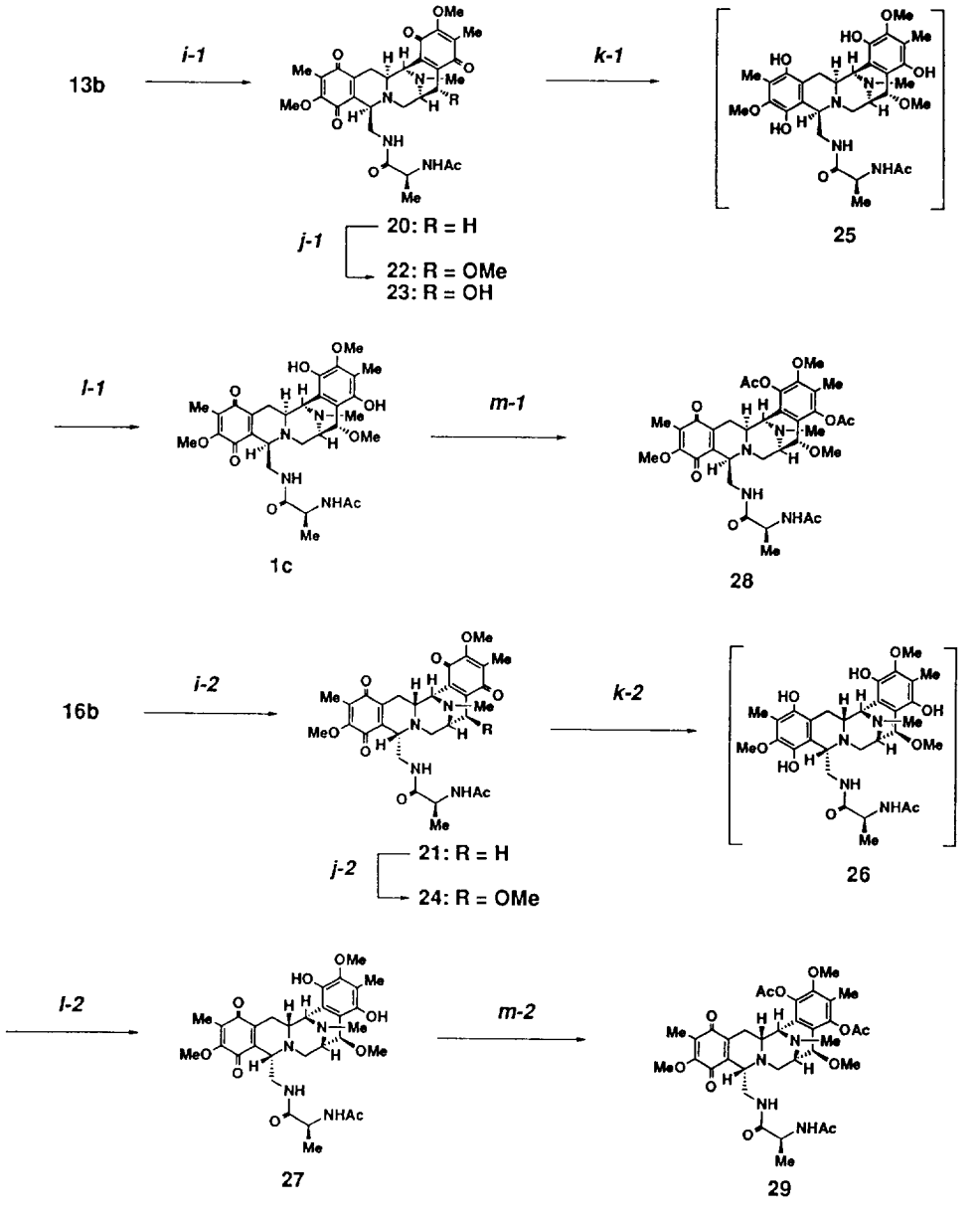
reagents and conditions: a series: d) Cbz-(*L*)-alanine, DCC, DMAP, CH_2Cl_2, room temperature, 14 h, 82%; e) H_2, 10% Pd/C, EtOH, room temperature, 48 h (**12a**, 42%; **15a**, 44%); f) Ac_2O, pyridine (**13a** from **12a**, 89%; **16a** from **15a**, 86%); *b series*: d) Cbz-(*L*)-alanine, DCC, DMAP, CH_2Cl_2, room temperature (**11b**, 42%; **14b**, 36%); e) H_2, 10% Pd/C, EtOAc, room temperature, 22 h (**12b** from **11b**, 79%; **15b** from **12b**, 93%); f) Ac_2O, pyridine (**13b** from **12b**, 88%; **16b** from **15b**, 77%); g) BBr_3, CH_2Cl_2; h) 8M HNO_3, 0 °C, 1 h (**17**, 40% and **18**, 16% from **13a**; **19**, 49 % from **16a**).

The next stage was to establish a method for the synthesis of optically active monoquinones **17** and **19** with an alanyl amide side chain at C-9 position (Scheme 2). Condensation of the amine **10a**[1] and Cbz-(*L*)-alanine with DCC furnished the amides **11a** and **14a** in 82% yield as an inseparable diastereomeric mixture.[8] Deprotection of a mixture of the amides **11a** and **14a** gave the amines which were separated by chromatography on a preparative silica gel layer to give **12a** and **15a** in 42% and 44% yields, respectively. These amines were separated by chromatography on a preparative silica gel layer and carried on separately to the final quinones. The stereochemistries of **12a** and **15a** were undetermined at this stage. Acetylation of **12a** with acetic anhydride in pyridine gave the acetate **13a** in 89% yield. Treatment of **13a** with 2.5 equiv of boron tribromide in CH_2Cl_2 at -78 °C for 1 h and then at 0 °C for 1h gave the mixture of phenols which was subjected to oxidative demethylation with 8M HNO_3 at 0 °C for 1 h to afford quinones **17** and **18** in 40% and 16% yields, respectively. Similarly, **15a** was converted into **19** in a three-step sequence. The CD spectra of **17** and **19** were the mirror images. The ^1H NMR spectrum of **17** displayed the alanine methine at δ 3.34, whereas the ^1H NMR spectrum of **19** showed this peak (δ 3.74) at lower fields. Thus, we have efficiently synthesized *N*-acetyl-1-deshydroxysafracin A (**17**) in optically active form.

Encouraged by the results of these model transformations, we applied this strategy to the transformation of the amine **10b**[5a] to the *N*-acetylsaframycin Mx-2 (**1c**) and its *epi*-enantiomer **27**. Condensation of **10b** and Cbz-(*L*)-alanine with DCC furnished the amides **11b** and **14b** in 42% and 36% isolated yields, respectively (Scheme 2). Deprotection of **11b** gave the amine **12b** in 79% yield. Acetylation of **12b** with acetic anhydride in pyridine gave the acetate **13b** in 88% yield. Similarly, **14b** was converted into **16b** in excellent yield.[9] Compound **16b** is a highly crystalline compound, and presented an opportunity to determine its relative stereochemistry by X-ray. An ORTEP drawing of this compound is presented in Fig. 2. This data allowed the assignment of the absolute stereochemistry of **16b** as 5*R*,6*S*,9*S*,14a*R*,15*S*,19*S*. The CD spectra of **13b** and **16b** are of opposite sign.

Conversion of the polymethoxyarene **13b** to the bisquinone **20** was accomplished using partial demethylation with boron tribromide followed by oxidative demethylation in 36% overall yield (Scheme 3). The introduction of a methoxyl group into the C-5 position of **20** was achieved using selenium dioxide in methanol at room temperature for 76 h to give **22** in 42% yield along with the 5-hydroxy compound **23** in 37% yield. The methoxyl stereochemistry of **22** was assigned on the basis of the signal of the 5-H (δ 3.88, s).[7] The final transformation of the polymethoxyarene **13b** was accomplished with hydrogenation followed by air oxidation. Hydrogenation of **22** with 10% Pd/C in ethyl acetate for 1h gave the leuco compound **25**, and after removal of the solvent in vacuo, **25** was treated with SiO_2 in ethyl acetate at room temperature for 24 h in the presence of oxygen to afford **1c** and **22** in 56% and 4% yields, respectively. This hydroquinone **1c** was also very sensitive to light and oxygen. Thus, producing the more stable derivatives of **1c**, and acetylation of **1c** with acetic anhydride in pyridine furnished the diacetate **28** in 70% yield along with restored **22** (19%). Similarly, **16b** was converted into the *epi*-enantiomer **27** in a four-step sequence. Acetylation of **27** gave **29** in 68% yield along with restored **24** (1%). Assignment of the monoquinones **28** and **29** were also made by 500-MHz ^1H NMR analysis. In the ^1H NMR spectra of **28** and **29**, the diagnostic homoallylic coupling was observed, together with the data of natural saframycin Mx 1 (**1a**).[10]

Having established the synthetic scheme to *N*-acetylsaframycin Mx 2 (**1c**) and its *epi*-enantiomer **27**, we now have an authentic CD spectra of two enantiomeric isomers of the saframycin core, that are useful for the determination of the absolute stereochemistry of the natural saframycin family. Among the saframycin A-F (**2a-f**), the structure of **2c** was elucidated by X-ray crystallography, however, the absolute

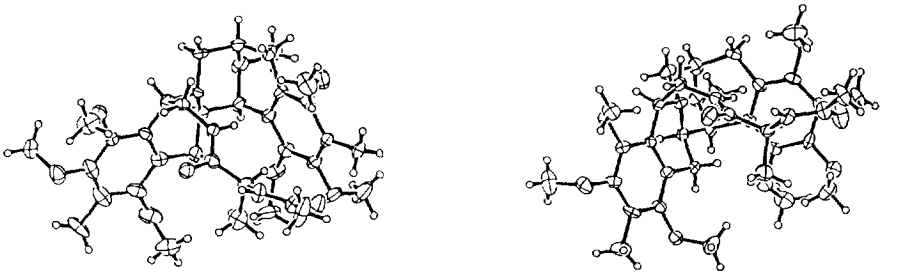


Scheme 3

reagents and conditions: i-1) BBr_3, CH_2Cl_2 and then 10M HNO_3, 36%; j-1) SeO_2, MeOH, room temperature, 76 h (**22**, 42%; **23**, 37%); k-1) H_2, 10% Pd/C, EtOAc, room temperature, 1 h; l-1) O_2, SiO_2, EtOAc, room temperature, 24 h (1c, 56%, **22**, 4%, 2 steps); m-1) Ac_2O, pyridine (**28**, 70%, **22**, 19%); i-2) BBr_3, CH_2Cl_2 and then 10M HNO_3, 42%; j-2) SiO_2, MeOH, room temperature, 72 h, 49.1%; k-2) H_2, 10% Pd/C, EtOAc, room temperature, 1 h; l-2) O_2, SiO_2, EtOAc, room temperature, 24 h (**27**, 51%, **24**, 12%); m-2) Ac_2O, pyridine (**29**: 68%, **24**, 1.4%).

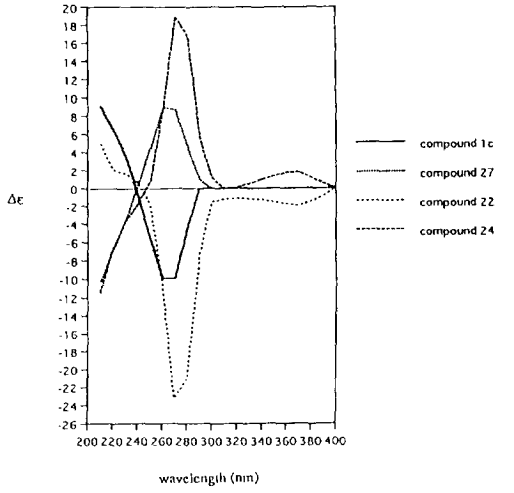
configuration was not determined.[11] The CD spectra of **1c** and **22** displayed a negative Cotton effect in the 270 nm region, as do the natural saframycins A-C (**2a-c**) (Fig. 3). On the other hand, the *epi*-enantiomers **27** and **24** showed a positive Cotton effect in the 270 nm region. Thus, we conclude that the assignment of the absolute configuration of saframycins A-C (**2a-c**) is the same as that of saframycins Mx 1 (**1a**) and Mx 2 (**1b**).

Fig. 2. ORTEP drawing of compound **16b** (two molecules are included in an asymmetric unit).



Molecular Structure I **Molecular Structure II**

Fig. 3. CD spectra of compound **1c** and its congeners in MeOH.



Conclusion

In summary, we have succeeded in the first total synthesis of *N*-acetylsaframycin Mx 2 (-)-**1c** and its *epi*-enantiomer (+)-**27** from (±)-**10b**. These results indicate that safracins are plausible and important biogenetic intermediates of all the saframycin families.[12-14] The preparation and biological activity of the optically active saframycins and their enantiomeric analogs will be reported in future publications from this laboratory.[15]

Experimental Section

All melting points were determined with a Yanagimoto micromelting point apparatus and uncorrected. IR spectra were measured with a Hitachi 260 spectrophotometer. UV spectra were determined in methanol. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ at 270 and 67.5 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. Thin-layer chromatography was performed on Merck precoated silica gel 60F-254 plates. Column chromatography was performed with Merck silica gel 60 (70-230 mesh). Elemental analyses were obtained by using a Perkin-Elmer Model 240B elemental analyzer. Optical rotations were performed with a Horiba SEPA-200 automatic digital polarimeter. CD spectra were measured with a JASCO J-500A spectrometer for solutions in methanol.

***N*-[(6,7,9,10,13,14,14a,15-Octahydro-1,4-dihydroxy-2,5,11-trimethoxy-3,12,16-trimethyl-10,13-dioxo-(5α,6α,9α,14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]-2-oxo-propanamide (7).** A solution of (±)-**1c** (45.4 mg, 0.08 mmol) in ethyl acetate (10 mL) was hydrogenated over 10% palladium on carbon (23 mg) at 1 atm for 1.5 h. The catalyst was removed by filtration and washed with ethyl acetate (100 mL). The combined filtrates were concentrated in vacuo to give a colorless solid (**6**, 70.4 mg), which was used for the next step without further purification. Silica gel (200 mg) was added to a solution of **6** in ethyl acetate (10 mL), and the mixture was stirred in an oxygen atmosphere at room temperature for 40 h. The reaction mixture was filtered and washed it with ethyl acetate (100 mL). The combined filtrates were concentrated in vacuo to give a solid (70.3 mg), recrystallization of which from ethyl acetate-methanol to give **7** (26.5 mg, 58.2%) as pale yellow needles: mp 183-185 °C dec; IR (KBr) 3410, 1725, 1695, 1660, 1645, 1625 cm^{-1}; UV λ_{max} (log ε) nm240 (3.68), 270 (3.98), 276 (3.98), 374 (2.65); ^1H NMR δ (CD_3OD) 1.60 (1H, ddd, J = 18.1, 10.9, 3.0 Hz, H-14β), 1.91 (3H, s, 12-CH_3), 2.19 (3H, s, 3-CH_3), 2.22 (3H, s, $COCH_3$), 2.44 (3H, s, NCH_3), 2.63 (1H, ddd, J = 10.9, 3.0, 3.0 Hz, H-14a), 2.93 (1H, dd, J = 18.1, 3.0 Hz, H-14α), 3.02 (1H, dd, J = 10.6, 2.0 Hz, H-7), 3.18 (1H, dd, J = 10.6, 2.0 Hz, H-7), 3.25 (2H, m, 9-CH_2N), 3.48 (1H, br, H-6), 3.54 (1H, br s, H-9), 3.61 (3H, s, 5-OCH_3), 3.77 (3H, s, 2-OCH_3), 4.00 (3H, s, 11-OCH_3), 4.31 (1H, s, 5-H), 4.35 (1H, d, J = 3.0 Hz, 15-H), 6.78 (1H, br s, NH); ^{13}C NMR δ (CD3OD) 7.8 (q, 3-CH_3), 8.5 (q, 12-CH_3), 23.5 (q, $COCH_3$), 24.5 (t, C-14), 39.8 (t, 9-CH_2), 41.0 (q, NCH_3), 55.7 (d, C-6), 55.7 (q, 5-OCH_3), 55.9 (t, C-7), 56.5 (d, C-15), 56.9 (d, C-14a), 57.7 (d, C-9), 59.8 (q, 2-OCH_3), 60.3 (q, 11-OCH_3), 74.7 (d, C-5), 114.6 (s), 116.6 (s), 118.3 (s), 127.5 (s), 136.0 (s), 140.1 (s), 142.4 (s), 145.9 (s), 146.0 (s), 155.7 (s), 160.4 (s), 182.8 (s), 185.9 (s), 195.1 (s); EI-MS m/z (relative intensity) 569 (M^+, 4), 537 (22), 469 (30), 467 (11), 439 (22), 438 (31), 437 (100), 235 (14), 234 (28), 220 (56), 219 (22), 218 (38), 205 (12), 204 (13), 43 (15); high-resolution EIMS calcd for $C_{29}H_{35}N_3O_9$ 569.2373, found 569.2377. Anal. Calcd for $C_{29}H_{35}N_3O_9 \cdot 1/2H_2O$: C, 60.20; H, 6.27; N, 7.26. Found: C, 60.28; H, 6.33; N, 7.00.

***N*-[(1,4-Diacetoxy-6,7,9,10,13,14,14a,15-octahydro-2,5,11-trimethoxy-3,12,16-trimethyl-10,13-dioxo-(5α,6α,9α,14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]-2-oxo-propanamide (9).** Acetic anhydride (0.2 mL) was added to a solution of **7** (14.1 mg, 0.0248 mmol) in dry pyridine (0.5 mL), and the mixture was left to stand at room temperature for 24 h. After being diluted with water (10 mL), the mixture was extracted with chloroform (10 mL x 3). The combined extracts were washed with 5% $NaHCO_3$, dried, and concentrated in vacuo to give the residue (17.5 mg). Chromatography on a silica gel (5 g) column with 100:1 dichloromethane-methanol afforded **9** (6.4 mg, 39.5%) as pale yellow amorphous powder: IR ($CHCl_3$) 3350, 1745, 1710, 1665, 1645, 1610 cm^{-1}; UV λ_{max} (log ε) nm 240 (3.68), 270 (3.98), 276 (3.98), 374 (2.65); ^1H NMR δ 1.36 (1H, ddd, J = 17.5, 11.2, 2.6 Hz, H-14β), 1.89 (3H, s, 12-CH_3), 2.09 (3H, s, $COCH_3$), 2.20 (3H, s, 3-CH_3), 2.39 (3H, s, OAc), 2.40 (q, OAc), 2.47 (3H, s, NCH_3), 2.65 (1H, ddd, J = 11.2, 2.6, 2.6 Hz, H-14a), 2.78 (1H, dd, J = 17.5, 2.6 Hz, H-14α), 2.88 (1H, dd, J = 10.9, 2.3 Hz, H-7), 2.95 (1H, dd, J = 10.9, 1.6 Hz, H-7), 2.97 (1H, m, 9-C*H*N), 3.34 (1H, br s, H-6), 3.49 (3H, s, 5-OCH_3), 3.60 (1H, br s, H-9), 3.66 (1H, m, 9-C*H*N), 3.74 (1H, s, H-5), 3.76 (1H, d, J = 2.6 Hz, H-15), 3.78 (3H, s, 2-OCH_3), 4.06 (3H, s, 11-OCH_3), 6.94 (1H, br s, NH); EI-MS m/z (relative intensity) 653 (M^+, 32), 555 (12), 554 (41), 553 (100), 511 (13), 350 (16), 334 (23), 304 (22), 292 (12), 262 (12), 220 (11); high-resolution EIMS calcd for $C_{33}H_{39}N_3O_{11}$ 653.2585, found 653.2585.

(±)-2SR-(Benzyloxycarbonyl)amino-*N*-[(6,7,9,14,14a,15-hexahydro-2,10,11,13-tetramethoxy-3,12,16-trimethyl-(6α,9α(RS),14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (11a*) and (±)-2SR-(Benzyloxycarbonyl)amino-*N*-[(6,7,9,14,14a,15-hexahydro-2,10,11,13-tetramethoxy-3,12,16-trimethyl-(6β,9β(SR),14aβ,15β)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (14a*).

A stirred solution of the amine **10a** (220.1 mg, 0.471 mmol), 4-(dimethylamino)pyridine (138.2 mg, 0.113 mmol), and Cbz-(*DL*)-alanine (126.3 mg, 0.566 mmol) in dry dichloromethane (10 mL) was cooled with ice-water, a dichloromethane (2 mL) solution of DCC (116.7 mg, 0.566 mmol) was added dropwise over 10 min. The solution was stirred at room temperature for 14 h, and the reaction mixture was concentrated in vacuo. The residue was dissolved with benzene (10 mL), and extracted with 3N HCl (10 mL x 3). The combined aqueous extracts were made alkaline with diluted NH_4OH and extracted with chloroform (10 mL x 3). The combined extracts were washed with water (10 mL), dried, and concentrated in vacuo. The residue (535 mg) was subjected to chromatography (silica gel, 50 g; elution with 20:1 dichloromethane-methanol) to give the residue (240.2 mg, 75.1%) as colorless amorphous powder. Crystallization of which from ethyl acetate gave **11a*** (87.3 mg) as colorless prisms. The combined mother liquor was concentrated in vacuo to give the residue (153.0 mg) as amorphous powder, whose ^1H NMR spectrum showed ca 2:3 mixture of the diastereomer **11a*** and **14a***.

Compound 11a*: mp 161-162 °C; IR (KBr) 3380, 3180, 1725, 1685, 1615, 1655, 1510, 1465, 1410, 1365, 1345, 1330, 1315, 1290, 1255, 1235, 1225, 1210, 1160, 1115, 1080, 1045, 1015, 975, 960, 865, 850, 765, 745, 705 cm^{-1}; UV λ_{max} nm (log ε) 226 (4.28), 280 (3.62), 289 (3.53); ^1H NMR δ 0.96 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$), 2.10 (1H, dd, *J* = 15.2, 11.6 Hz, H-14β), 2.12 (3H, s, 12-CH_3), 2.20 (3H, s, 3-CH_3), 2.40 (3H, s, NCH_3), 2.54 (1H, d, *J* = 17.1 Hz, 5-Hβ), 2.88 (2H, m, 14a-H and 14-Hβ), 3.02 (3H, m, 9-C*H*N and 2 x H-7), 3.11 (1H, dd, *J* = 17.1, 7.6 Hz, H-5α), 3.18 (1H, br d, H-6), 3.31 (1H, m, C*H*CH_3), 3.53 (3H, s, OCH_3), 3.64 (2H, br, 9-C*H*N and 15-H), 3.74 (3H, s, OCH_3), 3.78 (1H, d, *J* = 2.4 Hz, H-9), 3.85, 3.87 (each 3H, s, OCH_3), 4.97 (2H, s, OCH_2Ph), 5.18 (1H, d, *J* = 7.1 Hz, NH), 5.42 (1H, br d, NH), 6.56 (1H, s, H-1), 6.92 (1H, s, H-4), 7.26-7.36 (5H, m, ArH x 5); ^{13}C NMR δ 9.2 (q, 12-CH_3), 16.1 (q, 3-CH3), 19.3 (q, CH*C*H_3), 26.8 (t, C-5), 27.1 (t, C-14), 41.4 (q, NCH_3), 43.2 (t, 9-CH_2), 50.3 (d, *C*HCH_3), 53.6 (d, C-6), 55.5 (q, OCH_3), 57.9 (d, C-9), 58.7 (d, C-14a), 59.9 (q, OCH_3), 60.1 (q, OCH_3), 60.2 (q, OCH_3), 60.6 (t, C-7), 64.2 (d, C-15), 66.4 (t, OCH_2), 111.3 (d, C-1), 123.7 (s), 124.4 (s), 125.4 (s), 125.9 (s), 127.2 (s), 128.0 (d x 2), 128.1 (d), 128.5 (d x 2), 129.6 (d, C-4), 131.0 (s), 136.5 (s), 146.0 (s), 149.5 (s), 150.7 (s), 155.0 (s), 155.2 (s, CO), 171.4 (s, CO); EI-MS *m/z* (relative intensity) no M^+, 438 (32), 437 (100), 188 (26). Anal. Calcd for $C_{38}H_{48}N_4O_7$: C, 67.83; H, 7.19; N, 8.33. Found: C, 67.57; H, 7.19; N, 8.15.

(±)-2SR-Amino-*N*-[(6,7,9,14,14a,15-hexahydro-2,10,11,13-tetramethoxy-3,12,16-trimethyl-(6α,9α(RS),14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (12a*).

A solution of **11a*** (70.4 mg, 0.1048 mmol) in ethanol (8 mL) was hydrogenated over 10% palladium on carbon (35 mg) at 1 atm for 4 h. The catalyst was removed by filtration and washed with ethanol (50 mL). The combined filtrates were concentrated in vacuo and the residue (63.1 mg) was subjected to chromatography (silica gel, 15 g; elution with 100:3-10:1 chloroform-methanol) to give **12a*** (43.9 mg, 77.9%) as colorless amorphous powder; IR ($CHCl_3$) 3340, 2900, 2840, 2820, 1655, 1612, 1455, 1402, 1358, 1340, 1320, 1300, 1282, 1145, 1105, 1070, 1045, 1008, 962, 890, 850 cm^{-1}; UV λ_{max} (log ε) nm 228 (4.27), 272sh (3.08), 278 (3.16); ^1H NMR δ 0.88 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 1.64 (2H, br s, NH_2), 2.15 (3H, s, 12-CH_3), 2.15 (1H, dd, *J* = 17.5, 10.2 Hz, 14-Hβ), 2.17 (3H, s, 3-CH_3), 2.37 (3H, s, NCH_3), 2.60 (1H, d, *J* = 17.2 Hz, H-5β), 2.84 (1H, q, *J* = 6.9 Hz, C*H*CH_3), 2.86 (1H, ddd, *J* = 10.2, 2.3, 2.0, H-14a), 2.86 (1H, dd, *J* = 17.5, 2.3 Hz, H-14α), 2.96 (1H, dd, *J* = 10.6, 2.3 Hz, H-7), 3.05 (1H, dd, *J* = 10.6, 2.3 Hz, H-7), 3.06 (1H, dd, *J* = 17.2, 7.6 Hz, H-5α), 3.19 (1H, br d, H-6), 3.31 (1H, ddd, *J* = 13.2, 4.6, 4.6 Hz, 9-C*H*N), 3.52 (1H, ddd, *J* = 13.2, 6.9, 2.0 Hz, 9-C*H*N), 3.61 (3H, s, OCH_3), 3.61 (1H, dd, *J* = 2.0, 0.5 Hz, H-15), 3.74 (3H, s, OCH_3), 3.77 (1H, dd, *J* = 4.3, 2.0 Hz, H-9), 3.83, 3.86 (each 3H, s, OCH_3), 6.36 (1H, dd, *J* = 6.9, 4.3 Hz, NH), 6.54 (1H, s, H-1), 6.90 (1H, s, H-4); ^{13}C NMR δ 9.2 (q, 12-CH_3), 15.9 (q, 3-CH_3), 21.3 (q, CH*C*H_3), 26.5 (t, C-5), 27.5 (t, C-14), 41.3 (q, NCH_3), 42.2 (t, 9-CH_2), 50.6 (d, *C*HCH_3), 53.6 (d, C-6), 55.5 (q, OCH_3), 58.3 (d, C-9), 58.5 (d, C-14a), 59.9 (q, OCH_3), 60.1 (q, OCH_3), 60.3 (q, OCH_3), 60.3 (t, C-7), 64.2 (d, C-15), 111.1 (d, C-1), 123.5 (s), 124.7 (s), 125.0 (s), 126.1 (s), 127.7 (s), 129.4 (d, C-4), 130.9 (s), 146.1 (s), 149.6 (s), 150.6 (s), 154.8 (s), 175.4 (s, CO); positive FABMS (magic bullet) *m/z* 539 (M^+ + 1).

(±)-2SR-Amino-*N*-[(6,7,9,14,14a,15-hexahydro-2,10,11,13-tetramethoxy-3,12,16-trimethyl-(6β,9β(SR),14aβ,15β)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (15a*).

The mother liquor (64.7 mg, containing ca 2:3 = **11a*:14a***; 0.0963 mmol) as described above, dissolved in ethanol (8 mL) and this reaction mixture was hydrogenated over 10% palladium on carbon (32 mg) at 1 atm for 4 h. The catalyst was removed by filtration and washed with ethanol (50 mL). The combined filtrates were concentrated in vacuo and the residue (53.1 mg) was subjected to chromatography on preparative layer silica gel plates (Merck 5715, solvent 20:3 chloroform-methanol) to afford **12a*** (6.6 mg, 12.7%) and **15a*** (24.0 mg, 46.3%).

Compound 15a* (not crystallizable); IR ($CHCl_3$) 3350, 2910, 2840, 2820, 1655, 1612, 1455, 1402, 1358, 1340, 1325, 1300, 1282, 1145, 1105, 1072, 1045, 1008, 960, 890, 850 cm^{-1}; UV λ_{max} nm (log ε) 228 (4.27), 272sh (3.08), 278 (3.16); ^1H NMR δ 0.88 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 1.68 (2H, br s, NH_2), 2.14 (3H, s, 12-CH_3), 2.17 (1H, dd, *J* = 17.5, 10.2 Hz, H-14α), 2.19 (3H, s, 3-CH_3), 2.39 (3H, s, NCH_3), 2.57 (1H, d, *J* = 17.2 Hz, H-5α), 2.81 (1H, q, *J* = 6.9 Hz, C*H*CH_3), 2.83-2.90 (2H, m, H-14a and H-14β), 3.13 (2H, br s, 2 x H-7), 3.12 (1H, dd, *J* = 17.2, 7.6 Hz, H-5β), 3.15 (1H, ddd, *J* = 13.2, 6.9, 2.0 Hz, 9-C*H*N), 3.21 (1H, br d, H-6), 3.58 (3H, s, OCH_3), 3.64 (1H, ddd, *J* = 13.2, 6.9, 2.0 Hz, 9-C*H*N), 3.64 (1H, dd, *J* = 2.0, 0.5 Hz, H-15), 3.74 (3H, s, OCH_3), 3.80 (1H, dd, *J* = 4.3, 2.0 Hz, H-9), 3.82, 3.87 (each 3H, s, OCH_3), 6.27 (1H, dd, *J* = 6.9, 4.3 Hz, NH), 6.54 (1H, s, H-1), 6.90 (1H, s, H-4); ^{13}C NMR δ 9.2 (q, 12-CH_3), 15.9 (q, 3-CH_3), 21.3 (q, CH*C*H_3), 26.7 (t, C-5), 27.3 (t, C-14), 41.4 (q, NCH_3), 42.8 (t, 9-CH_2), 50.6 (d, *C*HCH_3), 53.7 (d, C-6), 55.5 (q, OCH_3), 58.0 (d, C-9), 58.6 (d, C-14a), 59.9 (q, OCH_3), 60.1 (q, OCH_3), 60.2 (q, OCH_3), 60.4 (t, C-7), 64.2 (d, C-15), 111.2 (d, C-1), 123.6 (s), 124.4 (s), 125.3 (s), 126.1 (s), 127.5 (s), 129.7 (d, C-4), 130.8 (s), 146.1 (s), 149.6 (s), 150.6 (s), 155.0 (s), 175.5 (s, CO); positive FABMS (magic bullet) *m/z* 539 (M^+ + 1).

2S-Amino-*N*-[(6,7,9,14,14a,15-hexahydro-2,10,11,13-tetramethoxy-3,12,16-trimethyl-(6α,9α(R),14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (12a) and 2S-Amino-*N*-[(6,7,9,14,14a,15-hexahydro-2,10,11,13-tetramethoxy-3,12,16-trimethyl-(6β,9β(S),14aβ,15β)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (15a).

Condensation of the amine **10a** (227.8 mg, 0.488 mmol) with Cbz-(*L*)-alanine (130.7 mg, 0.585 mmol) as described above afforded the residue (464 mg), which was subjected to chromatography (silica gel, 140 g; elution with 20:1 dichloromethane-methanol) to give the residue (268.8 mg, 82.0%) as colorless amorphous powder [an inseparable the diastereomeric mixture of **11a** and **14a**: $[\alpha]^{20}_D$ -10.9° (*c* 0.51, methanol)] which was used for the next step without isolation. A solution of the above mixture in ethanol (25 mL) was hydrogenated over 10% palladium on carbon (0.1 g) at 1 atm for 48 h. After usual work-up, the residue (243.2 mg) was subjected to chromatography on preparative layer silica gel plates (Merck 5744, solvent 15:1 chloroform-methanol) to afford **12a** (90.5 mg, 42.1%) and **15a** (94.8 mg, 44.1%). The compound **12a**

($[\alpha]^{20}_D$ -14.9° (*c* 1.48, methanol)) was identical with a racemic one **12a*** on comparison of spectroscopic ^1H NMR, ^{13}C NMR, IR, UV, MS, and TLC data. The *epi*-enantiomer **15a** ($[\alpha]^{20}_D$ -1.4° (*c* 0.8, methanol)) was also identical with a racemic one **15a***.

(-)-2S-Acetylamino-*N*-[(6,7,9,14,14a,15-hexahydro-2,10,11,13-tetramethoxy-3,12,16-trimethyl-(6α,9α(R),14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (13a).

Acetic anhydride (1.0 mL) was added to a solution of **12a** (148.0 mg, 0.275 mmol) in dry pyridine (2.0 mL), and the mixture was left to stand at room temperature for 1 h. After being diluted with water (10 mL), the mixture was extracted with chloroform (10 mL x 3). The combined extracts were washed with 5% $NaHCO_3$, dried, and concentrated in vacuo to give the residue (164.2 mg) as a solid, recrystallization of which from ethyl acetate gave **13a** (141.7 mg, 88.8%) as colorless needles: mp 111-113 °C; $[\alpha]^{20}_D$ -21.8° (*c* 1.16, methanol); IR (KBr) 3375, 3275, 1670, 1655 1505 cm^{-1}; UV λ_{max} (log ε) nm 226 (4.24), 280 (3.58), 288 (3.50); ^1H NMR δ 0.94 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 1.80 (3H, s, COCH$_3$), 2.09 (1H, dd, *J* = 15.1, 11.8 Hz, H-14β), 2.13, 2.21 (each 3H, s, Ar CH$_3$), 2.37 (3H, s, NCH$_3$), 2.46 (1H, d, *J* = 17.0 Hz, H-5β), 2.84 (1H, ddd, *J* = 11.8, 2.6, 2.6, H-14a), 2.91 (1H, dd, *J* = 15.1, 2.7 Hz, H-14α), 3.00 (2H, d, *J* = 2.5 Hz, 2 x H-7), 3.11 (1H, ddd, *J* = 13.1, 4.5, 3.0 Hz, 9-C*H*N), 3.12 (1H, dd, *J* = 17.0, 7.6 Hz, H-5α), 3.17 (1H, br d, H-6), 3.56 (1H, m, C*H*CH$_3$), 3.57 (3H, s, OCH$_3$), 3.60 (1H, d, *J* = 2.6 Hz, H-15), 3.66 (1H, ddd, *J* = 13.1, 8.3, 2.3 Hz, 9-C*H*NH), 3.78 (1H, dd, *J* = 4.2, 2.0 Hz, H-9), 3.87, 3.89 (each 3H, s, OCH$_3$), 5.35 (1H, dd, *J* = 8.3, 2.0 Hz, NH), 6.16 (1H, br d, *J* = 6.9 Hz, NH), 6.58 (1H, s, H-1), 6.91 (1H, s, H-4); ^{13}C NMR δ 9.2 (q, 12-CH$_3$), 16.1 (q, 3-CH$_3$), 19.3 (q, CH*C*H$_3$), 23.1 (q, CO*C*H$_3$), 26.9 (t, C-5), 27.1 (t, C-14), 41.3 (q, NCH$_3$), 43.3 (t, 9-CH$_2$), 48.5 (d, *C*HCH$_3$), 53.8 (d, C-6), 55.6 (q, OCH$_3$), 57.9 (d, C-9), 58.5 (d, C-14a), 59.9 (q, OCH$_3$), 60.1 (q, OCH$_3$), 60.3 (q, OCH$_3$), 60.4 (t, C-7), 64.2 (d, C-15), 111.2 (d, C-1), 123.8 (s), 124.3 (s), 125.7 (s), 125.8 (s), 126.8 (s), 129.5 (d, C-4), 145.9 (s), 149.6 (s), 150.9 (s), 155.4 (s), 168.6 (s, CO), 171.6 (s, CO); positive FABMS (NBA) *m/z* 581 (M^++ 1). Anal. Calcd for $C_{32}H_{44}N_4O_6 \cdot 1/2H_2O$: C, 65.17; H, 7.69; N, 9.50. Found: C, 65.14; H, 7.53; N, 9.27.

(-)-2S-Acetylamino-*N*-[(6,7,9,14,14a,15-hexahydro-2,10,11,13-tetramethoxy-3,12,16-trimethyl-(6β,9β(S),14aβ,15β)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (16a).

Acetylation of **15a** (133.6 mg, 0.2483 mmol) with acetic anhydride in dry pyridine afforded the residue (149.1 mg). This material was subjected to chromatography (silica gel, 18 g; elution with 15:1 dichloromethane-methanol) to give **16a** (126.0 mg, 85.9%) as colorless amorphous powder: $[\alpha]^{20}_D$ - 5.2° (*c* 1.26, methanol); IR ($CHCl_3$) 3350, 1655 cm^{-1}; UV λ_{max} nm (log ε) 226 (4.26), 272sh (3.42), 280 (3.58), 288 (3.50); ^1H NMR δ 0.72 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 1.87 (3H, s, COCH$_3$), 2.05 (1H, dd, *J* = 15.8, 11.9 Hz, H-14α), 2.14 (3H, s, 12-CH$_3$), 2.30 (3H, s, 3-CH$_3$), 2.42 (3H, s, NCH$_3$), 2.57 (1H, d, *J* = 17.2 Hz, H-5α), 2.88 (1H, dd, *J* = 15.8, 2.3, H-14β), 2.93 (1H, ddd, *J* = 11.9, 2.3, 2.0 Hz, H-14a), 3.02 (2H, d, *J* = 1.5 Hz, 2 x H-7), 3.12 (1H, dd, *J* = 17.2, 7.3 Hz, H-5β), 3.21 (1H, ddd, *J* = 13.2, 11.6, 2.0 Hz, 9-C*H*NH), 3.21 (1H, br d, *J* = 7.6 Hz, H-6), 3.57 (3H, s, OCH$_3$), 3.67 (1H, d, *J* = 2.0 Hz, H-15), 3.69 (1H, ddd, *J* = 13.2, 7.9, 1.6 Hz, 9-C*H*N), 3.74 (3H, s, OCH$_3$), 3.77 (1H, m, C*H*CH$_3$), 3.78 (1H, dd, *J* = 4.6, 1.6 Hz, H-9), 3.82, 3.88 (each 3H, s, OCH$_3$), 5.55 (1H, dd, *J* = 7.9, 2.0 Hz, NH), 6.06 (1H, d, *J* = 7.3 Hz, NH), 6.56 (1H, s, H-1), 7.01 (1H, s, H-4); ^{13}C NMR δ 9.2 (q, 12-CH$_3$), 15.9 (q, 3-CH$_3$), 18.5 (q, CH*C*H$_3$), 23.1 (q, CO*C*H$_3$), 26.7 (t, C-5), 27.1 (t, C-14), 41.4 (q, NCH$_3$), 42.8 (t, 9-CH$_2$), 48.4 (d, *C*HCH$_3$), 53.7 (d, C-6), 55.4 (q, OCH$_3$), 57.3 (d, C-9), 58.3 (d, C-14a), 59.8 (q, OCH$_3$), 60.0 (q, OCH$_3$), 60.2 (t, C-7), 60.2 (q, OCH$_3$), 64.2 (d, C-15), 111.3 (d, C-1), 123.8 (s), 123.8 (s), 126.0 (s), 126.3 (s), 127.2 (s), 129.7 (d, C-4), 130.6 (s), 146.0 (s), 149.6 (s), 150.6 (s), 155.3 (s), 169.1 (s, CO), 171.6 (s, CO); positive FABMS (NBA) *m/z* 581 (M^+ + 1). Anal. Calcd for $C_{32}H_{44}N_4O_6 \cdot 1/2H_2O$: C, 65.17; H, 7.69; N, 9.50. Found: C, 65.17; H, 7.55; N, 9.37.

Oxidative Demethylation of 13a.

A solution of **13a** (58.0 mg, 0.1 mmol) in dichloromethane (4 mL) was cooled with dry ice-acetone, a dichloromethane solution of boron tribromide (1.0 M, 0.25 mL, 0.25 mmol) was added dropwise over 5 min. After being kept at -78 °C for 1 h, and then 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 x 3). The combined extracts were washed with water (20 mL), dried, and concentrated in vacuo to give the residue (65.0 mg). A solution of this residue in 8M HNO_3 (2 mL) was stirred at 0 °C for 1 h. The reaction mixture was diluted with water (10 mL) and extracted with chloroform (10 mL x 3). The combined extracts were washed with water (10 mL), dried, and concentrated in vacuo. The residue (41.3 mg) was subjected to chromatography on preparative layer silica gel plates (Merck 5715, solvent 200:15 dichloromethane-methanol) to afford **17** (22.0 mg, 40.0%) as pale yellow amorphous powder and **18** (9.0 mg, 15.5%) as pale yellow amorphous powder.

(-)-2S-Acetylamino-*N*-[(6,7,9,10,13,14,14a,15-octahydro-2,11-dimethoxy-3,12,16-trimethyl-10,13-dioxo-6,15-(6α,9α(R),14aα,15α)-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (17) (not crystallizable); $[\alpha]^{20}_D$ -25.0° (*c* 0.07, $CHCl_3$); IR ($CHCl_3$) 3400, 3360, 1670, 1655, 1615 cm^{-1}; UV λ_{max} nm (log ε) 278 (4.02), 370 (2.86); ^1H NMR δ 0.96 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$), 1.78 (3H, s, COCH$_3$), 1.88 (3H, s, 12-CH$_3$), 2.05 (1H, ddd, *J* = 17.8, 11.2, 2.9 Hz, H-14β), 2.21 (3H, s, 3-CH$_3$), 2.43 (3H, s, NCH$_3$), 2.53 (1H, d, *J* = 17.5 Hz, H-5β), 2.83 (1H, dd, *J* = 17.8, 2.7 Hz, H-14α), 2.90 (1H, ddd, *J* = 11.2, 2.7, 1.0 Hz, H-14a), 2.95 (1H, ddd, *J* = 13.2, 3.9, 2.2 Hz, 9-C*H*N), 3.05 (2H, m, 7-H$_2$), 3.15 (1H, dd, *J* = 17.5, 7.3 Hz, H-5α), 3.21 (1H, br d, H-6), 3.34 (1H, m, C*H*CH$_3$), 3.58 (1H, ddd, *J* = 3.9, 2.9, 1.0 Hz, H-9), 3.67 (1H, dd, *J* = 1.0, 0.5 Hz, H-15), 3.76 (1H, ddd, *J* = 13.2, 9.8, 1.0 Hz, 9-C*H*N), 3.86 (3H, s, 2-OCH$_3$), 4.00 (3H, s, 11-OCH$_3$), 5.04 (1H, dd, *J* = 9.8, 2.2 Hz, NH), 5.71 (1H, d, *J* = 7.3 Hz, NH), 6.55 (1H, s, H-1), 6.92 (1H, s, H-4); ^{13}C NMR δ 8.5 (q, 12-CH$_3$), 16.1 (q, 3-CH$_3$), 18.6 (q, CH*C*H$_3$), 22.8 (q, CO*C*H$_3$), 24.8 (t, C-14), 26.8 (t, C-5), 41.3 (t, 9-CH$_2$), 41.4 (q, NCH$_3$), 48.8 (d, *C*HCH$_3$), 53.5 (d, C-6), 55.7 (q, 2-OCH$_3$), 57.0 (d, C-9), 57.1 (d, C-14a),

59.6 (t, C-7), 60.9 (q, 11-OCH_3), 63.7 (d, C-15), 111.7 (d, C-1), 125.5 (s), 126.8 (s), 127.2 (s), 129.1 (d, C-4), 130.2 (s), 136.4 (s), 141.5 (s), 155.4 (s), 156.3 (s), 168.8 (s, CO), 172.9 (s, CO), 181.5 (s, C-10), 186.0 (s, C13); positive FABMS (NBA) *m/z* 551 (M^+ + 1). CD Δ ε nm (c 0.19 mmol/L, MeOH, 27°C) +6.55 (212), -6.55 (278).

(-)-2S-Acetylamino-*N*-[(6,7,9,10,13,14,14a,15-octahydro-2-hydroxy-11-methoxy-3,12,16-trimethyl-1-nitro-10,13-dioxo-6,15-(6α,9α(R),14aα,15α)-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (18) (not crystallizable); $[\alpha]^{20}_D$ -247.6° (*c* 0.25, methanol); IR ($CHCl_3$) 3400, 1675, 1655, 1615 cm^{-1}; UV λ_{max} nm (log ε) 268 (4.08), 360 (3.28); ^1H NMR δ 1.06 (3H, d, *J* = 6.6 Hz, $CHCH_3$), 1.44 (1H, ddd, *J* = 17.5, 11.2, 3.0 Hz, H-14β), 1.84 (3H, s, $COCH_3$), 1.88 (3H, s, 12-CH_3), 2.35 (3H, s, 3-CH_3), 2.48 (3H, s, NCH_3), 2.62 (1H, d, *J* = 17.5 Hz, H-5β), 2.82-3.02 (4H, m, H-14a, H-14α, and 2 x H-7), 3.14-3.20 (2H, m, H-5α, H-6), 3.43 (1H, ddd, *J* = 13.9, 4.0, 4.0 Hz, 9-C*H*N), 3.58 (1H, m, C*H*CH_3), 3.57 (1H, s, H-9), 3.72 (1H, ddd, *J* = 13.9, 8.6, 2.0 Hz, 9-C*H*N), 4.01 (3H, s, 11-OCH_3), 4.76 (1H, br s, H-15), 5.23 (1H, br d, NH), 5.64 (1H, br d, NH), 7.16 (1H, s, H-4); positive FABMS (NBA) *m/z* 582 (M^+ + 1).

Oxidative Demethylation of 16a.

Partial *O*-demethylation of **16a** (108.8 mg, 0.1876 mmol) with boron tribromide and then 8N HNO_3 as described above afforded a soid (62.7 mg), recrystallization of which from benzene-chloroform gave **19** (50.7 mg, 49.1%) as pale yellow needles, mp 118-121 °C dec.

(-)-2S-Acetylamino-*N*-[(6,7,9,10,13,14,14a,15-octahydro-2,11-dimethoxy-3,12,16-trimethyl-10,13-dioxo-6,15-(6β,9β(S),14aβ,15β)-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (19); $[\alpha]^{20}_D$ -602.0° (*c* 1.0, methanol); IR (KBr) 3400, 3280, 1675, 1655, 1640, 1620 cm^{-1}; UV λ_{max} nm (log ε) 274 (4.07), 370 (2.92); ^1H NMR δ 0.69 (3H, d, *J* = 7.1 Hz, $CHCH_3$), 1.80 (1H, ddd, *J* = 17.8, 11.0, 3.2 Hz, H-14α), 1.82 (3H, s, $COCH_3$), 1.90 (3H, s, 12-CH_3), 2.26 (3H, s, 3-CH_3), 2.45 (3H, s, NCH_3), 2.60 (1H, d, *J* = 17.6 Hz, H-5α), 2.74 (1H, dd, *J* = 17.8, 2.0 Hz, H-14β), 2.93 (1H, ddd, *J* = 11.0, 2.0, 2.0 Hz, H-14a), 3.09 (2H, m, 2 x H-7), 3.12 (1H, dd, *J* = 17.6, 7.8 Hz, H-5β), 3.19 (1H, ddd, *J* = 13.9, 4.2, 3.7 Hz, 9-C*H*N), 3.28 (1H, br d, H-6), 3.56 (1H, ddd, *J* = 4.2, 3.2, 1.0 Hz, H-9), 3.68 (1H, dd, *J* = 2.0, 0.5 Hz, H-15), 3.70 (1H, ddd, *J* = 13.9, 9.0, 1.0 Hz, 9-C*H*N), 3.74 (1H, m, C*H*CH_3), 3.81 (3H, s, 2-OCH_3), 4.02 (3H, s, 11-OCH_3), 5.34 (1H, dd, *J* = 9.0, 3.7 Hz, NH), 5.72 (1H, d, *J* = 7.1 Hz, NH), 6.49 (1H, s, H-1), 6.99 (1H, s, H-4); ^{13}C NMR δ 8.5 (q, 12-CH_3), 15.8 (q, 3-CH_3), 17.9 (q, $CHCH_3$), 22.9 (q, $COCH_3$), 25.3 (t, C-14), 26.6 (t, C-5), 40.2 (t, 9-CH_2), 41.3 (q, NCH_3), 48.4 (d, $CHCH_3$), 53.5 (d, C-6), 55.5 (q, 2-OCH_3), 56.6 (d, C-14a), 57.2 (d, C-9), 59.0 (t, C-7), 61.0 (q, 11-OCH_3), 63.6 (d, C-15), 111.5 (d, C-1), 126.4 (s), 127.1 (s), 127.3 (s), 129.7 (d, C-4), 129.7 (s), 137.0 (s), 140.5 (s), 155.3 (s), 156.4 (s), 169.3 (s, CO), 172.2 (s, CO), 181.4 (s, C10), 186.2 (s, C13); positive FABMS (NBA) *m/z* 551 (M^+ + 1). Anal. Calcd for $C_{30}H_{38}N_4O_6 \cdot 3/5CHCl_3$: C, 59.06; H, 6.25; N, 9.00. Found: C, 58.82; H, 6.19; N, 9.00. CD Δ ε nm (c 0.18 mmol/L, MeOH, 27°C) -8.73 (213), +7.90 (274).

(-)-2S-(Benzyloxycarbonyl)amino-*N*-[(6,7,9,14,14a,15-hexahydro-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-(6α,9α(R),14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (11b) and (-)-2S-(Benzyloxycarbonyl)amino-*N*-[(6,7,9,14,14a,15-hexahydro-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-(6β,9β(S),14aβ,15β)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (14b).

Condensation of the amine **10b** (125.7 mg, 0.239 mmol) with Cbz-(*L*)-alanine (63.9 mg, 0.286 mmol) as described above afforded the residue (309.4 mg), which was subjected to chromatography (silica gel, 12 g; elution with 20:1 dichloromethane-methanol) to give the residue (138.3 mg, 79.2%) as colorless amorphous powder, which was chromatography on preparative layer silica gel plates (merck 5715, solvent 20:1 dichloromethane-methanol) to afford **11b** (74.0 mg, 42.2%) and **14b** (62.2 mg, 35.6%).

Compound 11b (not crystallizable): $[\alpha]^{20}_D$ - 5.5° (*c* 1.46, $CHCl_3$); IR ($CHCl_3$) 3360, 1710, 1665 cm^{-1}; UV λ_{max} (log ε) nm 230 (4.18), 270sh (3.12), 280 (3.16); ^1H NMR δ 1.01 (3H, d, *J* = 6.9 Hz, $CHCH_3$), 1.75 (1H, dd, *J* = 15.2, 11.6 Hz, H-14β), 2.11, 2.20 (each 3H, s, Ar CH_3), 2.34 (3H, s, NCH_3), 2.63 (1H, d, *J* = 17.8 Hz, H-5β), 2.81 (1H, br d, *J* = 11.6, H-14a), 2.94 (2H, br s, 2 x H-7), 2.99 (1H, dd, *J* = 17.8, 7.9 Hz, H-5α), 3.09 (1H, dd, *J* = 15.2, 2.3 Hz, H-14α), 3.13 (1H, br d, H-6), 3.18 (1H, ddd, *J* = 13.5, 4.3, 4.0 Hz, 9-C*H*N), 3.44 (1H, m, 9-C*H*N), 3.52 (3H, s, OCH_3), 3.56 (1H, m, C*H*CH_3), 3.71, 3.73 (each 3H, s, OCH_3), 3.74 (1H, br s, H-9), 3.85, 3.85, 3.85 (each 3H, s, OCH_3), 4.06 (1H, d, *J* = 2.6 Hz, H-15), 4.96, 5.04 (each 1H, d, *J* = 12.2 Hz, OCH_2Ph), 5.60 (1H, br s, NH), 5.63 (1H, d, *J* = 6.9 Hz, NH), 7.31-7.33 (5H, m, ArH x 5); ^{13}C NMR δ 9.2 (q), 9.4 (q), 19.2 (q, $CHCH_3$), 22.7 (t, C-5), 26.7 (t, C-14), 41.4 (q, NCH_3), 43.9 (t, 9-CH_2), 50.4 (d, $CHCH_3$), 52.8 (d, C-6), 57.7 (d, C-15), 58.1 (d, C-9), 59.5 (q, OCH_3), 59.6 (d, C-14a), 60.0 (q, OCH_3), 60.0 (q, OCH_3), 60.2 (q, OCH_3), 60.2 (q, OCH_3), 60.3 (q, OCH_3), 60.7 (t, C-7), 66.5 (t, OCH_2), 123.5 (s), 123.7 (s), 124.6 (s), 124.7 (s), 125.2 (s), 125.8 (s), 128.0 (d x 2), 128.1 (d), 128.5 (d x 2), 136.5 (s), 145.8 (s), 147.7 (s), 149.3 (s), 149.5 (s), 150.7 (s), 151.1 (s), 155.2 (s, CO), 171.4 (s, CO); EIMS *m/z* (relative intensity) 732 (M^+, 1>), 497 (100), 495 (29), 248 (26); positive FABMS (magic bullet) *m/z* 733 (M^+ + 1).

Compound 14b (not crystallizable): $[\alpha]^{20}_D$ - 17.5° (*c* 1.22, $CHCl_3$); IR ($CHCl_3$) 3360, 1708, 1660 cm^{-1}; UV λ_{max} nm (log ε) 230 (4.19), 272sh (3.14), 278 (3.17); ^1H NMR δ 0.76 (3H, d, *J* = 6.9 Hz, $CHCH_3$), 1.79 (1H, dd, *J* = 15.8, 11.5 Hz, H-14α), 2.12, 2.28 (each 3H, s, Ar CH_3), 2.36 (3H, s, NCH_3), 2.52 (1H, d, *J* = 17.8 Hz, H-5α), 2.89 (1H, ddd, *J* = 11.5, 3.0, 1.7 Hz, H-14a), 2.97 (2H, br s, 2 x H-7), 3.02-3.13 (2H, m, H-14β and H-5β), 3.11 (1H, m, C*H*NH), 3.20 (1H, br d, *J* = 6.6 Hz, H-6), 3.53 (1H, q, *J* = 6.6 Hz, C*H*CH_3), 3.56, 3.69, and 3.72 (each 3H, s, OCH_3), 3.77 (2H, m, 9-CH and H-9), 3.83, 3.86, and 3.86 (each 3H, s, OCH_3), 4.09 (1H, d, *J* = 1.7 Hz, H-15), 5.04 (2H, s, OCH_2Ph), 5.46 (1H, br s, NH), 5.64 (1H, d, *J* = 6.9 Hz, NH), 7.31-7.36 (5H, m, Ar-H x 5); ^{13}C NMR δ 9.2 (q), 9.3 (q), 19.5 (q, $CHCH_3$), 22.8 (t, C-5), 26.6 (t, C-14),

41.5 (q, NCH_3), 43.0 (t, 9-CH_2), 50.0 (d, *C*HCH_3), 52.8 (d, C-6), 57.6 (d, C-9), 57.7 (d, C-15), 58.7 (d, C-14a), 59.7 (q, OCH_3), 59.9 (q, OCH_3), 60.0 (q, OCH_3), 60.0 (q, OCH_3), 60.1 (q, OCH_3), 60.2 (t, C-7), 60.4 (q, OCH_3), 66.5 (t, OCH_2), 123.7 (s), 124.4 (s), 124.5 (s), 124.7 (s), 125.2 (s), 125.8 (s), 127.9 (d x 2), 128.0 (d), 128.4 (d x 2), 136.5 (s), 145.9 (s), 147.8 (s), 149.3 (s), 149.5 (s), 150.9 (s), 151.1 (s), 155.2 (s, CO), 171.3 (s, CO); EIMS *m/z* (relative intensity) 732 (M^+, 1>), 497 (100), 248 (21); positive FABMS (magic bullet) *m/z* 733 ($M^+ + 1$).

(+)-2S-Amino-*N*-[(6,7,9,14,14a,15-hexahydro-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-(6α,9α(R),14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (12b).

A solution of **11b** (69.1 mg, 0.0944 mmol) in ethyl acetate (10 mL) was hydrogenated over 10% palladium on carbon (40 mg) at 1 atm for 22 h. The catalyst was removed by filtration and washed with ethyl acetate (100 mL). The combined filtrates were concentrated in vacuo and the residue (51.7 mg) was subjected to chromatography (silica gel, 5 g; elution with 20:1 chloroform-methanol) to give **12b** (44.8 mg, 79.3%) as colorless amorphous powder: $[\alpha]^{20}_D$ + 10.7° (*c* 1.16, $CHCl_3$); IR ($CHCl_3$) 3360, 1645 cm^{-1}; UV λ_{max} nm (log ε) 228 (4.27), 272sh (3.08), 278 (3.16); ^1H NMR δ 0.83 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 1.60 (2H, br s, NH_2), 1.89 (1H, dd, *J* = 15.8, 11.9 Hz, H-14β), 2.13, 2.19 (each 3H, s, Ar CH_3), 2.33 (3H, s, NCH_3), 2.57 (1H, d, *J* = 18.2 Hz, H-5β), 2.86 (1H, ddd, *J* = 11.9, 2.3, 2.3, H-14a), 2.88 (1H, q, *J* = 6.9 Hz, C*H*CH_3), 2.93 (1H, dd, *J* = 10.9, 2.3 Hz, H-7), 3.01 (1H, dd, *J* = 18.2, 7.6 Hz, H-5α), 3.04 (1H, dd, *J* = 10.9, 2.3 Hz, H-7), 3.09 (1H, dd, *J* = 15.8, 2.3 Hz, H-14α), 3.15 (1H, ddd, *J* = 14.5, 3.6, 3.6 Hz, 9-C*H*N), 3.18 (1H, br d, H-6), 3.59 (3H, s, OCH_3), 3.70 (1H, m, 9-C*H*N), 3.71, 3.74 (each 3H, s, OCH_3), 3.77 (1H, br s, H-9), 3.80, 3.86, 3.87 (each 3H, s, OCH_3), 4.08 (1H, d, *J* = 2.3 Hz, H-15), 6.47 (1H, br d, *J* = 5.9 Hz, NH); ^{13}C NMR δ 9.2 (q), 9.3 (q), 21.2 (q, *C*H*C*H_3), 22.7 (t, C-5), 26.8 (t, C-14), 41.4 (q, NCH_3), 42.3 (t, 9-CH_2), 50.7 (d, *C*HCH_3), 52.8 (d, C-6), 57.7 (d, C-15), 58.6 (d, C-9), 59.1 (d, C-14a), 59.6 (q, OCH_3), 59.9 (q, OCH_3), 59.9 (q, OCH_3), 60.1 (q, OCH_3), 60.1 (q, OCH_3), 60.3 (q, OCH_3), 60.3 (t, C-7), 123.1 (s), 123.4 (s), 124.7 (s), 125.1 (s), 125.1 (s), 125.8 (s), 146.1 (s), 147.7 (s), 148.9 (s), 149.5 (s), 150.8 (s), 151.1 (s), 175.2 (s, CO); EIMS *m/z* (relative intensity) 598 (M^+, 1>), 497 (100), 495 (12), 248 (23); positive FABMS (magic bullet) *m/z* 599 ($M^+ + 1$).

(-)-2S-Amino-*N*-[(6,7,9,14,14a,15-hexahydro-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-(6β,9β(S),14aβ,15β)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (15b) was prepared by hydrogenation of **14b** (56.1 mg, 0.07664 mmol) as described above. Column chromatography of the crude product (50.0 mg) gave **15b** (42.4 mg, 92.6%) as colorless amorphous powder: $[\alpha]^{20}_D$ -9.0° (*c* 1.41, $CHCl_3$); IR ($CHCl_3$) 3360, 1645 cm^{-1}; UV λ_{max} nm (log ε) 228 (4.27), 272sh (3.08), 278 (3.16); ^1H NMR δ 0.87 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 1.62 (2H, br s, NH_2), 1.88 (1H, dd, *J* = 15.5, 11.6 Hz, H-14α), 2.13, 2.20 (each 3H, s, Ar CH_3), 2.33 (3H, s, NCH_3), 2.56 (1H, d, *J* = 17.8 Hz, H-5α), 2.83 (1H, q, *J* = 6.9 Hz, C*H*CH_3), 2.85 (1H, ddd, *J* = 11.6, 2.6, 2.6, H-14a), 2.93 (1H, dd, *J* = 10.9, 2.6 Hz, H-7), 3.01 (1H, dd, *J* = 17.8, 7.6 Hz, H-5β), 3.02 (1H, dd, *J* = 10.9, 2.6 Hz, H-7), 3.08 (1H, dd, *J* = 15.5, 2.6 Hz, H-14β), 3.14 (1H, m, 9-C*H*N), 3.19 (1H, br d, H-6), 3.57 (3H, s, OCH_3), 3.65 (1H, m, 9-C*H*N), 3.71, 3.74 (each 3H, s, OCH_3), 3.76 (1H, br s, H-9), 3.79, 3.85, 3.87 (each 3H, s, OCH_3), 4.07 (1H, d, *J* = 2.6 Hz, H-15), 6.39 (1H, br d, *J* = 6.6 Hz, NH); ^{13}C NMR δ 9.2 (q), 9.3 (q), 21.4 (q, *C*H*C*H_3), 22.7 (t, C-5), 26.8 (t, C-14), 41.5 (q, NCH_3), 42.6 (t, 9-CH_2), 50.6 (d, *C*HCH_3), 52.8 (d, C-6), 57.7 (d, C-15), 58.2 (d, C-9), 59.1 (d, C-14a), 59.6 (q, OCH_3), 59.8 (q, OCH_3), 59.9 (q, OCH_3), 60.1 (q, OCH_3), 60.1 (q, OCH_3), 60.3 (q, OCH_3), 60.3 (t, C-7), 123.2 (s), 123.5 (s), 124.7 (s), 125.0 (s), 125.0 (s), 125.9 (s), 146.0 (s), 147.7 (s), 149.0 (s), 149.4 (s), 150.8 (s), 151.1 (s), 175.3 (s, CO); EIMS *m/z* (relative intensity) 598 (M^+, 1>), 497 (100), 495 (15), 248 (30); positive FABMS (magic bullet) *m/z* 599 ($M^+ + 1$).

(-)-2S-Acetylamino-*N*-[(6,7,9,14,14a,15-hexahydro-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-(6α,9α(R),14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (13b).

Acetic anhydride (1.0 mL) was added to a solution of **12b** (37.7 mg, 0.063 mmol) in dry pyridine (0.5 mL), and the mixture was left to stand at room temperature for 1 h. After being diluted with water (10 mL), the mixture was extracted with chloroform (10 mL x 3). The combined extracts were washed with 5% $NaHCO_3$, dried, and concentrated in vacuo to give the residue (37.3 mg). This material was subjected to chromatography (silica gel, 5 g; elution with 25:1 dichloromethane-methanol) to give **13b** (35.4 mg, 87.7%) as colorless amorphous powder: $[\alpha]^{20}_D$ - 10.9° (*c* 1.16, $CHCl_3$); IR ($CHCl_3$) 3340, 1660, 1645 cm^{-1}; UV λ_{max} nm (log ε) 230 (4.18), 272sh (3.03), 278 (3.09); ^1H NMR δ 0.90 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 1.77 (1H, dd, *J* = 16.2, 11.5 Hz, H-14β), 1.85 (3H, s, NAc), 2.13, 2.22 (each 3H, s, Ar CH_3), 2.35 (3H, s, NCH_3), 2.62 (1H, d, *J* = 17.8 Hz, H-5β), 2.82 (1H, ddd, *J* = 11.5, 2.6, 2.3, H-14a), 2.93 (1H, dd, *J* = 10.9, 2.3 Hz, H-7), 3.00 (1H, dd, *J* = 17.8, 7.6 Hz, H-5α), 3.02 (1H, dd, *J* = 10.9, 2.3 Hz, H-7), 3.10 (1H, dd, *J* = 16.2, 2.3 Hz, H-14α), 3.20 (1H, br d, *J* = 7.6 Hz, H-6), 3.23 (1H, ddd, *J* = 13.5, 4.0, 3.6 Hz, 9-C*H*N), 3.54 (3H, s, OCH_3), 3.62 (1H, ddd, *J* = 13.5, 6.3, 2.0 Hz, 9-C*H*N), 3.67 (1H, q, *J* = 6.9 Hz, C*H*CH_3), 3.72, 3.74, 3.85 (each 3H, s, OCH_3), 3.86 (1H, br s, H-9), 3.87, 3.87 (each 3H, s, OCH_3), 4.06 (1H, d, *J* = 2.3 Hz, H-15), 5.42 (1H, br, NH), 6.29 (1H, br d, *J* = 6.6 Hz, NH); ^{13}C NMR δ 9.2 (q), 9.4 (q), 19.2 (q, *C*H*C*H_3), 22.6 (t, C-5), 23.1 (q, NAc), 26.8 (t, C-14), 41.5 (q, NCH_3), 43.0 (t, 9-CH_2), 48.6 (d, *C*HCH_3), 52.7 (d, C-6), 57.6 (d, C-15), 58.5 (d, C-9), 59.0 (d, C-14a), 59.5 (q, OCH_3), 59.9 (q, OCH_3), 60.0 (q, OCH_3), 60.1 (q, OCH_3), 60.1 (q, OCH_3), 60.1 (q, OCH_3), 60.3 (t, C-7), 123.7 (s), 124.5 (s), 124.5 (s), 124.7 (s), 125.1 (s), 125.5 (s), 145.8 (s), 147.8 (s), 149.3 (s), 149.4 (s), 150.8 (s), 151.1 (s), 168.9 (s, CO), 171.4 (s, CO); EIMS *m/z* (relative intensity) 640 (M^+, 1>), 497 (100), 495 (16), 248 (21); positive FABMS (magic bullet) *m/z* 641 ($M^+ + 1$); CD Δ ε nm (c 0.16 mmol/L, MeOH, 27°C) +14.67 (214), -1.80 (282).

(-)-2S-Acetylamino-*N*-[(6,7,9,14,14a,15-hexahydro-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-(6β,9β(S),14aβ,15β)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (16b) was

prepared by acetylation of **15b** (39.5 mg, 0.0661 mmol) as described above. Column chromatography of the crude product (46.0 mg) gave **16b** (32.7 mg, 77.4%) as a soild, recrystallization of which from ethyl acetate-ether gave colorless prisms: mp 202-202 °C (from ethyl acetate); $[\alpha]^{20}_D$ - 18.5° (*c* 1.39, $CHCl_3$); IR (KBr) 3700-3250, 1655 cm^{-1}; UV λ_{max} nm (log ε) 230 (4.07), 272sh (2.86), 278 (2.91); ^1H NMR δ 0.70 (3H, d, *J* = 6.9 Hz, $CHCH_3$), 1.81 (1H, dd, *J* = 16.2, 11.9 Hz, H-14α), 1.88 (3H, s, NAc), 2.13, 2.32 (each 3H, s, Ar CH_3), 2.35 (3H, s, NCH_3), 2.51 (1H, d, *J* = 17.8 Hz, H-5α), 2.89 (1H, ddd, *J* = 11.9, 3.0, 2.3, H-14a), 2.98 (1H, dd, *J* = 10.9, 2.3 Hz, H-7), 2.99 (1H, dd, *J* = 17.8, 7.6 Hz, H-5β), 3.04 (1H, dd, *J* = 10.9, 2.3 Hz, H-7), 3.09 (1H, m, 9-C*H*N), 3.12 (1H, dd, *J* = 16.2, 3.0 Hz, H-14β), 3.18 (1H, br d, *J* = 7.6 Hz, H-6), 3.56 (3H, s, OCH_3), 3.70 (1H, q, *J* = 6.9 Hz, C*H*CH_3), 3.71, 3.73 (each 3H, s, OCH_3), 3.79 (1H, br s, H-9), 3.80 (1H, m, 9-C*H*N), 3.85, 3.86, 3.88 (each 3H, s, OCH_3), 4.08 (1H, d, *J* = 2.3 Hz, H-15), 5.63 (1H, br, NH), 6.23 (1H, br d, *J* = 6.6 Hz, NH); ^{13}C NMR δ 9.1 (q), 9.3 (q), 19.4 (q, $CHCH_3$), 22.7 (t, C-5), 23.1 (q, NAc), 26.5 (t, C-14), 41.4 (q, NCH_3), 42.6 (t, 9-CH_2), 48.5 (d, $CHCH_3$), 52.7 (d, C-6), 57.5 (d, C-9), 57.7 (d, C-15), 58.7 (d, C-14a), 59.6 (q, OCH_3), 59.8 (q, OCH_3), 59.9 (q, OCH_3), 59.9 (q, OCH_3), 60.0 (q, OCH_3), 60.1 (t, C-7), 60.4 (q, OCH_3), 123.6 (s), 124.2 (s), 124.5 (s), 124.5 (s), 124.6 (s), 125.4 (s), 145.8 (s), 147.7 (s), 149.3 (s), 149.4 (s), 150.8 (s), 151.1 (s), 169.0 (s, CO), 171.4 (s, CO); EIMS *m/z* (relative intensity) 640 (M^+, 1>), 497 (100), 495 (18), 248 (21); positive FABMS (magic bullet) *m/z* 641 (M^+ + 1). Anal. Calcd for $C_{34}H_{48}N_4O_8$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.68; H, 7.51; N, 8.65. CD Δ ε nm (c 0.16 mmol/L, MeOH, 27°C) -19.25 (215), +2.67 (277).

X-ray Structure Determination of Compound 16b.

Crystals of **16b** ($C_{34}H_{48}N_4O_8$) belong to the orthorhombic space group $P2_12_12_1$ with cell constants *a* = 18.225 (2) Å, *b* = 31.639 (3) Å, *c* = 11.974 (1) Å, *Z* = 8 (two molecules are included in an asymetric unit), d_C = 1.233 g/cm^3. All measurements were made on a Rigaku AFC5S diffractometer with graphite monochromated Cu-Kα radiation. The data were collected at a tempetarure of 23 ± 1 °C using the ω-2θ scan technique to a maximum 2θ value of 135.3°. A total of 6787 reflections was collected. The intensities of three representative reflection were measured after every 150 reflections. No decay correction was applied. The linear absorption coefficient, μ, for Cu-Kα radiation is 7.2 cm^{-1}. An empirical absorption correction using the program DIFABS was applied which resulted in transmission factors ranging from 0.78 to 1.29. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods (SAPI91)[16] and expanded using Fourier techniques[17]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. The final cycle of full-matrix least-squares refinement was based on 3245 observed reflections (I > 300 δ(I)) and 1213 variable parameters and converged (largest parameter was 5.30 times its esd) with unweighted and weighted agreement factors of R = 0.064 and Rω = 0.061. The drawing of the molecule was made by ORTEP.

A Large Scale Preparation of Compounds 13b and 16b from 10b in 3 Steps.

Condensation of the amine **10b** (1.261 g, 2.393 mmol) with Cbz-(*L*)-alanine (641 mg, 2.871 mmol) as described above afforded the residue (1.752 g). Hydrogenation of this residue in ethyl acetate (100 mL) with 10% palladium on carbon for 3 days afforded the crude amine (1.137 g). Acetylation of which as described above gave the crude acetate (1.32 g). This material was subjected to chromatography (silica gel, 60 g; elution with 20:1 dichloromethane-methanol) to give the acetate (1.082 g, 70.7%) as colorless amorphous powder. Crystallization of which from ethyl acetate-ether with addition of a little crystal of **16b** afforded pure **16b** (313.6 mg) as colorless prisms. The mother liquor was concentrated in vacuo to give the residue (0.75 g), which showed ca 7:3 mixtures of **13b** and **16b** by ^1H NMR.

(-)-2S-Acetylamino-*N*-[(1,5,6,7,9,10,13,14,14a,15-decahydro-2,11-dimethoxy-3,12,16-trimethyl-1,4,10,13-tetraoxo-(6α,9α(R),14aα,15α)-6,15-imino-4*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (20).

A solution of **13b** (305.0 mg, 0.477 mmol) in dichloromethane (20 mL) was cooled with dry ice-acetone, a dichloromethane solution of boron tribromide (1.0 M, 1.90 mL, 1.90 mmol) was added dropwise over 10 min. After being kept at -78 °C for 1h, and then 0 °C for 1 h, the reaction mixture was poured onto ice-water and then the phase separated. The aqueous layer was extracted with chloroform (30 mL x 3). The combined extracts were washed with water (30 mL), dried, and concentrated in vacuo to give the residue (202.1 mg). A solution of this residue in 10M HNO_3 (6 mL) was stirred at 0 °C for 30 min. The reaction mixture was diluted with water (20 mL) and extracted with chloroform (20 mL x 3). The combined extracts were washed with water (20 mL), dried, and concentrated in vacuo. The residue (153.4 mg) was subjected to chromatography (silica gel, 10 g; elution with 10:1 dichloromethane-methanol) to give **20** (98.1 mg, 35.5%) as pale yellow amorphous powder: $[\alpha]^{20}_D$ - 74.6°(*c* 0.56, $CHCl_3$); IR ($CHCl_3$) 3380, 1660, 1648, 1603 cm^{-1}; UV λ_{max} nm (log ε) 270 (4.14), 370 (3.04); ^1H NMR δ 1.13 (3H, d, *J* = 6.9 Hz, $CHCH_3$), 1.64 (1H, ddd, *J* = 18.1, 11.5, 3.3 Hz, H-14β), 1.72 (3H, s, NAc), 1.88, 1.95 (each 3H, s, Ar CH_3), 2.26 (3H, s, NCH_3), 2.28 (1H, d, *J* = 20.8 Hz, H-5β), 2.64-2.75 (3H, m, H-7, H-14a, H-14α), 2.75 (1H, dd, *J* = 20.5, 7.6 Hz, H-5α), 3.03 (1H, dd, *J* = 10.6, 2.3 Hz, H-7), 3.09 (1H, ddd, *J* = 14.2, 3.3, 3.3 Hz, 9-C*H*N), 3.17 (1H, br d, *J* = 7.6 Hz, H-6), 3.53 (1H, br s, 9-H), 3.82 (1H, ddd, *J* = 14.2, 7.3, 2.0 Hz, 9-C*H*N), 3.99 (1H, q, *J* = 6.9 Hz, C*H*CH_3), 4.01 (1H, d, *J* = 2.3 Hz, H-15), 4.04, 4.07 (each 3H, s, OCH_3), 5.59 (1H, d, *J* = 7.6 Hz, NH), 6.15 (1H, dd, *J* = 7.3, 3.3 Hz, NH); ^{13}C NMR δ 8.5 (q), 8.6 (q), 17.1 (q, $CHCH_3$), 22.6 (q, $COCH_3$), 22.7 (t, C-5), 25.7 (t, C-14), 39.8 (t, 9-CH_2), 41.1 (q, NCH_3), 48.6 (d, $CHCH_3$), 52.3 (d, C-6), 54.8 (d, C-15), 57.3 (d, C-14a), 58.6 (d, C-9), 58.8 (t, C-7), 60.9 (q, OCH_3), 60.9 (q, OCH_3), 126.7 (s), 127.6 (s), 136.4 (s), 136.8 (s), 141.7 (s), 142.6 (s), 155.8 (s), 156.4 (s), 169.5 (s), 172.3 (s), 181.6 (s), 182.9 (s), 186.0 (s), 187.4 (s); positive FAB-MS (NBA) *m/z* 581 (M^+ + 1).

(+)-2S-Acetylamino-*N*-[(1,5,6,7,9,10,13,14,14a,15-decahydro-2,11-dimethoxy-3,12,16-trimethyl-1,4,10,13-tetraoxo-(6β,9β(S),14aβ,15β)-6,15-imino-4*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (21).

A solution of **16b** (115.4 mg, 0.180 mmol) in dichloromethane (10 mL) was cooled with dry ice-acetone, a dichloromethane solution of boron tribromide (1.0 M, 0.72 mL, 0.72 mmol) was added dropwise over 5 min. After being kept at -78 °C for 1h, and then 0 °C for 1 h, the reaction mixture was poured onto ice-water and then the phase separated. The aqueous layer was extracted with chloroform (20 mL x 3). The combined extracts were washed with water (20 mL), dried, and concentrated in vacuo to give the residue (127.1 mg). A solution of this residue in 10M HNO_3 (2 mL) was stirred at 0 °C for 30 min. The reaction mixture was diluted with water (10 mL) and extracted with chloroform (10 mL x 3). The combined extracts were washed with water (10 mL), dried, and concentrated in vacuo. The residue (110.5 mg) was subjected to chromatography (silica gel, 4 g; elution with 10:1 dichloromethane-methanol) to give **21** (43.7 mg, 41.8%) as pale yellow amorphous powder: $[\alpha]^{20}_D$ +41.0° (*c* 0.71, $CHCl_3$); IR ($CHCl_3$) 3390, 3280, 1665, 1655, 1605 cm^{-1}; UV λ_{max} nm(log ε) 270 (4.20), 374 (2.83); ^1H NMR δ 1.01 (3H, d, *J* = 6.9 Hz, $CHCH_3$), 1.40 (1H, ddd, *J* = 17.5, 11.2, 3.0 Hz, H-14α), 1.86 (3H, s, NAc), 1.90, 1.98 (each 3H, s, Ar CH_3), 2.25 (3H, s, NCH_3), 2.26 (1H, d, *J* = 20.8 Hz, H-5α), 2.68 (1H, ddd, *J* = 11.2, 3.0, 2.6 Hz, H-14a), 2.73 (1H, dd, *J* = 11.2, 1.0 Hz, H-7), 2.77 (1H, dd, *J* = 20.8, 7.6 Hz, H-5α), 2.78 (1H, dd, *J* = 17.5, 2.6 Hz, H-14β), 3.03 (1H, dd, *J* = 11.2, 2.3 Hz, H-7), 3.09 (1H, ddd, *J* = 13.9, 3.6, 3.6 Hz, 9-CHN), 3.17 (1H, br d, *J* = 7.6 Hz, H-6), 3.53 (1H, br s, H-9), 3.79 (1H, ddd, *J* = 13.9, 8.9, 2.0 Hz, 9-CHN), 3.98 (1H, d, *J* = 3.0 Hz, H-15), 3.99 (3H, s, OCH_3), 4.02 (1H, q, *J* = 6.9 Hz, $CHCH_3$), 4.05 (3H, s, OCH_3), 5.84 (1H, d, *J* = 6.9 Hz, NH), 6.37 (1H, dd, *J* = 8.9, 3.6 Hz, NH); ^{13}C NMR δ 8.6 (q), 8.8 (q), 17.6 (q, $CHCH_3$), 22.7 (t, C-5), 22.8 (q, $COCH_3$), 26.3 (t, C-14), 40.6 (t, 9-CH_2), 41.1 (q, NCH_3), 48.4 (d, $CHCH_3$), 52.3 (d, C-6), 54.9 (d, C-15), 57.4 (d, C-14a), 59.0 (t, C-7), 59.1 (d, C-9), 60.9 (q, OCH_3), 61.0 (q, OCH_3), 127.0 (s), 129.0 (s), 136.0 (s), 137.6 (s), 141.2 (s), 143.2 (s), 155.3 (s), 156.6 (s), 170.0 (s), 172.2 (s), 181.5 (s), 182.9 (s), 186.0 (s), 187.1 (s); positive FAB-MS (NBA) *m/z* 581 (M^+ + 1).

Oxidation of (-)-20 with Selenium Oxide in methanol.

A solution of **20** (49.2 mg, 0.085 mmol) and selenium oxide (28.3 mg, 0.255 mmol) in methanol (6 mL) was stirred for 76 h at room temperature. The reaction mixture was diluted with water (25 mL), made alkaline with 5% $NaHCO_3$, and extracted with chloroform (20 mL x 3). The combined extracts were washed with water (20 mL), dried, and concentrated in vacuo to give the residue (48.7 mg). Chromatography on a silica gel (10 g) column with 200:3 dichloromethane-methanol afforded **22** (21.5 mg, 41.6%) as pale yellow amorphous powder. Further elution with 50:1 dichloromethane-methanol afforded **23** (18.8 mg, 37.2%) as pale yellow amorphous powder.

(-)-2S-Acetylamino-*N*-[(1,5,6,7,9,10,13,14,14a,15-decahydro-2,5,11-trimethoxy-3,12,16-trimethyl-1,4,10,13-tetraoxo-(5β,6α,9α(R),14aα,15α)-6,15-imino-4*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (22): $[\alpha]^{20}_D$ - 86.4° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3440, 3000, 2930, 1690, 1655, 1630, 1510, 1450, 1375, 1305, 1210, 1160, 1100, 970 cm^{-1}; UV λ_{max} nm (log ε) 266 (4.17), 370 (2.93); ^1H NMR δ 1.12 (3H, d, *J* = 6.9 Hz, $CHCH_3$), 1.59 (1H, ddd, *J* = 18.5, 12.2, 3.0 Hz, H-14β), 1.69 (3H, s, NAc), 1.87, 1.97 (each 3H, s, Ar CH_3), 2.46 (3H, s, NCH_3), 2.58 (1H, ddd, *J* = 12.2, 3.0, 2.6 Hz, H-14a), 2.63 (1H, dd, *J* = 18.5, 2.6 Hz, H-14α), 2.72 (1H, dd, *J* = 10.9, 3.0 Hz, H-7), 3.08 (1H, dd, *J* = 10.9, 2.3 Hz, H-7), 3.08 (1H, ddd, *J* = 14.2, 3.3, 3.3 Hz, 9-CHN), 3.25 (1H, br s, H-6), 3.50 (1H, br s, H-9), 3.53 (3H, s, OCH_3), 3.80 (1H, ddd, *J* = 14.2, 7.3, 1.7 Hz, 9-CHN), 3.88 (1H, s, H-5), 3.94 (1H, q, *J* = 6.9 Hz, $CHCH_3$), 4.04 and 4.04 (each 3H, s, OCH_3), 4.07 (1H, d, *J* = 2.6 Hz, H-15), 5.54 (1H, d, *J* = 7.3 Hz, NH), 6.06 (1H, dd, *J* = 7.3, 3.3 Hz, NH); ^{13}C NMR δ 8.5 (q), 8.7 (q), 16.9 (q, $CHCH_3$), 22.5 (q, $COCH_3$), 25.3 (t, C-14), 39.7 (t, 9-CH_2), 42.1 (q, NCH_3), 48.5 (d, $CHCH_3$), 54.9 (d, C-15), 55.7 (d, C-14a), 55.8 (t, C-7), 57.5 (d, C-6), 58.8 (d, C-9), 59.2 (q, OCH_3), 60.8 (q, OCH_3), 60.8 (q, OCH_3), 71.7 (d, C-5), 126.6 (s), 129.0 (s), 136.4 (s), 136.7 (s), 141.4 (s), 141.6 (s), 155.5 (s), 156.3 (s), 169.5 (s), 172.3 (s), 181.5 (s), 183.2 (s), 185.8 (s), 187.1 (s); EIMS *m/z* (relative intensity) 610 (M^+, 1>), 467 (7), 257 (12), 256 (21), 236 (17), 233 (13), 218 (16), 83 (100); positiveFABMS (magic bullet) *m/z* 611 (M^+ + 1); CD Δε nm (c 0.17 mmol/L, MeOH, 27 °C) -24.82 (274), -1.05 (314),-2.20 (368).

(-)-2S-Acetylamino-*N*-[(1,5,6,7,9,10,13,14,14a,15-decahydro-5-hydroxy-2,11-dimethoxy-3,12,16-trimethyl-1,4,10,13-tetraoxo-(5β,6α,9α(R),14aα,15α)-6,15-imino-4*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (23): $[\alpha]^{20}_D$ - 136.5° (*c* 0.45, $CHCl_3$); IR ($CHCl_3$) 3435, 3005, 2940, 1680, 1655, 1615, 1510, 1450, 1375, 1310, 1225, 1160, 1075, 980, 965, 905 cm^{-1}; UV λ_{max} nm (log ε) 268 (4.23), 372 (3.10) nm; ^1H NMR δ 1.12 (3H, d, *J* = 6.9 Hz, $CHCH_3$), 1.60 (1H, ddd, *J* = 18.8, 11.9, 3.0 Hz, H-14β), 1.69 (3H, s, NAc), 1.87, 1.96 (each 3H, s, Ar CH_3), 2.43 (3H, s, NCH_3), 2.59 (1H, ddd, *J* = 11.9, 3.0, 3.0 Hz, H-14a), 2.65 (1H, dd, *J* = 18.8, 3.0 Hz, H-14α), 2.66 (1H, dd, *J* = 10.9, 2.6 Hz, H-7), 3.09 (1H, ddd, *J* = 13.9, 3.3, 3.3 Hz, 9-CHN), 3.15 (1H, dd, *J* = 10.9, 2.0 Hz, H-7), 3.20 (1H, br s, H-6), 3.47 (1H, d, *J* = 2.0 Hz, OH), 3.50 (1H, br s, H-9), 3.80 (1H, ddd, *J* = 13.9, 9.2, 1.7 Hz, 9-CHN), 4.00 (1H, q, *J* = 7.3 Hz, $CHCH_3$), 4.04 (3H, s, OCH_3), 4.06 (1H, d, *J* = 3.0 Hz, H-15), 4.10 (3H, s, OCH_3), 4.41 (1H, d, *J* = 2.0 Hz, H-5), 5.65 (1H, d, *J* = 7.3 Hz, NH), 6.28 (1H, dd, *J* = 9.2, 3.3 Hz, NH); ^{13}C NMR δ 8.5 (q), 8.5 (q), 16.8 (q, $CHCH_3$), 22.6 (q, $COCH_3$), 25.5 (t, C-14), 39.8 (t, 9-CH_2), 42.0 (q, NCH_3), 48.6 (d, $CHCH_3$), 55.6 (d, C-15), 56.4 (t, C-7), 56.4 (d, C-14a), 58.9 (d, C-9), 60.4 (d, C-6), 60.9 (q, OCH_3), 61.1 (q, OCH_3), 63.8 (d, C-5), 126.6 (s), 127.7 (s), 136.6 (s), 136.8 (s), 141.4 (s), 141.6 (s), 156.2 (s), 156.4 (s), 169.7 (s), 172.2 (s), 181.5 (s), 183.3 (s), 186.0 (s), 189.2 (s); EIMS *m/z* (relative intensity) 596 (M^+, 1>), 454 (7), 231 (14), 234 (11), 232 (11), 231 (14), 220 (11), 219 (11), 218 (13), 86 (68), 44 (100), 43 (38); positive FABMS (magic bullet) *m/z* 597 (M^+ + 1); CD Δε nm (c 0.17 mmol/L, MeOH, 27 °C) -17.70 (276), -1.25 (314), -2.80 (363).

(-)-2S-Acetylamino-*N*-[(1,5,6,7,9,10,13,14,14a,15-decahydro-2,5,11-trimethoxy-3,12,16-trimethyl-1,4,10,13-tetraoxo-(5α,6β,9β(S),14aβ,15β)-6,15-imino-4*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (24).

A solution of **21** (51.3 mg, 0.088 mmol) and selenium oxide (29.5 mg, 0.266 mmol) in methanol (6 mL) was stirred for 72 h at room temperature. The reaction mixture was diluted with water (25 mL), made alkaline with 5% $NaHCO_3$, and extracted with chloroform (20 mL x 3). The combined extracts were washed with water (20 mL), dried, and concentrated in

vacuo to give the residue (48.7 mg). Chromatography on a silica gel (10 g) column with 200:3 dichloromethane-methanol afforded **24** (26.5 mg, 49.1%) as pale yellow amorphous powder: $[\alpha]^{20}_D$ - 391.6° (*c* 1.33, $CHCl_3$); IR ($CHCl_3$) 3420, 3000, 2940, 1690, 1655, 1620, 1505, 1455, 1375, 1310, 1210, 1160, 1100, 965 cm^{-1}; UV λ_{max} nm (log ε) 266 (4.21), 366 (3.13) ; ^1H NMR δ 1.05 (3H, d, *J* = 7.3 Hz, $CHCH_3$), 1.30 (1H, ddd, *J* = 17.8, 11.2, 3.0 Hz, H-14α), 1.86 (3H, s, NAc), 1.90 and 2.02 (each 3H, s, Ar CH_3), 2.46 (3H, s, NCH_3), 2.59 (1H, ddd, *J* = 12.2, 3.0, 2.6 Hz, H-14a), 2.74 (1H, dd, *J* = 17.8, 2.6 Hz, H-14β), 2.75 (1H, dd, *J* = 10.6, 3.0 Hz, H-7), 3.07 (1H, dd, *J* = 10.6, 2.3 Hz, H-7), 3.10 (1H, ddd, *J* = 13.9, 4.0, 3.0 Hz, 9-C*H*N), 3.25 (1H, br s, H-6), 3.51 (1H, br s, H-9), 3.54 (3H, s, OCH_3), 3.76 (1H, ddd, *J* = 13.9, 8.6, 2.3 Hz, 9-C*H*N), 3.88 (1H, s, H-5), 3.98 (3H, s, OCH_3), 3.99 (1H, q, *J* = 6.9 Hz, $CHCH_3$), 4.02 (1H, d, *J* = 3.0 Hz, H-15), 4.04 (3H, s, OCH_3), 5.74 (1H, d, *J* = 6.9 Hz, NH), 6.17 (1H, dd, *J* = 7.3, 3.3 Hz, NH); ^{13}C NMR δ 8.5 (q), 8.9 (q), 17.5 (q, $CHCH_3$), 22.8 (q, $COCH_3$), 25.9 (t, C-14), 40.7 (t, 9-CH_2), 42.1 (q, NCH_3), 48.5 (d, $CHCH_3$), 55.0 (d, C-15), 55.9 (d, C-14a), 56.0 (t, C-7), 57.6 (d, C-6), 59.2 (q, OCH_3), 59.3 (d, C-9), 60.9 (q, OCH_3), 60.9 (q, OCH_3), 71.8 (d, C-5), 127.0 (s), 130.1 (s), 136.4 (s), 137.5 (s), 141.1 (s), 141.8 (s), 155.2 (s), 156.5 (s), 170.0 (s), 172.2 (s), 181.4 (s), 183.1 (s), 185.8 (s), 186.7 (s); EIMS *m/z* (relative intensity) 610 (M^+, 1>), 467 (7), 257 (12), 256 (21), 236 (17), 233 (13), 218 (16), 83 (100); positive FABMS (magic bullet) *m/z* 611 (M^+ + 1); CD Δ ε nm (c 0.17 mmol/L, MeOH, 27 °C) +19.85 (274), +0.04 (310), +1.91 (366).

(-)-2S-Acetylamino-*N*-[(6,7,9,10,13,14,14a,15-octahydro-1,4-dihydroxy-2,5,11-trimethoxy-3,12,16-trimethyl-10,13-dioxo-(5β,6α,9α(R),14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (1c).

A solution of **22** (32.0 mg, 0.0525 mmol) in ethyl acetate (8 mL) was hydrogenated over 10% palladium on carbon (16 mg) at 1 atm for 1 h. The catalyst was removed by filtration and washed with ethyl acetate (80 mL). The combined filtrates were concentrated in vacuo to give a colorless solid (**25**, 29.2 mg), which was used for the next step without further purification. Silica gel (150 mg) was added to a solution of **25** in ethyl acetate (10 mL), and the mixture was stirred in an oxygen atmosphere at room temperature for 24 h. The reaction mixture was filtered and washed it with ethyl acetate (80 mL). The combined filtrates were concentrated in vacuo. The residue (26.0 mg) which showed two major spots on TLC (R_f 0.40 and 0.17, 4:5 acetone-chloroform) was subjected to chromatography on preparative layer silica gel plates (Merck 5715, solvent 20:1 dichloromethane-methanol) to afford **1c** (18.0 mg, 56.1 %) and **25** (1.4 mg, 4.4% recovery): **1c**: (not crystallizable): $[\alpha]^{20}_D$ - 62.8° (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) 3545, 3280, 3260, 2830, 2770, 1675, 1665, 1650, 1605, 1440, 1405, 1360, 1330, 1275, 1145, 1105, 1060, 1020, 1000, 975 cm^{-1}; UV λ_{max} nm (log ε) 272 (3.97), 294sh (3.81), 370 (2.76) nm; ^1H NMR δ 0.79 (3H, d, *J* = 6.9 Hz, $CHCH_3$), 1.74 (1H, ddd, *J* = 18.8, 10.9, 3.0 Hz, H-14β), 1.86 (3H, s, NAc), 1.86 (3H, s, 12-CH_3), 2.22 (3H, s, 3-CH_3), 2.36 (3H, s, NCH_3), 2.72 (1H, ddd, *J* = 10.9, 3.0, 2.0 Hz, H-14a), 2.87 (1H, dd, *J* = 10.9, 2.6 Hz, H-7), 2.95 (1H, dd, *J* = 18.8, 2.0 Hz, H-14α), 3.06 (1H, dd, *J* = 10.9, 2.6 Hz, H-7), 3.27 (1H, ddd, *J* = 13.5, 3.3, 3.3 Hz, 9-C*H*N), 3.39 (1H, br s, H-6), 3.52 (1H, br s, H-9), 3.58 (3H, s, 5-OCH_3), 3.62 (1H, ddd, *J* = 13.5, 7.3, 1.7 Hz, 9-C*H*N), 3.66 (1H, q, *J* = 6.9 Hz, $CHCH_3$), 3.76 (3H, s, 2-OCH_3), 3.99 (3H, s, 11-OCH_3), 4.22 (1H, dd, *J* = 3.0, 0.5 Hz, H-15), 4.25 (1H, s, H-5), 5.41 (1H, d, *J* = 7.3 Hz, NH), 6.03 (1H, dd, *J* = 7.3, 3.3 Hz, NH), 6.10 (1H, br s, OH), 7.05 (1H, s, OH); ^{13}C NMR δ 8.6 (q), 9.2 (q), 18.6 (q, $CHCH_3$), 22.9 (q, $COCH_3$), 25.1 (t, C-14), 40.4 (t, 9-CH_2), 41.9 (q, NCH_3), 48.6 (d,$CHCH_3$), 55.7 (d, C-6), 55.8 (q, OCH_3), 57.0 (d, C-15), 57.1 (t, C-7), 57.3 (d, C-14a), 58.1 (d, C-9), 60.8 (q, OCH_3), 60.9 (q, OCH_3), 75.2 (d, C-5), 117.1 (s), 117.3 (s), 118.0 (s), 127.5 (s), 136.2 (s), 140.3 (s), 142.6 (s), 146.2 (s), 146.8 (s), 156.0 (s), 169.4 (s), 172.4 (s), 181.6 (s), 186.2 (s); EIMS *m/z* (relative intensity) no M^+, 442 (28), 441 (100), 439 (55), 317 (24), 299 (19), 245 (12), 244 (32), 243 (13), 234 (19), 233 (41), 232 (52), 231 (68), 230 (22), 229 (34), 219 (34), 218 (53), 217 (22), 216 (30), 215(13), 206 (20), 205 (15), 204 (37), 203 (32), 202 (39), 201 (21), 190 (29), 189 (26), 188 (27), 187 (46), 186 (24), 176 (18), 175 (15), 174 (18), 87 (21), 86 (62), 44 (92), 43 (16), 42 (14); positive FABMS (magic bullet) *m/z* 613 (M^+ + 1); CD Δ ε nm (c 0.17 mmol/L, MeOH, 27 °C) +10.61 (212), -10.61 (268).

(+)-2S-Acetylamino-*N*-[(6,7,9,10,13,14,14a,15-octahydro-1,4-dihydroxy-2,5,11-trimethoxy-3,12,16-trimethyl-10,13-dioxo-(5α,6β,9β(S),14aβ,15β)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (27).

A solution of **24** (33.7 mg, 0.0553 mmol) in ethyl acetate (8 mL) was hydrogenated over 10% palladium on carbon (16.8 mg) at 1 atm for 1 h. The catalyst was removed by filtration and washed with ethyl acetate (80 mL). The combined filtrates were concentrated in vacuo to give a colorless solid (**26**, 27.2 mg), which was used for the next step without further purification. Silica gel (150 mg) was added to a solution of **26** in ethyl acetate (10 mL), and the mixture was stirred in an oxygen atmosphere at room temperature for 24 h. The reaction mixture was filtered and washed with ethyl acetate (80 mL). The combined filtrates were concentrated in vacuo. The residue (22.9 mg) which showed two major spots on TLC (R_f 0.38 and 0.16, 4:5 acetone-chloroform) was subjected to chromatography on preparative layer silica gel plates (Merck 5715, solvent 20:1 dichloromethane-methanol) to afford **27** (17.1, 50.6 %) and **24** (4.0 mg, 11.9% recovery):

27 (not crystallizable): $[\alpha]^{20}_D$ + 26.0° (*c* 0.68, $CHCl_3$); IR ($CHCl_3$) 3545, 3275, 3250, 1675, 1665, 1655, 1610, 1475, 1440, 1405, 1360, 1330, 1300, 1275, 1145, 1105, 1060, 1020, 1000, 965 cm^{-1}; UV λ_{max} nm (log ε) 270 (3.89), 294sh (3.78), 370 (2.80) nm; ^1H NMR δ 0.84 (3H, d, *J* = 6.9 Hz, $CHCH_3$), 1.58 (1H, ddd, *J* = 18.5, 10.9, 3.3 Hz, H-14α), 1.80 (3H, s, NAc), 1.90 (3H, s, 12-CH_3), 2.28 (3H, s, 3-CH_3), 2.39 (3H, s, NCH_3), 2.74 (1H, ddd, *J* = 10.9, 3.0, 1.7 Hz, H-14a), 2.84 (1H, dd, *J* = 10.6, 2.6 Hz, H-7), 2.96 (1H, dd, *J* = 18.5, 1.7 Hz, H-14β), 3.10 (1H, dd, *J* = 10.6, 2.3 Hz, H-7), 3.37 (1H, ddd, *J* = 13.9, 3.3, 3.3 Hz, 9-C*H*N), 3.40 (1H, br s, H-6), 3.53 (1H, br s, H-9), 3.57 (1H, ddd, *J* = 13.9, 7.3, 1.7 Hz, 9-C*H*N), 3.58 (3H, s, 5-OCH_3), 3.79 (3H, s, 2-OCH_3), 3.89 (1H, q, *J* = 6.9 Hz, $CHCH_3$), 4.00 (3H, s, 11-OCH_3), 4.22 (1H, dd, *J* = 3.0, 0.5 Hz, H-15), 4.24 (1H, s, H-5), 5.46 (1H, s, OH), 5.59 (1H, d, *J* = 7.3 Hz, NH), 5.80 (1H, dd, *J* = 7.3, 3.3 Hz, NH), 7.11 (1H, s, OH); ^{13}C NMR δ 8.6 (q), 9.4 (q), 17.7 (q, $CHCH_3$), 22.8 (q, NAc), 25.3 (t, C-14), 39.8 (t, 9-CH_2), 42.0 (q, NCH_3), 48.3 (d, $CHCH_3$), 56.0 (d, C-6), 56.3 (q, OCH_3), 56.7 (t, C-7), 56.8 (d, C-15), 57.1 (d, C-14a), 57.9 (d, C-9), 60.9

(q, OCH_3), 60.9 (q, OCH_3), 74.8 (d, C-5), 116.5 (s), 117.9 (s), 118.0 (s), 127.8 (s), 136.6 (s), 140.0 (s), 142.1 (s), 145.1 (s), 147.0 (s), 156.0 (s), 169.9 (s), 172.0 (s), 181.6 (s), 186.2 (s); EIMS *m/z* (relative intensity) no M^+, 442 (128), 441 (100), 439 (31), 317 (21), 299 (12), 244 (27), 233 (33), 232 (41), 231 (70), 230 (25), 229 (16), 220 (31), 219 (28), 217 (18), 216 (29), 206 (22), 205 (13), 204 (32), 203 (25), 202 (36), 201 (16), 190 (23), 189 (20), 188 (32), 187 (43), 186 (22), 176 (16), 175 (11), 174 (16), 87 (15), 86 (39), 44 (67), 43 (22); positive FABMS (magic bullet) *m/z* 613 ($M^+ + 1$); CD $\Delta\varepsilon$ nm (c 0.16 mmol/L, MeOH, 27 °C) -11.05 (213), +9.61 (264).

(-)-2S-Acetylamino-*N*-[1,4-diacetoxy-(6,7,9,10,13,14,14a,15-octahydro-2,5,11-trimethoxy-3,12,16-trimethyl-10,13-dioxo-(5β,6α,9α(R),14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (28).

Acetic anhydride (0.2 mL) was added to a solution of **1c** (18.0 mg, 0.0294 mmol) in dry pyridine (0.5 mL), and the mixture was left to stand at room temperature for 24 h. After being diluted with water (10 mL), the mixture was extracted with chloroform (10 mL x 3). The combined extracts were washed with 5% $NaHCO_3$, dried, and concentrated in vacuo to give the residue (19.6 mg). Chromatography on a silica gel (5 g) column with 50:1 dichloromethane-methanol restored **22** (3.4 mg, 19.0%) and further elution with 40:1 dichloromethane-methanol afforded **28** (14.4 mg, 70.3%) as pale yellow amorphous powder: $[\alpha]^{20}_D$ - 60.6° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3335, 1760, 1738, 1660, 1645, 1605 cm^{-1}; UV λ_{max} nm (log ε) 266 (3.80), 280sh (3.72), 374 (2.31); ^1H NMR δ 0.98 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$), 1.48 (1H, ddd, *J* = 16.9, 11.4, 2.6 Hz, H-14β), 1.74 (3H, s, NAc), 1.87 (3H, s, 12-CH_3), 2.14 (3H, s, 3-CH_3), 2.43, 2.44 (each 3H, s, OAc), 2.44 (3H, s, NCH_3), 2.63 (1H, ddd, *J* = 11.4, 2.4, 2.4 Hz, H-14a), 2.75 (1H, dd, *J* = 16.9, 2.4 Hz, H-14α), 2.83 (1H, dd, *J* = 10.5, 2.4 Hz, H-7), 2.83 (1H, ddd, *J* = 13.9, 3.3, 3.3 Hz, 9-C*H*N), 2.98 (1H, dd, *J* = 10.5, 1.0 Hz, H-7), 3.33 (1H, br s, H-6), 3.49 (1H, br s, H-9), 3.50 (3H, s, 5-OCH_3), 3.65 (1H, s, H-5), 3.73 (1H, q, *J* = 6.9 Hz, C*H*CH$_3$), 3.75 (3H, s, 2-OCH_3), 3.76 (1H, ddd, *J* = 13.9, 9.0, 1.7 Hz, 9-C*H*N), 3.82 (1H, dd, *J* = 3.0, 0.5 Hz, H-15), 4.08 (3H, s, 11-OCH_3), 5.78 (1H, d, *J* = 7.1 Hz, NH), 6.05 (1H, dd, *J* = 9.0, 3.3 Hz, NH); ^{13}C NMR δ 8.4 (q), 9.8 (q), 18.3 (q, CH*C*H$_3$), 20.8 (q, OAc), 20.9 (q, OAc), 22.8 (q, NAc), 24.6 (t, C-14), 41.2 (t, 9-CH_2), 42.4 (q, NCH_3), 49.0 (d, *C*HCH$_3$), 56.0 (d, C-6), 57.0 (t, C-7), 57.3 (d, C-14a), 57.9 (d, C-15), 58.1 (q, OCH_3), 58.8 (d, C-9), 60.8 (q, OCH_3), 61.1 (q, OCH_3), 74.0 (d, C-5), 124.3 (s), 124.4 (s), 125.6 (s), 126.0 (s), 137.1 (s), 139.1 (s), 140.0 (s), 145.4 (s), 150.3 (s), 157.0 (s), 168.5 (s), 168.9 (s), 170.2 (s), 172.9 (s), 181.2 (s), 186.1 (s); EIMS *m/z* (relative intensity) 696 (M^+, 90), 555 (33), 554 (100), 553 (99), 511 (29), 350 (35), 336 (13), 334 (27), 304 (34), 292 (19), 262 (20), 234 (11), 228 (19), 219 (10), 218 (16), high-resolution MS calcd for $C_{35}H_{44}N_4O_{11}$ 696.3007, found 696.3011. CD $\Delta\varepsilon$ nm (c 0.15 mmol/L, MeOH, 20 °C) +11.11 (217), -9.30 (267).

(+)-2S-Acetylamino-*N*-[1,4-diacetoxy-(6,7,9,10,13,14,14a,15-octahydro-2,5,11-trimethoxy-3,12,16-trimethyl-10,13-dioxo-(5α,6β,9β(S),14aβ,15β)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]propanamide (29).

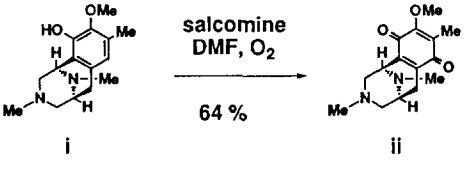
Acetic anhydride (0.2 mL) was added to a solution of **27** (14.2 mg, 0.0232 mmol) in dry pyridine (0.5 mL), and the mixture was left to stand at room temperature for 24 h. After being diluted with water (10 mL), the mixture was extracted with chloroform (10 mL x 3). The combined extracts were washed with 5% $NaHCO_3$, dried, and concentrated in vacuo to give the residue (19.0 mg). Chromatography on a silica gel (5 g) column with 50:1 dichloromethane-methanol restored **24** (0.2 mg, 1.4%) and further elution with 40:1 dichloromethane-methanol afforded **29** (11.0 mg, 68.1%) as pale yellow amorphous powder: $[\alpha]^{20}_D$ +99.0° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3335, 1760, 1738, 1660, 1645, 1605 cm^{-1}; UV λ_{max} nm (log ε) 266 (3.77), 280sh (3.68), 378 (2.21); ^1H NMR δ 0.57 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$), 1.46 (1H, ddd, *J* = 17.8, 11.2, 3.3 Hz, H-14α), 1.86 (3H, s, NAc), 1.90 (3H, s, 12-CH_3), 2.15 (3H, s, 3-CH_3), 2.41, 2.43 (each 3H, s, OAc), 2.44 (3H, s, NCH_3), 2.63 (1H, ddd, *J* = 11.2, 2.7, 2.7 Hz, 14a-H), 2.71 (1H, dd, *J* = 17.8, 2.7 Hz, H-14β), 2.77 (1H, dd, *J* = 10.7, 2.7 Hz, H-7), 2.93 (1H, ddd, *J* = 13.9, 4.2, 3.6 Hz, 9-C*H*N), 3.02 (1H, dd, *J* = 10.7, 2.4 Hz, H-7), 3.34 (1H, br s, H-6), 3.47 (1H, br s, H-9), 3.50 (3H, s, 5-OCH_3), 3.64 (1H, s, H-5), 3.69 (3H, s, 2-OCH_3), 3.80 (1H, dd, *J* = 2.7, 0.5 Hz, H-15), 3.83 (1H, ddd, *J* = 13.9, 8.0, 1.0 Hz, 9-C*H*N), 4.10 (3H, s, 11-OCH_3), 4.10 (1H, q, *J* = 6.6 Hz, C*H*CH$_3$), 6.20 (1H, d, *J* = 6.3 Hz, NH), 6.31 (1H, dd, *J* = 8.0, 4.2 Hz, NH); ^{13}C NMR δ 8.5 (q), 9.8 (q), 19.6 (q, CH*C*H$_3$), 20.7 (q, OAc), 20.9 (q, OAc), 23.2 (q, NAc), 24.7 (t, C-14), 40.2 (t, 9-CH_2), 42.4 (q, NCH_3), 47.9 (d, *C*HCH$_3$), 56.0 (d, C-6), 56.7 (t, C-7), 57.0 (d, C-14a), 57.7 (d, C-15), 58.2 (q, OCH_3), 58.8 (d, C-9), 60.8 (q, OCH_3), 60.8 (q, OCH_3), 73.8 (d, C-5), 124.3 (s), 124.7 (s), 125.8 (s), 126.2 (s), 137.3 (s), 139.4 (s), 140.0 (s), 145.6 (s), 150.2 (s), 157.0 (s), 168.3 (s), 168.1 (s), 170.3 (s), 172.8 (s), 181.3 (s), 186.2 (s); EIMS *m/z* (relative intensity) 696 (M^+, 70), 556 (11), 555 (45), 554 (100), 553 (92), 511 (28), 350 (32), 336 (13), 334 (27), 304 (35), 292 (19), 262 (21), 234 (12), 220 (19), 219 (11), 218 (17), high-resolution MS calcd for $C_{35}H_{44}N_4O_{11}$ 696.3007, found 696.3008. CD $\Delta\varepsilon$ nm (c 0.15 mmol/L, MeOH, 27 °C) -9.23 (219), +10.55 (267).

Acknowledgments

We are grateful to Professor Emeritus Tadashi Arai of Chiba University for the CD spectral charts of saframycin A-C. We thank Mr. N. Eguchi, Ms. S. Yoshioka in the Analytical Center of our college for the spectral data measurements (NMR and MS) and microanalytical data.

REFERENCES AND NOTES

1. Part XI; Saito, N.; Harada, S.; Yamashita, M.; Saito, T.; Yamaguchi, K.; Kubo, A. *Tetrahedron* **1995**, preceding paper.
2. a) Irschik, H.; Trowitzch-Kienast, W.; Gerth, K.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1988**, *41*, 993-998. b) Trowitzsch-Kienast, W.; Irschik, H.; Reichenbach, H.; Wray, V.; Höfle, G. *Liebigs Ann. Chem.* **1988**, 475-481. c) Reichenbach, H. Jpn. Kokai Tokkyo Koho 88 49092; *Chem. Abstr.* **1989**, *110*, 55972p.
3. Kubo, A.; Saito, N. *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier, Amsterdam, 1992, Vol. 10, pp 77-145.
4. a) Ueda, I.; Kawano, S.; Ikeda, Y.; Matsuki, H.; Ogawa, T. *Acta Crystallogr.* **1984**, *C40*, 1578-1580, and references cited therein. b) Cooper, R.; Unger, S. *J. Antibiot.* **1985**, **38**, 24-30, and references cited therein.
5. a) Kubo, A.; Saito, N.; Yamato, H.; Masubuchi, K.; Nakamura, M. *J. Org. Chem.* **1988**, *53*, 4295-4310. b) Fukuyama, T.; Sachleben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957-4958; Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *ibid.* **1990**, *112*, 3712-3713; Fukuyama, T.; Linton, S. D. Tun, T. T. *Tetrahedron Lett.* **1990**, *31*, 5989-5992.
6. a) Saito, N.; Nishida, M.; Kubo, A. *Chem. Pharm. Bull.* **1991**, *39*, 1343-1345. b) Saito, N.; Harada, S.; Nishida, M.; Inouye, I.; Kubo, A. *ibid.* **1995**, *43*, 777-782.
7. Saito, N.; Ohira, Y.; Wada, N.; Kubo, A. *Tetrahedron*, **1990**, *46*, 7711-7728.
8. A preliminary experiment was carried out by employing the racemic alanine derivative. Condensation of **10a** and Cbz (*DL*)-alanine with DCC furnished the amides **11a*** and **14a*** in 75% yield. We are able to crystallize **11a*** from ethyl acetate to afford pure **11a*** as colorless prisms (see obtain Experimental Section for details.).
9. In order to prepare a large quantity of **16b**, the three-step sequence from **10b** to **16b** could be accomplished with only one routine crystallization (see Experimental Section.).
10. Unfortunately, an authentic sample of naturally derived saframycin Mx 2 (**1b**) was not available.
11. Arai, T.; Takahashi, K.; Kubo, A.; Nakahara, S.; Sato, S.; Aiba, K.; Tamura, C.; *Tetrahedron Lett.* **1979**, 2355-2358.
12. A possible biogenetic pathway is the initial oxidation of safracins to form bisquinones. Introduction of a methoxyl group at the C-5 position would give saframycin C type compounds, which could then be reduced followed by air oxidation to afford saframycin Mxs. The first step is still speculative, but appears reasonable.[13]
13. While pursuing recent model studies, we succeeded in the conversion of the phenol **i** into the *p*-quinone **ii** using bis(salicylidene)ethylene-diiminocobalt (II) (salcomine) in 64% yield (Scheme 4): Saito, N.; Obara, Y.; Aihara, T.; Harada, S.; Shida, Y.; Kubo, A. *Tetrahedron*, **1994**, *50*, 3915-3928.



i ii

Scheme 4

14. The biosynthesis of this class of antibiotics has been studied, indicating that these compounds indeed contain two molecules of tyrosine, glycine, and alanine; Mikami, Y.; Takahashi, K.; Yazawa, K.; Arai, T.; Namikoshi, M.; Iwasaki, S.; Okuda, S. *J. Biol. Chem.* **1985**, *10*, 344-348; Arai, T.; Yazawa, K.; Takahashi, K.; Maeda, A.; Mikami, Y.; *Antimicrobial Agents and Chemother.* **1985**, *28*, 5-11.
15. After we finished writing this paper, Professor Fukuyama kindly send us information about his successful first total synthesis of safracin A. We thank Professor Fukuyama for communicating the results of his research prior to publication.
16. SIP91: Hai-Fu, F.; Structure Analysis Programs with Intelligent Control, Rigaku Corporation, Tokyo, Japan.
17. DIRDIF92: Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; Garcia-Granda, S.; Gould, R. O.; Smits, J. M. M.; Smykalla, C. 1992, The DIRDIF program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(*Received in Japan* 10 *May* 1995; *accepted* 5 *June* 1995)