SYNTHESIS OF SAFRAMYCINS. VII. THE SYNTHESIS OF NOVEL RENIERAMYCIN CONGENERS[1]

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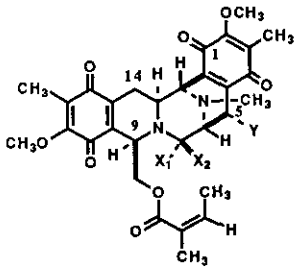
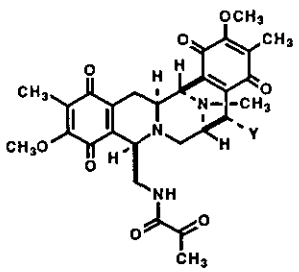
Abstract ——— Synthesis of the marine alkaloid renieramycin congeners (**13a-c**) has been investigated starting from the alcohol (**14a**) which was the key intermediate for saframycin B synthesis.

Marine organisms have been the source of a wide variety of novel natural products. The renieramycins A-D (**1a-d**) were isolated by Faulkner and co-workers from a bright blue sponge, *Reniera* sp. found near Isla Grande, Mexco in 1982.[2,3] The structures of the renieramycins A-D (**1a-d**) were first elucidated by analysis of spectral data, particularly ^{1}H nmr data. The ring system of the renieramycins A-D (**1a-d**) was identical with that of the saframycins (**2**)[4] and the relative stereochemistry differs only at the side chain at C-9 position, based on difference NOE studies. Renieramycins E (**1e**) and F (**1f**) were recently isolated from a bright blue sponge of the genus *Reniera* sp. collected from a marine lake in Palau, Western Caroline Islands by Faulkner, who pointed out that the stereochemistry of the renieramycins as published was incorrect and the correct stereochemistry was exactly the same as that reported for the saframycins including the carbon to which the side chain is attached.[5] Fukuyama and



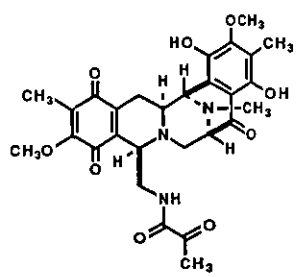
Renieramycins

A: (1a) $X_1 = X_2 = H$, Y = OH
B: (1b) $X_1 = X_2 = H$, Y = OCH_2CH_3
C: (1c) $X_1, X_2 = O$, Y = OH
D: (1d) $X_1, X_2 = O$, Y = OCH_2CH_3
E: (1e) X_1 = OH, X_2 = Y = H
F: (1f) X_1 = OH, X_2 = H, Y = OCH_3



Saframycins

B: (2a) Y = H
C: (2b) Y = OCH_3

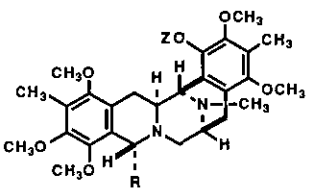


Saframycin D: (2c)

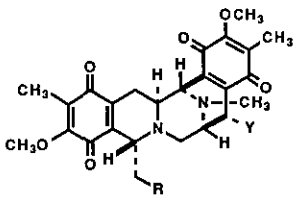
co-workers completed an elegant first total synthesis of (±)-renieramycin A (**1a**) and had independently reached the same conclusion.[6] We completed a total synthesis of saframycins B-D (**2b-d**),[7a,b] and report here the synthetic approach to the two possible isomers at C-9 position of renieramycins, as part of a study to elucidate the structure-activity relationships of saframycin-renieramycin family.

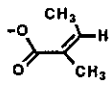
The means of synthesizing 9-*epi*-saframycin B (**9a**) is first described. Reduction of the ester (**3**)[7a] with lithium aluminum hydride afforded the alcohol (**4**) in 83.8% yield. Treatment of **4** with diethyl azodicarboxylate, triphenylphosphine, and phthalimide in THF at 25°C for 3 h gave the imide (**5**) which was followed by cleavage of the phthaloyl group with hydrazine hydrate to afford the amine (**6**). This was treated with pyruvoyl chloride to give the pyruvamide (**7**) in 77% overall yield. Conversion of the polymethoxyarene (**7**) to a bis-*p*-quinone system (**9a**) was initiated by oxidative demethylation. All attempts to effect direct oxidative demethylation of **7** gave only a polar polymeric material. Furthermore, treatment of **7** with boron tribromide in dichloromethane at -78°C gave the phenol (**8**) in 65% yield, and numerous efforts to convert **8** to **9a** were totally unsuccessful.

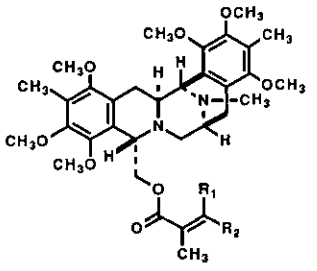
Next, we turned our attention to preparing 9-*epi*-renieramycin A (**9b**). Treatment of the alcohol (**4**) with angeloyl chloride,[8] DMAP, and triethylamine in dichloromethane at 0°C afforded the angelate ester (**10**) in 15.1% along with the corresponding tiglate ester (**11**) in 47.9% yield. The latter compound (**11**) was synthesized from **4** with tigloyl chloride in 63.0% yield. The ^{1}H nmr spectrum of **10** displayed the vinylic proton at δ 5.99 (dq, J = 7.3, 1.5 Hz), whereas the corresponding proton in **11** appeared at δ 6.77 (dq, J = 7.3, 2.0 Hz).[9] Conversely, when the alcohol (**4**) was treated with *n*-BuLi and the mixed anhydride (**12a**)[10] in THF at -15°C, it afforded **10** and **11** in 86.9% and 9.0% yields, respectively. Disappointingly, both the oxidative demethylation of **10** and the partial demethylation of **10** failed.



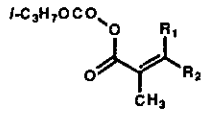
3: R = $COOC_4H_9$-*n*, Z = CH_3
4: R = CH_2OH, Z = CH_3
5: R = CH_2NPht, Z = CH_3
6: R = CH_2NH_2, Z = CH_3
7: R = $CH_2NHCOCOCH_3$, Z = CH_3
8: R = $CH_2NHCOCOCH_3$, Z = H



9a: R = $NHCOCOCH_3$, Y = H
9b: R =  Y = OH



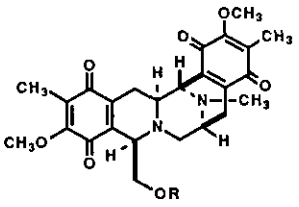
10: R_1 = CH_3, R_2 = H
11: R_1 = H, R_2 = CH_3

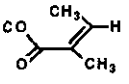


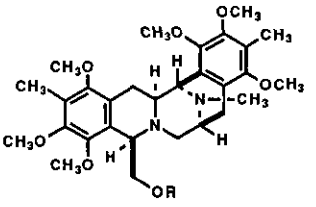
12a: R_1 = CH_3, R_2 = H
12b: R_1 = H, R_2 = CH_3

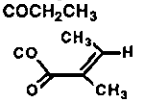
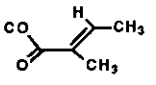
Renieramycin congeners (**13a-c**)[11] were then prepared from the alcohol (**14a**), which was our key intermediate of saframycin B synthesis. Acetylation of the alcohol (**14a**)[7a] with acetic anhydride in pyridine at room temperature for 1 h afforded **14b** in 68% yield. Treatment of the acetate (**14b**) in dichloromethane in the presence of 4 equiv. of boron tribromide at -78°C for 1 h and then 10 N HNO_3 at room temperature for 1 h provided the quinones (**13a**) and (**13b**) in 5% and 33% yields, respectively. Treatment of **14a** with propionic anhydride in pyridine gave **14c** in 78% yield. A similar partial demethylation and oxidative demethylation sequence of **14c** gave the quinones (**13a**) and (**13c**) in 20.4% and 28.5% yields. These quinones (**13a-c**) were stable and no degradation products could be detected.

Finally, we speculated that this approach might also be employed to construct 5-dehydroxyrenieramycin A (**13d**). Treatment of **14a** with *n*-BuLi and the mixed anhydride (**12a**) in THF at -15°C afforded the ester (**14d**) in 47% yield along with the carbonate (**15**)[12] in 7% yield (26.2% yield of **14a** was recovered), while treatment of **14a** with the mixed anhydride (**12b**)[10] in THF afforded the ester (**14e**) and **15** in 76% and 18% yields. The ^1H nmr spectrum of **14d** displayed 9-H at δ 3.88, 14a-H at δ 2.85, and14-Hβ at δ 1.87, whereas the ^1H nmr spectrum of the corresponding 9-*epi*-compound (**10**) showed the 9-H peak (δ 4.22), the 14a-H peak (δ 3.51), and the 14-Hβ peak (δ 2.41) at lower fields. The remarkable differences of the chemical shifts of the these protons strongly depends on the stereochemistry of the side chain at C-9 position. The same trend appeared in the chemical shifts of 9-Hα and 9-Hβ isomer pairs (**14e/11** and **14a/4**). Oxidative demethylation of **14d** failed; only starting material was recovered and partial demethylation of **14d** with boron tribromide gave large amounts of degradation products. Search for an alternative route to the total synthesis of the renieramycins from **14a** is currently in progress.



13a: R = H
13b: R = $COCH_3$
13c: R = $COCH_2CH_3$
13d: R = 



14a: R = H
14b: R = $COCH_3$
14c: R = $COCH_2CH_3$
14d: R = 
14e: R = 

15: R = $COOC_3H_7$-*i*

ACKNOWLEDGMENTS

We thank A. Koike, T. Goto, and M. Narita in the Analytical Center of our College for measurements of spectral data (nmr and ms) and microanalytical data. We are also grateful for financial support from the Ministry of Education, Science and Culture of Japan in the form of Grant-in-Aid (No. 63571010) for Scientific Research.

EXPERIMENTAL SECTION

All melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. Uv spectra were determined in methanol with a Hitachi 340 spectrophotometer. Ir spectra were obtained with a Hitachi 260-10 spectrophotometer and ^{1}H nmr spectra were recorded at 400 MHz with a JEOL GX 400 spectrometer. ^{13}C Nmr spectra were recorded at 100 MHz (multiplicity determined from off-reconance decoupled or DEPT spectra). Nmr spectra were measured in $CDCl_3$, and chemical shifts were recorded in δ_H values relative to internal tetramethylsilane standard. Ms was recorded on a JMS-DX 302 mass spectrometer. Elemental analyses were obtained by a Perkin-Elmer Model 240B elemental analyzer. All reactions were conducted under an argon atmosphere. Dry solvents and reagents were obtained using standard procedures. Anhydrous sodium sulfate was used for drying organic solvent extracts; removal of the solvent was done with a rotary evaporator and finally, under high vacuum. Column chromatography was performed with E. Merck silica gel 60 (70-230 mesh).

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-methanol (4) Lithium aluminum hydride (303 mg, 8.0 mmol) was added to a stirred solution of **3** (758 mg, 1.27 mmol) in dry THF (40 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 to give a solid, recrystallization of which from ethyl acetate gave **4** (562 mg, 83.8%) as colorless prisms, mp 200-201.5°C, ν_{max} (KBr) 3600-3100 cm^{-1}; λ_{max} nm (log ε) 224 (4.32), 272sh (3.23), 278 (3.27); δ_H 2.06 (3H, s, $ArCH_3$), 2.10 (3H, s, $ArCH_3$), 2.18 (3H, s, NCH_3), 2.35 (1H, dd, *J* = 17.6, 10.0 Hz, 14-Hβ), 2.47 (1H, d, *J* = 18.1 Hz, 5-Hβ), 2.85 (1H, dd, *J* = 17.6, 5.1 Hz, 14-Hα), 2.86 (1H, dd, *J* = 13.9, 2.1 Hz, H-7α), 2.94 (1H, dd, *J* = 18.1, 8.4 Hz, H-5α), 3.17 (1H, m, 6-H), 3.43 (1H, dd, *J* = 13.9, 3.0 Hz, 7-Hβ), 3.44 (1H, br s, OH), 3.48 (1H, ddd, *J* = 10.0, 5.1, 2.4 Hz, 14a-H), 3.52, 3.61, 3.65, 3.66 (each 3H, s, OCH_3), 3.69 (1H, dd, *J* = 11.2, 3.7 Hz, 9-C*H*OH), 3.73, 3.75 (each 3H, s, OCH_3), 3.92 (1H, dd, *J* = 4.4, 3.7 Hz, 9-H), 3.99 (1H, dd, *J* = 2.4, 0.5 Hz, 15-H), 4.04 (1H, dd, *J* = 11.2, 4.4 Hz, 9-C*H*OH); δ_H 9.1 (q), 9.3 (q), 22.3 (t, C^5), 25.5 (t, C^{14}), 41.7 (q, NCH_3), 52.4 (d, C^6), 54.4 (d, C^{14a}), 57.3 (d, C^{15}), 58.2 (t, C^7), 59.2, 59.4, 59.7, 59.9, 60.0, 60.1 (each q, OCH_3), 60.1 (d, C^9), 62.6 (t, CH_2OH), 123.2, 123.4, 123.9, 124.2, 124.5, 127.6, 144.9, 147.9, 148.8, 148.9, 151.2, 151.7 (each s); *m/z* (%) 528 (M^+, 0.1), 498 (41), 497 (100), 248 (24). Anal. Calcd for $C_{29}H_{40}N_2O_7$-1/5H_2O: C, 65.44; H, 7.65; N, 5.26. Found: C, 65.45; H, 7.75; N, 5.19.

N-[(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]benzazocin-9-yl)methyl]-2-oxopropanamide (7) A solution of diethyl azodicarbonate (0.47 ml, 3 mmol) in THF (2 ml) was added dropwise to a solution of **4** (351.6 mg, 0.666 mmol), phthalimide (442 mg, 3 mmol), and triphenylphosphine (787 mg, 3 mmol) in THF (8 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 (30 ml) and extracted with chloroform (20 ml x 3). The combined extracts were washed with water (30 ml), dried, and concentrated in vacuo to furnished **5** (438 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); ν_{max} ($CHCl_3$) 1765, 1705 cm^{-1}; λ_{max} nm 278, 302; δ_H 2.00

(3H, s, $ArCH_3$), 2.12 (3H, s, $ArCH_3$), 2.28 (3H, s, NCH_3), 2.54 (1H, d, J = 18.1 Hz, 5-Hβ), 2.68 (1H, dd, J = 18.2, 9.2 Hz, 14-Hβ), 3.00 (1H, dd, J = 18.2, 6.6 Hz, 14-Hα), 3.02 (1H, dd, J = 18.1, 8.4 Hz, H-5α), 3.11 (3H, s, OCH_3), 3.11 (1H, dd, J = 13.7, 2.7 Hz, 7-Hα), 3.30 (1H, m, 6-H), 3.38, 3.60 (each 3H, s, OCH_3), 3.63 (1H, dd, J = 13.7, 2.2 Hz, 7-Hβ), 3.66 (3H, s, OCH_3), 3.70 (1H, ddd, J = 9.2, 6.6, 2.4 Hz, 14a-H), 3.73 (3H, s, OCH_3), 3.82 (1H, dd, J = 12.9, 10.0 Hz, 9-CHN), 3.85 (3H, s, OCH_3), 4.15 (1H, dd, J = 2.4, 0.5 Hz, 15-H), 4.18 (1H, dd, J = 12.9, 3.8 Hz, 9-CHN), 4.31 (1H, dd, J = 10.0, 3.8 Hz, 9-H), 7.27-7.63 (2H, m), 7.70-7.73 (2H, m); δ_C 9.2 (q), 9.3 (q), 22.4 (t, C^5), 24.6 (t, C^{14}), 36.0 (t, 9-CH_2N), 41.8 (q, NCH_3), 52.6 (d, C^6), 53.9 (d, C^9), 54.3 (d, C^{14a}), 57.5 (d, C^{15}), 58.5 (t, C^7), 59.2, 59.3, 59.4, 59.5, 59.8, 60.1 (each q, OCH_3), 122.5 (d), 123.2 (s), 123.2 (s), 123.5 (s), 124.7 (s), 124.7 (s), 128.0 (s), 132.8 (s), 133.2 (d), 144.5 (s), 147.9 (s), 148.5 (s), 149.0 (s), 151.2 (s), 152.6 (s), 161.8 (s, CO); *m/z* (%) 657 (M^+, 1), 498 (33), 497 (100), 248 (22).

Hydrazine monohydrate (0.5 ml, 10.3 mmol) was added to a stirred solution of the crude **5** (438 mg, 0.666 mmol) in ethanol (10 ml), the resulting solution was heated under reflux for 13 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 x 3). The acidic aqueous layer was made alkaline with diluted NH_4OH and extracted with chloroform (30 ml x 3). The combined extracts were washed with water (30 ml), dried, and concentrated in vacuo to give **6** (351 mg, 100%) as a colorless amorphous powder, which was used for the next step without further purification; ν_{max} ($CHCl_3$) 3500-3000 cm^{-1}; λ_{max} nm 224, 272sh, 278; δ_H 2.11 (2H, br s, NH_2), 2.11 (3H, s, $ArCH_3$), 2.13 (3H, s, $ArCH_3$), 2.26 (3H, s, NCH_3), 2.44 (1H, dd, J = 17.8, 9.8 Hz, 14-Hβ), 2.53 (1H, d, J = 18.1 Hz, 5-Hβ), 2.81 (1H, dd, J = 13.4, 3.9 Hz, 9-CHN), 2.91 (1H, dd, J = 17.8, 5.4 Hz, 14-Hα), 2.91 (1H, dd, J = 10.5, 2.2 Hz, 7-Hα), 3.01 (1H, dd, J = 18.1, 8.1 Hz, 5-Hα), 3.26 (1H, dd, J = 13.4, 4.2 Hz, 9-CHN), 3.26 (1H, m, 6-H), 3.42 (1H, dd, J = 10.5, 3.2 Hz, 7-Hβ), 3.51 (1H, ddd, J = 9.8, 5.4, 2.4 Hz, 14a-H), 3.59, 3.68, 3.73, 3.73, 3.79, 3.82 (each 3H, s, OCH_3), 3.88 (1H, dd, J = 4.2, 3.9 Hz, 9-H), 4.07 (1H, dd, J = 2.4, 0.5 Hz, 15-H); *m/z* (%), 497 (M^+ - CH_2NH_2, 100), 248 (29), 218 (8).

A solution of the crude **6** (351 mg, 0.666 mmol), triethylamine (0.167 ml, 1.2 mmol), and 4-(dimethylamino)pyridine (147 mg, 1.2 mmol) in dichloromethane (10 ml) was cooled with ice-water, and a carbon tetrachloride solution of pyruvoyl chloride (1.0 M, 2.4 ml, 2.4 mmol) was added dropwise over 10 min. The solution was stirred for 1 h at room temperature, and the reaction mixture was diluted with water (10 ml) and extracted with dichloromethane (20 ml x 3). The combined extracts were washed with water (20 ml), dried, and concentrated in vacuo. The residue (584 mg) was subjected to chromatography (silica gel, 20 g; elution with 50:1 CH_2Cl_2-MeOH) to give **7** (276 mg, 77.0%) as a solid, which was recrystallized from ethyl acetate-ether to give **7** as colorless prisms, mp 170-171.5°C, ν_{max} (KBr) 3320, 1720, 1685 cm^{-1}; λ_{max} nm (log ε) 229 (4.22), 270 (3.37), 292 (2.82); δ_H 2.10 (3H, s, $ArCH_3$), 2.13 (3H, s, $ArCH_3$), 2.25 (3H, s, NCH_3), 2.41 (3H, s, $COCH_3$), 2.50 (1H, d, J = 18.1 Hz, 5-Hβ), 2.55 (1H, dd, J = 17.9, 9.6 Hz, 14-Hβ), 2.84 (1H, dd, J = 10.7, 2.0 Hz, 7-Hα), 2.89 (1H, dd, J = 17.9, 5.9 Hz, 14-Hα), 3.00 (1H, dd, J = 18.1, 8.3 Hz, 5-Hα), 3.24 (1H, m, 6-H), 3.29 (1H, ddd, J = 13.7, 6.7, 5.3 Hz, 9-CHN), 3.30 (1H, ddd, J = 9.6, 5.9, 2.9 Hz, 14a-H), 3.48 (1H, dd, J = 10.7, 2.7 Hz, 7-Hβ), 3.59, 3.67, 3.72, 3.73, 3.78, 3.82 (each 3H, s, OCH_3), 3.91 (1H, ddd, J = 13.7, 4.7, 4.0 Hz, 9-CHN), 4.06 (1H, dd, J = 2.9, 0.5 Hz, 15-H), 4.07 (1H, dd, J = 6.7, 4.0 Hz, 9-H), 7.36 (1H, dd, J = 5.3, 4.7 Hz, NH): δ_C 9.2 (q), 9.3 (q), 22.3 (t, C^5), 24.4 (q, $COCH_3$), 24.9 (t, C^{14}), 38.8 (t, 9-CH_2N), 41.7 (q, NCH_3), 52.3 (d, C^6), 54.1 (d, C^{14a}), 56.4 (d, C^9), 57.3 (d, C^{15}), 58.3 (t, C^7), 59.3, 59.4, 59.8, 60.0, 60.1, 60.2 (each q, OCH_3), 123.2, 123.4, 123.7, 124.0, 124.6, 127.6, 144.4, 147.8, 148.9, 148.9, 151.3, 152.2 (each s), 160.1

(s, NCO), 196.9 (s, $COCH_3$); *m/z* (%) 597 (M^+, 0.1), 497 (100), 264 (5), 248 (42), 234 (5), 233 (8), 218 (9). Anal. Calcd for $C_{32}H_{43}N_3O_8$: C, 64.30; H, 7.25; N, 7.03. Found: C, 64.43; H, 7.41; N, 6.99.

Partial demethylation of **7** A solution of **7** (29.9 mg, 0.05 mmol) in dichloromethane (4 ml) was cooled at -78°C, and a dichloromethane solution of boron tribromide (1.0 M, 0.2 ml, 0.2 mmol) was added. After being kept at the same temperature for 1 h, and then at 0°C for 1 h, the reaction mixture was poured into ice-water. The aqueous layer was extracted with chloroform (20 ml x 3). The combined extracts were washed with brine (20 ml), dried, and concentrated in vacuo. The residue (34.8 mg) was subjected to chromatography (silica gel, 10 g; elution with 50:1 CH_2Cl_2-MeOH) to give the phenol (**8**, 18.8 mg, 65%) as a colorless amorphous powder; ν_{max} ($CHCl_3$) 3400-3200, 1715, 1675, 1660 cm^{-1}; λ_{max} nm 281; δ_H 2.00 (3H, s, $ArCH_3$), 2.09 (3H, s, $ArCH_3$), 2.26 (3H, s, NCH_3), 2.40 (3H, s, $COCH_3$), 2.42 (1H, d, *J* = 17.3 Hz, 5-Hβ), 2.54 (1H, dd, *J* = 18.1, 9.8 Hz, 14-Hβ), 2.86 (1H, dd, *J* = 10.5, 2.2 Hz, 7-Hα), 2.87 (1H, dd, *J* = 17.3, 8.1 Hz, 5-Hα), 3.27 (1H, m, 6-H), 3.30 (1H, ddd, *J* = 13.7, 6.8, 2.8 Hz, 9-CHN), 3.42 (1H, dd, *J* = 10.5, 2.8 Hz, 7-Hβ), 3.46 (1H, ddd, *J* = 9.8, 5.9, 3.4 Hz, 14a-H), 3.57, 3.70, 3.72 (each 3H, s, OCH_3), 3.74 (1H, br s, OH), 3.76, 3.79 (each 3H, s, OCH_3), 3.93 (1H, ddd, *J* = 13.7, 6.8, 5.4 Hz, 9-CHN), 4.07 (1H, dd, *J* = 6.8, 2.4 Hz, 9-H), 4.07 (1H, dd, *J* = 3.4, 0.5 Hz, 15-H), 7.39 (1H, dd, *J* = 6.8, 5.4 Hz, NH); δ_C 8.7 (q), 9.2 (q), 22.1 (t, C^5), 24.5 (q, $COCH_3$), 25.0 (t, C^{14}), 38.6 (t, 9-CH_2N), 41.6 (q, NCH_3), 52.2 (d, C^6), 54.0 (d, C^{14a}), 56.6 (t, C^9), 56.9 (d, C^{15}), 58.1 (t, C^7), 59.3, 60.0, 60.0, 60.2, 60.3 (each s, OCH_3), 116.2, 117.1, 123.2, 123.4, 123.8, 127.4, 144.4, 145.3, 146.7, 148.8, 148.9, 152.2 (each s), 160.0 (s, NCO), 196.9 (s, $COCH_3$); *m/z* (%) 583 (M^+, 0.2), 483 (100), 250 (8), 234 (26), 219 (5).

(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]benzazocin-9-yl)methyl Angelate (**10**) **Method A**: A solution of **4** (52.8 mg, 0.1 mmol), triethylamine (0.018 ml, 0.13 mmol), and 4-(dimethylamino)pyridine (15.9 mg, 0.13 mmol) in dichloromethane (4 ml) was cooled with ice-water, and a dichloromethane (1 ml) solution of angeloyl chloride (17.5 mg, 0.13 mmol) was added dropwise over 10 min. The solution was stirred for 3 h at 0°C, and the reaction mixture was diluted with water (10 ml), and extracted with chloroform (20 ml x 3). The combined extracts were washed with water (20 ml), dried, and concentrated in vacuo to give a residue. Chromatography on a silica gel (10 g) column with hexane-ethyl acetate (1:1-1:3) as an eluent gave **10** (9.2 mg, 15.1%) as a colorless amorphous powder. Further elution with ethyl acetate gave **11** (29.2 mg, 47.9%) as colorless prisms. **Method B**: A solution of **4** (52.8 mg, 0.1 mmol) in THF (4.5 ml) was cooled at -15°C, and a hexane solution of *n*-BuLi (1.57 M, 0.19 ml, 0.3 mmol) was added and stirring was continued for 30 min at the same temperature. The mixed anhydride (**12a**, 55.7 mg, 0.3 mmol) in THF (1.5 ml) was added over 10 min, and the reaction mixture was stirred for 1 h at -15°C. The reaction mixture was concentrated in vacuo, and the residue 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 to give a residue. Chromatography on a silica gel (10 g) column with hexane-ethyl acetate (1:1-1:3) as an eluent gave **10** (53 mg, 86.9%) as a colorless amorphous powder. Further elution with ethyl acetate gave **11** (5.5 mg, 9.0%) as colorless prisms. **10**: ν_{max} ($CHCl_3$) 1710 cm^{-1}; λ_{max} nm (log ε) 224 (4.43), 272sh (3.26), 278 (3.29); δ_H 1.83 (3H, dd, *J* = 1.7, 1.5 Hz, $COC(CH_3)$=C), 1.90 (3H, dd, *J* = 7.3, 1.7 Hz, COC=CH*CH*$_3$), 2.10 (3H, s, $ArCH_3$), 2.15 (3H, s, $ArCH_3$), 2.26 (3H, s, NCH_3), 2.42 (1H, dd, *J* = 17.8, 10.3 Hz, 14-Hβ), 2.51 (1H, d, *J* = 18.1 Hz, 5-Hβ), 2.87 (1H, dd, *J* = 10.5, 2.2 Hz, 7-Hα), 2.92 (1H, dd, *J* = 17.5, 5.4 Hz, 14-Hα), 3.01 (1H, dd, *J* = 18.1, 8.3 Hz, 5-Hα), 3.24 (1H, m, 6-H), 3.35 (1H, dd, *J* = 10.5, 1.2 Hz, 7-Hβ), 3.51 (1H, ddd, *J* = 10.3, 5.4, 2.2 Hz, 14a-H), 3.59, 3.68, 3.70, 3.74, 3.81, 3.84 (each 3H, s, OCH_3), 4.10 (1H, dd, *J* = 2.2, 0.5 Hz, 15-H), 4.22 (1H, dd, *J* = 5.4, 1.2 Hz, 9-H), 4.30 (1H, dd, *J* = 12.2, 1.2 Hz, 9-

CH), 4.54, (1H, dd, J = 12.2, 5.4 Hz, 9-CH), 5.99 (1H, dq, J = 7.3, 1.5 Hz, CH=C); δ_C 9.1 (q), 9.2 (q), 15.5 (q, =C-*C*H$_3$ (Z)), 20.7 (q, COC-*C*H$_3$), 22.2 (t, C^5), 25.4 (t, C^{14}), 41.8 (q, NCH$_3$), 52.4 (d, C^6), 54.6 (d, C^{14a}), 57.0 (d, C^9), 57.4 (d, C^{15}), 58.7 (t, C^7), 59.3, 59.5, 59.8, 59.9, 60.1, 60.1 (each s, OCH$_3$), 62.8 (t, 9-CH$_2$), 123.4, 123.4, 124.2, 124.3, 124.8, 126.2 (each, s), 127.8 (s, CO*C*=), 137.8 (d, CO*C*H=C), 145.8, 148.0, 148.7, 148.9, 151.2, 151.5 (each s), 167.5 (s, CO); *m/z* (%) 610 (M$^+$, 0.8), 511 (2), 499 (6), 498 (32), 497 (100), 263 (15), 250 (11), 249 (15), 248 (69), 234 (8), 218 (12). High-resolution ms Calcd for $C_{28}H_{37}N_2O_6$ (M$^+$-113): 497.2652. Found: 497.2664.

(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]benzazocin-9-yl)methyl Tiglate (**11**) The same procedure as described above (method A) but using **4** (79.2 mg, 0.15 mmol), triethylamine (0.027 ml, 0.195 mmol), 4-(dimethylamino)pyridine (23.9 mg, 0.195 mmol), and tigloyl chloride (26.2 mg, 0.195 mmol) afforded the residue, which was subjected to chromatography (silica gel, 10 g; elution with ethyl acetate) to give **11** (57.6 mg, 63.0%), which was recrystallized from ethyl acetate-ether to give **11** as colorless prisms, mp 187-189°C, ν_{max} (KBr) 1745, 1705 cm^{-1}; λ_{max} nm (log ε) 210 (4.79), 224sh (4.43), 272sh (3.10), 278 (3.16); δ_H 1.76 (3H, d, J = 2.0 Hz, COC(CH$_3$)=C), 1.78 (3H, d, J = 7.3 Hz, COC=CHC*H*$_3$), 2.10 (3H, s, ArCH$_3$), 2.14 (3H, s, ArCH$_3$), 2.25 (3H, s, NCH$_3$), 2.44 (1H, dd, J = 18.1, 10.3 Hz, 14-Hβ), 2.51 (1H, d, J = 18.3 Hz, 5-Hβ), 2.88 (1H, dd, J = 10.8, 2.4 Hz, 7-Hα), 2.92 (1H, dd, J = 18.1, 5.4 Hz, 14-Hα), 3.01 (1H, dd, J = 18.3, 8.3 Hz, 5-Hα), 3.23 (1H, m, 6-H), 3.34 (1H, dd, J = 10.7, 1.2 Hz, 7-Hβ), 3.51 (1H, ddd, J = 10.3, 5.4, 2.2 Hz, 14a-H), 3.59, 3.68, 3.70, 3.74, 3.80, 3.84 (each 3H, s, OCH$_3$), 4.09 (1H, dd, J = 2.4, 0.5 Hz, 15-H), 4.22 (1H, dd, J = 5.6, 1.2 Hz, 9-H), 4.29 (1H, dd, J = 12.2, 1.5 Hz, 9-CH), 4.47 (1H, dd, J = 12.2, 5.4 Hz, 9-CH), 6.77 (1H, dq, J = 7.3, 2.0 Hz, CH=C); δ_C 9.2 (q), 9.3 (q), 12.1 (q, COC-*C*H$_3$), 14.4 (q, =C-*C*H$_3$ (E)), 22.2 (t, C^5), 25.3 (t, C^{14}), 41.8 (q, NCH$_3$), 52.5 (d, C^6), 54.6 (d, C^{14a}), 56.9 (d, C^9), 57.5 (d, C^{15}), 58.8 (t, C^7), 59.3, 59.5, 59.8, 59.9, 60.0, 60.1 (each s, OCH$_3$), 63.3 (t, 9-CH$_2$), 123.4, 123.4, 124.2, 124.2, 124.8, 126.2 (each, s), 128.6 (s, CO*C*=), 137.0 (d, CO*C*H=C), 145.0, 148.0, 148.7, 148.9, 151.2, 151.5 (each s), 167.7 (s, CO); *m/z* (%) 610 (M$^+$, 0.5), 511 (3), 499 (6), 498 (32), 497 (100), 263 (11), 250 (11), 249 (15), 248 (70), 234 (9), 233 (9), 232 (7), 218 (15). Anal. Calcd for $C_{34}H_{46}N_2O_8$-1/2H_2O: C, 65.98; H, 7.64; N, 4.52. Found: C, 66.07; H, 7.78; N, 4.44.

Synthesis of the mixed anhydrides **12a** and **12b** **12a**: A solution of angelic acid (50.1 mg, 0.5 mmol) and anhydrous K_2CO_3 (70 mg, 0.5 mmol) in dichloromethane (4 ml) was stirred for 10 min. Isopropyl chloroformate (0.058 ml, 0.5 mmol) was then added dropwise over 5 min, and the mixture was stirred for 2 h ar room temperature and filtered. The filter cake was carefully washed with dichloromethane (50 ml), the combined filtrates were concentrated in vacuo. The resulting pale yellow oil (61.0 mg) was essentially pure **12a** as judged by nmr (CCl_4), δ_H 1.32 (6H, d, J = 7.0 Hz, CH(C*H*$_3$)$_2$), 1.90 (3H, d, J = 2.0 Hz), 1.98 (3H, d, J = 7.2 Hz), 4.83 (1H, sep, J = 7.0 Hz, CH), 6.13 (1H, dq, J = 7.2, 2.0 Hz). **12b**: The same procedure as described above but using tiglic acid (200 mg, 0.2 mmol), anhydrous K_2CO_3 (276 mg, 0.2 mmol), and isopropyl chloroformate (0.234 ml, 2.0 mmol) afforded **12b** (137.1 mg, 36.9%) as a pale yellow oil, δ_H 1.33 (6H, d, J = 7.0 Hz, CH(C*H*$_3$)$_2$), 1.82 (6H, br m), 4.82 (1H, sep, J = 7.0 Hz, CH), 6.80 (1H, m).

(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 Acetate (**14b**) Acetic anhydride (0.5 ml, 5.3 mmol) was added to a solution of the alcohol (**14a**) (84.5 mg, 0.16 mmol) in pyridine (1.0 ml), and the mixture was left to stand at room temperature for 1 h. After being diluted with water (5 ml), the mixture was extracted with chloroform (20 ml x 3). The combined extracts were washed with water (20 ml), dried, and concentrated in vacuo to give a

residue (120 mg), which was subjected to chromatography (silica gel, 6 g; elution with 50:1 CH_2Cl_2-MeOH) to give **14b** (62.0 mg, 68%) as a solid. This was recrystallized from ethyl acetate-ether to give **14b** as colorless prisms, mp 160-161°C, ν_{max} (KBr) 1735 cm^{-1}; λ_{max} nm (log ε) 228 (4.27), 272sh (3.15), 280 (3.21); δ_H 1.62 (3H, s, $COCH_3$), 1.82 (1H, dd, J = 14.4, 11.7 Hz, 14-Hβ), 2.17 (3H, s, $ArCH_3$), 2.20 (3H, s, $ArCH_3$), 2.31 (3H, s, NCH_3), 2.58 (1H, d, J = 17.6 Hz, 5-Hβ), 2.82 (1H, ddd, J = 11.7, 3.4, 2.9 Hz, 14a-H), 2.99 (1H, dd, J = 17.6, 8.1 Hz, 5-Hα), 3.00 (1H, dd, J = 10.1, 1.0 Hz, 7-Hα), 3.01 (1H, dd, J = 10.1, 2.0 Hz, 7-Hβ), 3.09 (1H, dd, J = 14.4, 2.2 Hz, 14-Hα), 3.16 (1H, m, 6-H), 3.63 (3H, s, OCH_3), 3.66 (1H, dd, J = 10.5, 4.4 Hz, 9-CH), 3.66, 3.74, 3.76, 3.80, 3.84 (each 3H, s, OCH_3), 3.85 (1H, dd, J = 4.4, 3.7 Hz, 9-H), 4.03 (1H, dd, J = 2.0, 0.5 Hz, 15-H), 4.21 (1H, dd, J = 10.5, 3.7 Hz, 9-CH); δ_C 9.2 (q), 9.2 (q), 20.4 (q, $COCH_3$), 22.5 (t, C^5), 26.9 (t, C^{14}), 41.3 (q, NCH_3), 53.1 (d, C^6), 57.9 (d, C^9), 57.9 (d, C^{15}), 59.5, 59.6, 59.8, 59.9, 60.0, 60.1 (each s, OCH_3), 60.2 (d, C^{14a}), 61.4 (t, C^7), 67.6 (t, 9-CH_2), 122.8, 123.4, 124.5, 125.5, 125.8, 126.4, 145.8, 147.4, 148.7, 149.2, 151.0, 151.1 (each, s), 170.6 (s, CO); *m/z* (%) 570 (M^+, 2), 510 (6), 497 (38), 263 (12), 248 (100), 234 (8), 218 (12). Anal. Calcd for $C_{31}H_{42}N_2O_8$-1/2H_2O: C, 64.23; H, 7.48; N, 4.83. Found: C, 64.50; H, 7.51; N, 4.86.

(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 Propionate (**14c**) Propionic anhydride (0.5 ml, 3.9 mmol) was added to a solution of the alcohol (**14a**) (139.5 mg, 0.265 mmol) in pyridine (1.0 ml), and the mixture was left to stand at room temperature for 1 h. After being diluted with water (5 ml), the mixture was extracted with chloroform (20 ml x 3). The combined extracts were washed with water (20 ml), dried, and concentrated in vacuo to give a residue, which was subjected to chromatography (silica gel, 10 g; elution with 50:1 CH_2Cl_2-MeOH) to give **14c** (135.8 mg, 78%) as a solid. This was recrystallized from ethyl acetate-ether to give **14c** as colorless prisms, mp 145-147°C, ν_{max} (KBr) 1735 cm^{-1}; λ_{max} nm (log ε) 224 (4.35), 272sh (3.06), 278 (3.14); δ_H 0.87 (3H, t, J = 7.6 Hz, CH_2CH_3), 1.84 (1H, dd, J = 15.4, 11.7 Hz, 14-Hβ), 1.90 (3H, ABq, J = 16.6, 7.6 Hz, $COCH_2$), 2.16 (3H, s, $ArCH_3$), 2.19 (3H, s, $ArCH_3$), 2.29 (3H, s, NCH_3), 2.55 (1H, d, J = 18.5 Hz, 5-Hβ), 2.79 (1H, ddd, J = 11.7, 2.7, 2.2 Hz, 14a-H), 2.97 (1H, dd, J = 10.5, 2.2 Hz, 7-Hα), 2.98 (1H, dd, J = 18.5, 8.1 Hz, 5-Hα), 3.06 (1H, dd, J = 10.5, 2.2 Hz, 7-Hβ), 3.09 (1H, dd, J = 15.4, 2.2 Hz, 14-Hα), 3.14 (1H, m, 6-H), 3.63, 3.72 (each 3H, s, OCH_3), 3.73 (1H, dd, J = 10.5, 2.9 Hz, 9-CH), 3.76, 3.78, 3.80, 3.84 (each 3H, s, OCH_3), 3.85 (1H, dd, J = 3.7, 2.9 Hz, 9-H), 4.12 (1H, dd, J = 2.7, 0.5 Hz, 15-H), 4.17 (1H, dd, J = 10.5, 3.7 Hz, 9-CH); δ_C 8.8 (q, $COCH_2CH_3$), 9.0 (q), 9.2 (q), 22.5 (t, C^5), 26.9 (t, C^{14}), 27.8 (t, $COCH_2CH_3$), 41.4 (q, NCH_3), 53.1 (d, C^6), 57.4 (d, C^{15}), 58.0 (d, C^9), 59.5, 59.8, 59.9, 60.1 (each s, OCH_3), 60.1 (d, C^{14a}), 60.2, 60.2 (each s, OCH_3), 61.4 (t, C^7), 67.6 (t, 9-CH_2), 122.8, 123.3, 124.5, 125.4, 125.6, 126.3, 145.8, 147.4, 148.7, 149.2, 151.0, 151.1 (each, s), 173.9 (s, CO); *m/z* (%) 584 (M^+, 21), 498 (25), 497 (79), 263 (11), 249 (21), 248 (100), 218 (14). Anal. Calcd for $C_{32}H_{44}N_2O_8$: C, 65.73; H, 7.59; N, 4.79. Found: C, 65.55; H, 7.76; N, 4.70.

(2,11-Dimethoxy-3,12,16-trimethyl-1,4,10,13-tetraoxo-(6α,9α,14aα,15α)-1,4,6,7,9,10,13,14,14a,15-decahydro-6,15-imino-4*H*-isoquino[3,2-*b*][3]benzazocin-9-yl)methyl Acetate (**13b**) A solution of **14b** (34.2 mg, 0.06 mmol) in dichloromethane (3 ml) was cooled at -78°C, and a dichloromethane solution of boron tribromide (1.0 M, 0.24 ml, 0.24 mmol) was added. After being kept at the same temperature for 1 h and then at 0°C for 1 h, the reaction mixture was poured into ice-water. The aqueous layer was extracted with chloroform (20 ml x 3). The combined extracts were washed with brine (20 ml), dried, and concentrated in vacuo. A solution of this residue (37.5 mg) in 10 M HNO_3 (1.5 ml) was stirred at room temperature for 45 min. The reaction mixture was diluted with water (10 ml) and extracted with chloroform (20 ml x 3). The combined extracts were washed with water (10 ml), dried, and concentrated in vacuo. The residue (24.2 mg) was subjected to chromatography on

preparative layer silica gel plates (Merck 5715, solvent 1:4 benzene-ethyl acetate) to afford **13a** (1.6 mg, 5.7%) and **13b** (10.0 mg, 32.7%). **13a** (not crystallizable): ν_{max} ($CHCl_3$) 3600-3200, 1735, 1655, 1620 cm^{-1}; λ_{max} nm (log ε) 270 (4.35), 368 (3.14); δ_H 1.41 (1H, ddd, *J* = 18.1, 11.7, 2.9 Hz, 14-Hβ), 1.92 (3H, s, C-CH_3), 1.94 (3H, s, C-CH_3), 2.24 (1H, d, *J* = 21.0 Hz, 5-Hβ), 2.26 (3H, s, NCH_3), 2.30-2.40 (1H, br s, OH), 2.80 (1H, dd, *J* = 21.0, 7.6 Hz, 5-Hα), 2.80 (1H, dd, *J* = 11.0, 2.4 Hz, 7-Hα), 2.81 (1H, dd, *J* = 18.1, 2.4 Hz, 14-Hα), 2.81 (1H, ddd, *J* = 11.7, 2.7, 2.4 Hz, 14a-H), 3.03(1H, dd, *J* = 11.0, 2.4 Hz, 7-Hβ), 3.18 (1H, m, 6-H), 3.51 (1H, ddd, *J* = 3.7, 2.9, 1.0 Hz, 9-H), 3.52 (1H, ddd, *J* = 11.2, 1.0, 1.0 Hz, 9-C*H*OH), 3.75 (1H, dd, *J* = 11.2, 3.7 Hz, 9-C*H*OH), 3.96 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 4.06 (1H, dd, *J* = 2.7, 0.5 Hz, 15-H); δ_C 8.7 (q), 8.7 (q), 22.7 (t, C^5), 26.2 (t, C^{14}), 41.1 (q, NCH_3), 52.2 (d, C^6), 54.8 (d, C^{14a}), 57.2 (d, C^{15}), 58.7 (d, C^9), 58.7 (t, C^7), 60.9 (q, OCH_3), 61.0 (q, OCH_3), 61.5 (t, 9-CH_2), 128.6, 128.8 (each s, C^3, C^{12}), 136.3, 137.3 (each s, C^{9a}, C^{15a}), 142.0, 142.8 (each s, C^{4a}, C^{13a}), 155.5, 155.6 (each s, C^2, C^{11}), 182.1, 182.6 (each s, C^1, C^{10}), 185.8, 185.9 (each s, C^4, C^{13}); *m/z* (%) 468 (M^+, 42), 453 (99), 437 (65), 355 (42), 295 (16), 281 (30), 235 (41), 234 (54), 221 (61), 220 (100), 219 (44), 218 (63), 206 (23), 204 (35). **13b** was crystallized from ethyl acetate-ether to give pale yellow prisims, mp 144-147°C (decomp.), ν_{max} (KBr) 1715, 1655, 1645, 1610 cm^{-1}; λ_{max} nm (log ε) 270 (4.36), 368 (3.14); δ_H 1.28 (1H, ddd, *J* = 17.1, 11.2, 2.7 Hz, 14-Hβ), 1.75 (3H, s, $COCH_3$), 1.94 (3H, s, C-CH_3), 1.95 (3H, s, C-CH_3), 2.25 (3H, s, NCH_3), 2.35 (1H, d, *J* = 21.0 Hz, 5-Hβ), 2.69 (1H, dd, *J* = 21.0, 7.1 Hz, 5-Hα), 2.69 (1H, ddd, *J* = 11.2, 2.7, 2.7 Hz, 14a-H), 2.78 (1H, dd, *J* = 10.7, 2.7 Hz, 7-Hα), 2.82 (1H, dd, *J* = 17.1, 2.7 Hz, 14-Hα), 3.04 (1H, dd, *J* = 10.7, 2.4 Hz, 7-Hβ), 3.11 (1H, m, 6-H), 3.61 (1H, ddd, *J* = 3.7, 2.9, 2.7 Hz, 9-H), 3.87 (1H, dd, *J* = 11.2, 2.9 Hz, 9-CH), 3.96 (1H, dd, *J* = 2.7, 0.5 Hz, 15-H), 3.98 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 4.49 (1H, dd, *J* = 11.2, 3.7 Hz, 9-CH); δ_C 8.6 (q), 8.8 (q), 20.6 (q, $COCH_3$), 22.4 (t, C^5), 26.2 (t, C^{14}), 41.1 (q, NCH_3), 52.4 (d, C^6), 55.0 (d, C^{14a}), 57.6 (d, C^{15}), 57.7 (d, C^9), 59.2 (t, C^7), 60.9 (q, OCH_3), 60.9 (q, OCH_3), 63.4 (t, 9-CH_2), 128.5, 128.5 (each s, C^3, C^{12}), 135.6, 136.8 (each s, C^{9a}, C^{15a}), 142.3, 143.7 (each s, C^{4a}, C^{13a}), 155.2, 155.7 (each s, C^2, C^{11}), 170.0 (s, CO), 181.1, 182.9 (each s, C^1, C^{10}), 185.9, 186.6 (each s, C^4, C^{13}); *m/z* (%) 510 (M^+, 10), 439 (46), 437 (27), 292 (13), 234 (44), 220 (100), 218 (39). Anal. Calcd for $C_{27}H_{30}N_2O_8$-1/5H_2O: C, 63.07; H, 5.96; N, 5.45. Found: C, 63.11; H, 6.07; N, 5.30.

(2,11-Dimethoxy-3,12,16-trimethyl-1,4,10,13-tetraoxo-(6α,9α,14aα,15α)-1,4,6,7,9,10,13,14,14a,15-decahydro-6,15-imino-4*H*-isoquino[3,2-*b*][3]benzazocin-9-yl)methyl Propionate (**13c**) A solution of **14b** (87.6 mg, 0.15 mmol) in dichloromethane (9 ml) was cooled at -78°C, and a dichloromethane solution of boron tribromide (1.0 M, 0.6 ml, 0.6 mmol) was added. After being kept at the same temperature for 1 h and then at 0°C for 1 h, the reaction mixture was poured into ice-water. The aqueous layer was extracted with chloroform (20 ml x 3). The combined extracts were washed with brine (20 ml), dried, and concentrated in vacuo. A solution of this residue (95.5 mg) in 10 M HNO_3 (6 ml) was stirred at room temperature for 45 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 (10 ml), dried, and concentrated in vacuo. The residue (47.0 mg) was subjected to chromatography on preparative layer silica gel plates (Merck 5715, solvent 1:5 hexane-ethyl acetate) to afford **13a** (14.3 mg, 20.4%) and **13c** (22.4 mg, 28.5%). **13c** was crystallized from ethyl acetate-ether to give pale yellow prisims, mp 162-164°C (decomp.), ν_{max} (KBr) 1745, 1655, 1645, 1620 cm^{-1}; λ_{max} nm (log ε) 268 (4.37), 368 (3.02); δ_H 0.91 (3H, t, *J* = 7.6 Hz, $COCH_2CH_3$), 1.29 (1H, ddd, *J* = 17.3, 11.2, 2.9 Hz, 14-Hβ), 1.94 (3H, s, C-CH_3), 1.95 (3H, s, C-CH_3), 2.03 (2H, ABq, *J* = 7.6 Hz, OCH_2CH_3), 2.24 (3H, s, NCH_3), 2.33 (1H, d, *J* = 21.0 Hz, 5-Hβ), 2.68 (1H, ddd, *J* = 11.2, 2.7, 1.7 Hz, 14a-H), 2.70 (1H, dd, *J* = 21.0, 7.1 Hz, 5-Hα), 2.76 (1H, dd, *J* = 10.8, 2.4 Hz, 7-Hα), 2.81 (1H, dd, *J* = 17.3, 1.7 Hz, 14-Hα), 3.06 (1H, dd, *J* = 10.8, 2.2 Hz, 7-Hβ), 3.12

(1H, m, 6-H), 3.60 (1H, ddd, J = 3.7, 3.4, 2.9 Hz, 9-H), 3.96 (1H, dd, J = 2.7, 0.5 Hz, 15-H), 3.98 (1H, dd, J = 11.2, 3.7 Hz, 9-CH), 3.99 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 4.44 (1H, dd, J = 11.2, 3.4 Hz, 9-CH); δ_C 8.6 (q), 8.7 (q), 9.0 (q, $COCH_2CH_3$), 22.4 (t, C^5), 26.2 (t, C^{14}), 27.5 (t, $COCH_2CH_3$), 41.1 (q, NCH_3), 52.4 (d, C^6), 55.0 (d, C^{14a}), 57.6 (d, C^{15}), 58.0 (d, C^9), 59.2 (t, C^7), 60.9 (q, OCH_3), 60.9 (q, OCH_3), 63.3 (t, 9-CH_2), 128.3, 128.5 (each s, C^3, C^{12}), 135.7, 136.9 (each s, C^{9a}, C^{15a}), 142.1, 143.5 (each s, C^{4a}, C^{13a}), 155.3, 155.8 (each s, C^2, C^{11}), 173.5 (s, CO), 181.7, 182.8 (each s, C^1, C^{10}), 185.9, 186.6 (each s, C^4, C^{13}); m/z (%) 524 (M^+, 100), 440 (11), 439 (41), 438 (29), 437 (99), 435 (12), 306 (28), 236 (12), 235 (57), 234 (72), 221 (21), 220 (97), 219 (37), 218 (48), 205 (17), 204 (28), 203 (10), 190 (13), 189 (11), 176 (12). Anal. Calcd for $C_{28}H_{32}N_2O_8$: C, 64.11; H, 6.15; N, 5.35. Found: C, 63.87; H, 6.18; N, 5.33.

(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 Angelate (**14d**) A solution of **14a** (105.6 mg, 0.2 mmol) in THF (6 ml) was cooled at -15°C, and a hexane solution of *n*-BuLi (1.57 M, 0.382 ml, 0.6 mmol) was added and stirring was continued for 30 min at the same temperature. The mixed anhydride (**12a**, 81.2 mg, 0.437 mmol) in THF (2 ml) was added over 10 min and the reaction mixture was stirred for 2 h at -15°C. The solution was acidified with 1 N HCl and extracted with benzene (20 ml x 3). The organic layer was washed with water (20 ml), dried, and concentrated in vacuo to give a neutral fraction (36.3 mg), which was subjected to chromatography (silica gel, 8 g) with 1:4 hexane-ethyl acetate as an eluent to give 15.8 mg of crystals, which were identical with the starting material (**14a**, 26.7%). The acidic aqueous layer was 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 to give the residue (109.1 mg). Chromatography on a silica gel (8 g) column with 4:5 hexane-ethyl acetate as an eluent gave **15** (8.6 mg, 7.0%) as a colorless amorphous powder. Further elution with 1:1-1:2 hexane-ethyl acetate as an eluent gave **14d** (57.3 mg, 47.0%) as a colorless amorphous powder. **14d**: ν_{max} ($CHCl_3$) 1705 cm^{-1}; λ_{max} nm (log ε) 224 (4.43), 272sh (3.26), 278 (3.29); δ_H 1.46 (3H, t, J = 1.5 Hz, $COC(CH_3)$=C), 1.74 (3H, dd, J = 7.3, 1.5 Hz, COC=CHCH_3), 1.87 (1H, dd, J = 15.4, 11.7 Hz, 14-Hβ), 2.15 (3H, s, $ArCH_3$), 2.16 (3H, s, $ArCH_3$), 2.31 (3H, s, NCH_3), 2.54 (1H, d, J = 17.8 Hz, 5-Hβ), 2.85 (1H, ddd, J = 11.7, 2.2, 2.2 Hz, 14a-H), 2.99 (1H, dd, J = 10.5, 1.0 Hz, 7-Hα), 2.99 (1H, dd, J = 17.8, 7.8 Hz, 5-Hα), 3.06 (1H, dd, J = 15.4, 2.2 Hz, 14-Hα), 3.10 (1H, dd, J = 10.5, 2.4 Hz, 7-Hβ), 3.20 (1H, m, 6-H), 3.59, 3.62, 3.74, 3.78, 3.81, 3.83 (each 3H, s, OCH_3), 3.88 (1H, dd, J = 3.9, 2.9 Hz, 9-H), 4.05 (1H, dd, J = 10.7, 3.9 Hz, 9-CH), 4.06 (1H, dd, J = 2.2, 0.5 Hz, 15-H), 4.14 (1H, dd, J = 10.7, 2.9 Hz, 9-CH), 5.85 (1H, dq, J = 7.3, 1.5 Hz, CH=C); δ_C 9.2 (q), 9.2 (q), 15.4 (q, =C-CH_3 (Z)), 20.3 (q, COC-CH_3), 22.8 (t, C^5), 26.8 (t, C^{14}), 41.2 (q, NCH_3), 53.2 (d, C^6), 57.8 (d, C^{15}), 58.3 (d, C^9), 59.6 (q, OCH_3), 59.7 (d, C^{14a}), 59.9, 60.0, 60.0, 60.1, 60.1 (each s, OCH_3), 60.3 (t, C^7), 67.2 (t, 9-CH_2), 123.2, 123.3, 123.8, 124.9, 125.6, 126.0 (each, s), 127.8 (s, COC=), 137.6 (d, COCH=C), 145.9, 147.4, 148.8, 149.3, 151.0, 151.2 (each s), 167.5 (s, CO); m/z (%) 610 (M^+, 13), 510 (11), 498 (27), 497 (89), 263 (11), 262 (11), 249 (21), 248 (100), 218 (15). High-resolution ms Calcd for $C_{34}H_{46}N_2O_8$: 610.3255. Found: 610.3280. **17**: ν_{max} ($CHCl_3$) 1735 cm^{-1}; λ_{max} nm (log ε) 224 (4.40), 272sh (3.21), 278 (3.15); δ_H 1.19 (3H, d, J = 6.3, OCHCH_3), 1.22 (3H, d, J = 6.3, OCHCH_3), 1.79 (1H, dd, J = 15.4, 11.7 Hz, 14-Hβ), 2.15 (3H, s, $ArCH_3$), 2.19 (3H, s, $ArCH_3$), 2.29 (3H, s, NCH_3), 2.65 (1H, d, J = 17.8 Hz, 5-Hβ), 2.80 (1H, ddd, J = 11.7, 2.2, 2.2 Hz, 14a-H), 2.99 (1H, dd, J = 17.8, 7.6 Hz, 5-Hα), 3.02 (1H, dd, J = 10.7, 2.0 Hz, 7-Hα), 3.09 (1H, dd, J = 15.4, 2.2 Hz, 14-Hα), 3.12 (1H, dd, J = 10.7, 1.0 Hz, 7-Hβ), 3.14 (1H, m, 6-H), 3.62 (3H, s, OCH_3), 3.68 (1H, dd, J = 10.0, 6.8 Hz, 9-CH), 3.72, 3.75, 3.79, 3.81, 3.85 (each 3H, s, OCH_3), 3.93 (1H, dd, J = 10.0, 4.2 Hz, 9-CH), 3.97 (1H, dd, J = 6.8, 4.2 Hz, 9-H), 4.03

(1H, dd, J = 2.2, 0.5 Hz, 15-H), 4.69 (1H, sep, J = 6.3 Hz, OCH); m/z (%) 614 (M^+, 11), 498 (15), 497 (47), 263 (15), 249 (24), 248 (100), 234 (11), 218 (17).

(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 Tiglate (**14e**) A solution of **14a** (126.7 mg, 0.24 mmol) in THF (6 ml) was cooled at -15°C, and a hexane solution of *n*-BuLi (1.57 M, 0.42 ml, 0.66 mmol) was added and stirring was continued for 30 min at the same temperature. The mixed anhydride (**12b**, 131.7 mg, 0.7 mmol) in THF (2 ml) was added over 10 min and the reaction mixture was stirred for 1.5 h at -15°C. The solution was acidified with 1 N HCl and extracted with benzene (20 ml x 3). The organic layer was washed with water (20 ml), dried, and concentrated in vacuo to give a neutral fraction (4.0 mg). The combined extracts were washed with water (10 ml), dried, and concentrated in vacuo to give a residue (191.1 mg). Chromatography on a silica gel (12 g) column with 4:5 hexane-ethyl acetate as an eluent gave **15** (26.3 mg, 17.9%) as a colorless amorphous powder. Further elution with 1:1-1:2 hexane-ethyl acetate as an eluent gave **14e** (110.9 mg, 75.8%) as a colorless amorphous powder. ν_{max} ($CHCl_3$) 1700 cm^{-1}; λ_{max} nm (log ε) 224 (4.45), 272sh (3.30), 278 (3.25); δ_H 1.53 (3H, d, J = 1.2 Hz, $COC(CH_3)$=C), 1.66 (3H, dd, J = 7.1, 1.2 Hz, COC=CHC*H*$_3$), 1.85 (1H, dd, J = 15.1, 11.7 Hz, 14-Hβ), 2.16 (3H, s, $ArCH_3$), 2.16 (3H, s, $ArCH_3$), 2.32 (3H, s, NCH_3), 2.55 (1H, d, J = 18.1 Hz, 5-Hβ), 2.88 (1H, ddd, J = 11.7, 2.2, 1.7 Hz, 14a-H), 2.99 (1H, dd, J = 18.1, 7.8 Hz, 5-Hα), 3.06 (1H, dd, J = 10.0, 2.9 Hz, 7-Hα), 3.08 (1H, dd, J = 15.1, 2.2 Hz, 14-Hα), 3.10 (1H, dd, J = 10.0, 2.4 Hz, 7-Hβ), 3.21 (1H, m, 6-H), 3.60, 3.62, 3.74, 3.79, 3.81, 3.85 (each 3H, s, OCH_3), 3.88 (1H, dd, J = 9.5, 2.2 Hz, 9-CH), 3.91 (1H, dd, J = 2.2, 2.2 Hz, 9-H), 4.09 (1H, dd, J = 1.7, 0.5 Hz, 15-H), 4.12 (1H, dd, J = 9.5, 2.2 Hz, 9-CH), 6.52 (1H, dq, J = 7.1, 1.2 Hz, CH=C); δ_C 9.2 (q), 9.2 (q), 11.8 (q, COC-*C*H_3), 14.1 (q, =C-*C*H_3 (Z)), 22.7 (t, C^5), 26.8 (t, C^{14}), 41.2 (q, NCH_3), 53.2 (d, C^6), 57.7 (d, C^{15}), 58.1 (d, C^9), 59.5 (q, OCH_3), 59.8 (d, C^{14a}), 59.8, 59.9, 60.1, 60.2, 60.2 (each s, OCH_3), 61.1 (t, C^7), 68.2 (t, 9-CH_2), 123.1, 123.3, 123.4, 124.8, 125.3, 126.0 (each, s), 128.6 (s, CO*C*=), 136.2 (d, CO*C*H=C), 145.9, 147.3, 148.7, 149.3, 151.0, 151.1 (each s), 167.8 (s, CO); *m/z* (%) 610 (M^+, 16), 498 (32), 497 (100), 263 (13), 262 (9), 249 (21), 248 (99), 218 (14). High-resolution ms Calcd for $C_{34}H_{46}N_2O_8$: 610.3255. Found: 610.3292.

Hydrolysis of the carbonate **15** A mixture of **15** (27.5 mg, 0.045 mmol) and 85%KOH (20mg, 0.3 mmol) in methanol (2 ml) was stirred for 4 h at room temperature. 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 to furnished **14a** (14.6 mg, 62%), whose spectra were identical with those of an authentic sample.

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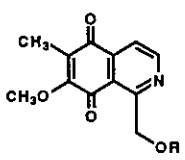
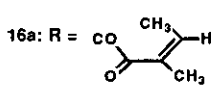
8 Angelic acid (mp 44-46°C) was prepared from tiglic acid in three steps [a) Br_2, CCl_4; b) KOH, K_2CO_3, MeOH; c) Na-Hg, H_2O] in 28.0% yield (R. E. Buckles and G. V. Mock, J. Org. Chem., 1950, **15**, 680). Angeloyl chloride was prepared from angelic acid in two steps [a) KOH, EtOH; b) $(COCl)_2$, ether] (P. J. Beeby, Tetrahedron Lett., 1977, 3379).

9 P. Joseph-Nathan, J. R. Wesener, and H. Gunther, Org. Magnetic Resonance, 1984, **22**, 190.

10 The mixed anhydrides (**12a** and **12b**) were prepared from the corresponding acids; *see* experimental section.

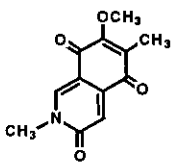
11 Frincke and Faulkner isolated "monomeric" products renierone (**16a**), minosamycin (**17**) and other simple isoquinolinequinones from the same sponge,[2] and He and Faulkner also reported to observe the decomposition of renieramycins E (**1e**) and F (**1f**).[5] Renierone (**16a**) and mimosamycin (**17**) were observed among the degradation products, suggesting the possibility that the monomeric products isolated were all artifacts of the isolation and chromatographic procedures employed. On the other hand, McKee and Ireland isolated renierol (**16b**) and mimosamycin (**17**) from a hard blue sponge, *Xestospongia caycedoi* in 1987.[14] Renierol acetate (**16c**) and renierol propionate (**16d**) have also been isolated independently from a marine sponge, *Xestospongia* sp. and its associated nudibranch *Jorunna funebris*.[15] These monomeric natural products are presumed to be produced from renieramycin type precursors (**13a-c**) by oxidative degradation.





16a: R =

16b: R = H
16c: R = $COCH_3$
16d: R = $COCH_2CH_3$



17

12 Hydrolysis of the carbonate (**15**) with KOH in ethanol gave **14a** in 62% yield; see experimental section.

13 A. E. Wright, D. A. Forleo, G. P. Gunawardana, S. P. Gunasekera, F. E. Koehn, and O. J. McConnell, J. Org. Chem., 1990, **55**, 4508; K. L. Reinhart, T. G. Holt, N. L. Fregeau, J. G. Stroh, P. A. Keifer, F. Sun, L. H. Li, and D. G. Martin, J. Org. Chem., 1990, **55**, 4512; Corrections: K. L. Reinhart, T. G. Holt, N. L. Fregeau, J. G. Stroh, P. A. Keifer, F. Sun, L. H. Li, and D. G. Martin, J. Org. Chem., 1991, **56**, 1676.

14 T. C. McKee and C. M. Ireland, J. Nat. Prod., 1987, **50**, 754.

15 E. D. de Silva and N. K. Gulavita, presented in part at 16th IUPAC International Symposium on the Chemistry of Natural Products, Kyoto, May, 1988, p. 610.

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