Regioselective and Stereospecific Amination of Iridoids: Conversion of Aucubin into Aminoside Antibiotic Analogues

Vokatsoa Christian Rakotondramasy,[‡] Raphaël Laschiazza,[§] Marylin Lecsö-Bornet,[§] Michel Koch,[‡] François Tillequin,[‡] and Brigitte Deguin*[,‡]

Laboratoire de Pharmacognosie, UMR/CNRS 8638, and Laboratoire de Microbiologie, Faculté des Sciences Pharmaceutiques et Biologiques de l'Université René Descartes, 4 Avenue de l'Observatoire, F-75006 Paris, France

Received July 26, 2006

Treatment of aucubin (**1**) with *tert*-butyldimethylsilyl chloride under alkaline conditions permitted regioselective silylation of either the primary hydroxyl groups at C-9 and C-6′ or both primary hydroxyl groups and the secondary allylic hydroxyl group at C-6. Acetylation with acetic anhydride, followed by selective removal of the silyl groups and Mitsunobu reaction involving phthalimide as nitrogen donor, gave a stereospecific entry to aminoside antibiotic analogues: 10,6′-diamino-10,6′-dideoxyaucubin (**16**) and (*6R*)-6,10,6′-triamino-6,10,6′-trideoxyaucubin (**17**).

The use of natural iridoid glycosides as starting materials for the synthesis of biologically active compounds received considerable attention in recent years.[1] Aucubin (**1**) is particularly suitable for such synthetic use, since it is readily available in large amounts from the fresh aerial parts of *Aucuba japonica* Thunb. (Cornaceae).[2] Indeed, the aucubin monoterpene basic core permitted the chiral syntheses of insect antifeedants,[3] carbocyclic nucleoside analogues,[4−6] aminocyclopentitol glycosidase inhibitors,[7] and numerous prostaglandins.[8−13] More recent synthetic applications took advantage of both aglycone and glucose moieties present in the natural iridoid, as illustrated by the syntheses of homochiral rigid γ-amino acid glucosides[14] and cytotoxic cyclopentenone glucosides.[15] In this context, the development of techniques permitting successive or simultaneous modifications of the aglycone and the glucose units appeared particularly desirable, in order to access an enlarged variety of synthetic congeners of aucubin. When performed on the aucubin-derived 2′,3′,4′,6′,10-penta-*O*-pivaloylaucubin, a modified Mitsunobu reaction involving phthalimide as nitrogen donor proved particularly efficient to introduce an amino group at C-6 with inversion of configuration.[16] Thus, we envisioned that the use of this reaction on conveniently protected aucubin derivatives should give an efficient entry to polyaminoiridoids whose structures should relate to those of aminoside antibiotics [i.e., gentamicine (**2**)]. The well-known selectivity of *tert*-butyldimethylsilyl chloride (TBDMSCl) toward primary alcoholic groups[17−19] permitted its use for the preparation of aucubin derivatives selectively protected at both C-10 of the aglycone and C-6′ of the sugar moiety. When aucubin (**1**) was treated with 3.5 equiv of TBDMSCl in CH_2Cl_2/pyridine, and then by excess Ac_2O, the expected 6,2′,3′,4′-tetra-*O*-acetyl-10,6′-di-*O*-*tert*-butyldimethylsilylaucubin (**3**) was obtained in 63% yield, accompanied by trace amounts of the two monosilylated 6,-10,2′,3′,4′-penta-*O*-acetyl-6′-*O*-*tert*-butyldimethylsilylaucubin (**4**) and 6,2′,3′,4′,6′-penta-*O*-acetyl-10-*O*-*tert*-butyldimethylsilylaucubin (**5**), and 16% of 2′,3′,4′-tri-*O*-acetyl-6,10,6′-tri-*O*-*tert*-butyldimethylsilylaucubin (**6**), silylated on both primary alcohols and the allylic secondary alcohol at C-6 of the aglycone. This latter compound could be further obtained on a preparative scale by treatment of aucubin (**1**) under similar conditions with 6 equiv of TBDMSCl instead of 3.5, affording **6** in an acceptable 60% yield. Selective removal of the silyl groups of **3** and **6** was performed by treatment with HOAc in THF/H_2O, which smoothly gave 6,2′,3′,4′-tetra-*O*-acetylaucubin (**7**) and 2′,3′,4′-tri-*O*-acetylaucubin (**8**) in 65% and

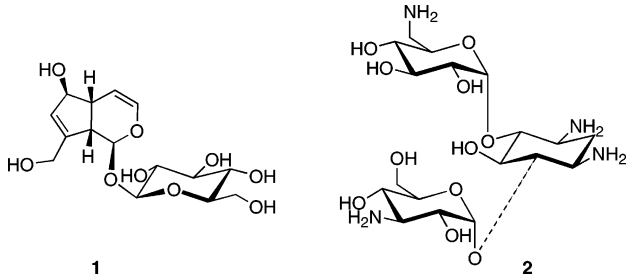


Figure 1.

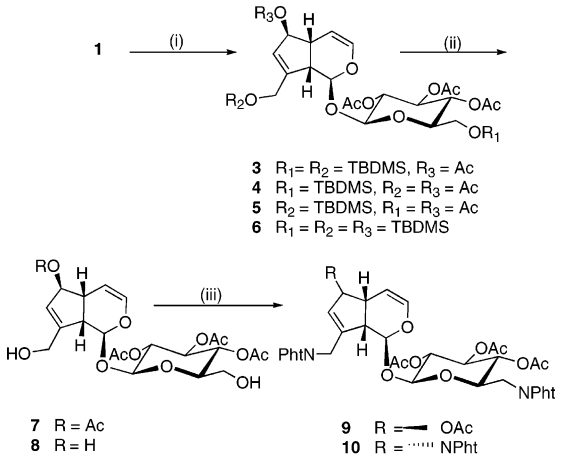
89.5% yields, respectively. As expected,[14,16] a modified Mitsunobu reaction involving phthalimide as nitrogen donor,[19] performed on **7** and **8** in the presence of triphenylphosphine and diisopropyl azodicarboxylate in anhydrous THF, permitted the regioselective introduction of phthalimido substituents at C-10 and C-6′, and C-6, C-10, and C-6′ with inversion of configuration at C-6, to give 10,6′-diphthalimido-6,2′,3′,4′-tetra-*O*-acetyl-10,6′-dideoxyaucubin (**9**) and (6*R*)-6,10,6′-triphthalimido-2′,3′,4′-tri-*O*-acetyl-6,10,6′-trideoxyaucubin (**10**) in 75% and 53% yields, respectively. Attempts to simultaneously deprotect the acetyl and phthalimido groups in **9** and **10** by the use of hydrazine hydrate[20] resulted in the unexpected formation of the products of *trans*-acetylation[21] at *N*-6′, 10-amino-6′-*N*-acetylamino-10,6′-dideoxyaucubin (**11**) and 6,10-diamino-6′-*N*-acetylamino-6,10,6′-trideoxyaucubin (**12**), which could not be further deacetylated. The use of LiOH[22] permitted simultaneous deprotection of acetyl groups and opening of the phthalimide residues to give 10,6′-bis(2-carboxybenzoylamino)-10,6′-dideoxyaucubin (**13**) from **9** and (6*R*)-6,10,6′-tris(2-carboxybenzoylamino)-2′,3′,4′-tri-*O*-acetyl-6,10,6′-trideoxyaucubin (**14**) from **10**. However, all attempts toward amino group deprotection, under alkaline as well as acidic conditions, were unsuccessful. Both **9** and **10** could be fully deprotected using a two-step process involving (i) catalytic methanolysis[23] of acetyl groups (e.g., **9** → **15**), followed by (ii) hydrazine removal of the phthalimido substituents. Under those latter conditions, the desired 10,6′-diamino-10,6′-dideoxyaucubin (**16**) and (*6R*)-6,10,6′-triamino-6,10,6′-trideoxyaucubin (**17**) were isolated in 34% and 20% yield, respectively, after purification through a IRC50 ion-exchange resin column. Compounds **16** and **17** did not show any significant activity, when tested against a large panel of Gram + and Gram − bacteria.

In summary, the use of *tert*-butyldimethylsilyl chloride permits the selective protection of aucubin at C-6′ of the sugar moiety and C-10, or C-6 and C-10, of the aglycone. After acetylation and deprotection of the silyl groups, a modified Mitsunobu reaction involving phthalimide as nitrogen donor gave a stereospecific entry

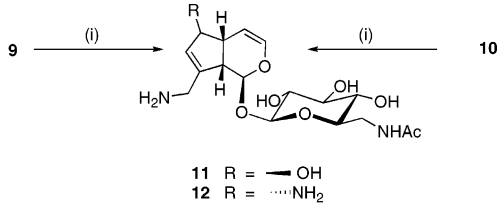
* To whom correspondence should be addressed. Tel: +33 1 53 73 15 81. Fax: +33 1 40 46 96 58. E-mail: brigitte.deguin@univ-paris5.fr.
‡ Laboratoire de Pharmacognosie, UMR/CNRS 8638.
§ Laboratoire de Microbiologie.

10.1021/np060368v CCC: $37.00
Published on Web 01/11/2007

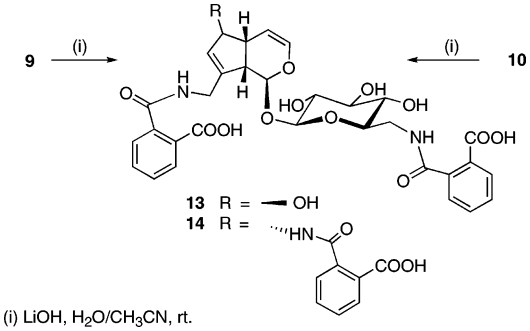
Scheme 1. Selective Protection of Aucubin (**1**) and Modified Mitsunobu Reaction



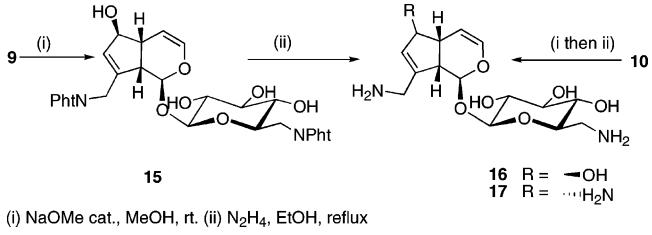
Scheme 2. Deprotection of **9** and **10** Using Hydrazine Hydrate



Scheme 3. Deprotection of **9** and **10** Using LiOH



Scheme 4. Two-Step Deprotection of **9** and **10** Successively Involving (i) Sodium Methoxide and (ii) Hydrazine Hydrate



to aminoside antibiotic analogues: 10,6′-diamino-10,6′-dideoxyaucubin (**16**) and (6*R*)-6,10,6′-triamino-6,10,6′-trideoxyaucubin (**17**).

Experimental Section

General Experimental Procedures. Melting points were determined on a hot stage Reichert microscope and are not corrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter [*c* in g/100 mL]. The IR spectra were obtained on a Perkin-Elmer FT-IR-1600 instrument. NMR spectra were recorded on Bruker Avance-400 and/or Bruker AC-300 spectrometers; chemical shifts are expressed in ppm downfield to TMS. When necessary, the structures of the novel compounds were confirmed via 2D NMR techniques: ^{1}H−^{1}H COSY, ^{1}H−^{1}H NOESY, ^{13}C−^{1}H HMQC, and ^{13}C−^{1}H HMBC. These experiments were performed using standard Bruker microprograms. ESIMS and HRESIMS were determined on a Waters Micromass Q-TOF apparatus equipped with an ESI-Z spray source. TLC were performed on Merck silica gel 60F_{254} aluminum sheets, using vanillin/H_2SO_4 as spray reagent. Column chromatography was conducted using Merck silica gel [6−35 mm, 20−45 mm, or 35−70 mm (flash)] with an overpressure of 300 mbars. Compound **1** was isolated from *A. japonica* essentially as previously described.[2]

Synthesis of *O*-*tert*-Butyldimethylsilylaucubin Derivatives. In a typical experiment, aucubin (**1**) (1 g, 2.88 mmol) was dissolved with stirring in a 1:1 mixture of anhydrous CH_2Cl_2 and anhydrous pyridine (10 mL) and cooled to 0 °C in an ice bath. An anhydrous solution of 0.67 M TBDMSCl in CH_2Cl_2 (15 mL, 10.1 mmol) was added, and the reaction mixture was allowed to reach room temperature. After 1 h the reaction mixture was cooled to 0 °C in an ice bath and excess Ac_2O was added dropwise (4.1 mL, 43.2 mmol). The reaction mixture was allowed to stand at room temperature and stirred during 24 h, then was quenched with ice (30 mL). After 1 h, the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were washed at 0 °C with aqueous 10% HCl and then until neutral with water and brine. The combined extracts were dried over Na_2SO_4. Filtration and evaporation of the solvent gave a residue (2.5 g), which was chromatographed on a silica gel column (eluent: cyclohexane/EtOAc, 98:2, 90:10, 80:20) to give successively compounds **6** (375 mg, 16%), **3** (1.35 g, 63%), **4** (20 mg, 1%), and **5** (22 mg, 1%).

2′,3′,4′-Tri-*O*-acetyl-6,10,6′-tri-*O*-*t*-butyldimethylsilylaucubin (6). Crystallization from MeOH gave **6** as colorless crystals: mp 38 °C; $[\alpha]^{20}_D$ −90.1 (*c* 2.14, CH_2Cl_2); IR (NaCl film) ν_{max} 3492, 2956, 2930, 2887, 2857, 1760, 1659, 1472, 1463, 1367, 1250, 1220, 1142, 1064, 1045, 966, 838, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (1H, dd, $J_{3,4}$ = 6 Hz, $J_{3,5}$ = 1.5 Hz, H-3), 5.69 (1H, m, H7), 5.21 (1H, t, $J_{3',4'} = J_{3',2'}$ = 9.5 Hz, 1H, H-3′), 4.96 (1H, t, $J_{4',3'} = J_{4',5'}$ = 9.5 Hz, H-4′), 4.96 (1H, dd, $J_{3',2'}$ = 9.5 Hz, $J_{2',1'}$ = 8 Hz, H2′), 4.94 (1H, d, $J_{1,9}$ = 7 Hz, H-1), 4.92 (1H, dd, $J_{4,3}$ = 6 Hz, $J_{4,5}$ = 3.5 Hz, H-4), 4.86 (1H, d, $J_{1',2'}$ = 8 Hz, H-1′), 4.43 (1H, m, H-6), 4.30 (1H, br d, $J_{10a,10b}$ = 16 Hz, H-10a), 4.15 (1H, br d, $J_{10a,10b}$ = 16 Hz, H-10b), 3.69 (1H, dd, $J_{6'a,6'b}$ = 11 Hz, $J_{6'a,5'}$ = 2.5 Hz, H-6′a), 3.64 (1H, dd, $J_{6'b,6'a}$ = 11 Hz, $J_{6'b,5'}$ = 5.5 Hz, H-6′b), 3.54 (1H, ddd, $J_{5',6'a}$ = 2.5 Hz, $J_{5',6'b}$ = 5.5 Hz, $J_{5',4'}$ = 9.5 Hz, H-5′), 2.87 (1H, br t, $J_{9,1} = J_{9,5}$ = 7 Hz, H-9), 2.65 (dtd, $J_{5,9}$ = 7 Hz, $J_{5,4} = J_{5,6}$ = 3.5 Hz, $J_{5,3}$ = 1.5 Hz, 1H, H-5), 2.02, 2.01, 1.99 (9H, 3s, 3 (C*H*$_3$CO), 0.92−0.86 (27H, 9s, (C*H*$_3$)$_3$C), 0.06−0.02 (18H, 6s, (C*H*$_3$)$_2$Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 169.6, 169.4 (CH_3CO), 145.9 (C-8), 139.8 (C-3), 129.1 (C-7), 105.2 (C-4), 95.9 (C-1′), 95.5 (C-1), 82.1 (C-6), 75.1 (C-5′), 73.1 (C-3′), 71.1 (C-2′), 69.2 (C-4′), 62.6 (C-6′), 61.4 (C-10), 46.3 (C-9), 44.4 (C-5), 25.9 (C(*C*H$_3$)$_3$), 20.8 (*C*H$_3$CO), 18.3 (Si*C*), −5.3 (Si(*C*H$_3$)$_2$); ESIMS *m*/*z* 837 [M + Na]$^+$, 853 [M + K]$^+$, *anal.* C 57.32%, H 8.71%, calcd for $C_{39}H_{70}O_{12}Si_3$ C 57.46%, H 8.65%.

6,2′,3′,4′-Tetra-*O*-acetyl-10,6′-di-*O*-*tert*-butyldimethylsilylaucubin (3). Crystallization from MeOH gave **3** as colorless crystals: mp 68 °C; $[\alpha]^{20}_D$ −80.8 (*c* 1.57, CH_2Cl_2); IR (NaCl film) ν_{max} 3481, 3061, 2955, 2930, 2886, 2857, 1759, 1659, 1473, 1463, 1433, 1366, 1320, 1250, 1219, 1139, 1067, 1012, 965, 939, 907, 876, 838, 815, 777, 739, 703, 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (1H, br d, $J_{3,4}$ = 6 Hz, H-3), 5.76 (1H, br s, H-7), 5.26 (1H, br s, H-6), 5.20 (1H, t, $J_{3',4'} = J_{3',2'}$ = 9.5 Hz, H-3′), 5.18 (1H, d, $J_{1,9}$ = 3.5 Hz, H-1), 4.98 (1H, t, $J_{4',3'} = J_{4',5'}$ = 9.5 Hz, H-4′), 4.95 (1H, dd, $J_{3',2'}$ = 9.5 Hz, $J_{2',1'}$ = 8 Hz, H-2′), 4.86 (1H, dd, $J_{4,3}$ = 6 Hz, $J_{4,5}$ = 3.5 Hz, H-4), 4.81 (1H, d, $J_{1',2'}$ = 8 Hz, H-1′), 4.30 (1H, br d, $J_{10a,10b}$ = 15 Hz, H-10a), 4.20 (1H, br d, $J_{10a,10b}$ = 15 Hz, H-10b), 3.69 (1H, dd, $J_{6'a,6'b}$ = 12 Hz, $J_{6'a,5'}$ = 2.5 Hz, H-6′a), 3.65 (1H, dd, $J_{6'b,6'a}$ = 12 Hz, $J_{6'b,5'}$ = 5.5 Hz, H-6′b), 3.54 (1H, ddd, $J_{5',6'a}$ = 2.5 Hz, $J_{5',6'b}$ = 5.5 Hz, $J_{5',4'}$ = 9.5 Hz, H-5′), 3.11 (1H, m, H-9), 2.79 (1H, m, H-5), 2.00−1.98 (12H, 4s, 4 (C*H*$_3$CO), 0.89−0.86 (18H, 6s, (C*H*$_3$)$_3$C), 0.05−0.02 (12H, 4s, (C*H*$_3$)$_2$Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 170.3, 169.4, 169.3 (CH_3CO), 150.1 (C-8), 139.7 (C-3), 124.3 (C-7), 104.3 (C-4), 95.5 (C-1′), 93.2 (C1), 82.6 (C-6), 74.9 (C-5′), 73.3 (C-3′), 72.9 (C-2′), 70.9 (C-4′), 62.5 (C-6′), 61.0 (C-10), 46.7 (C-9), 39.3 (C-5), 25.9 (C(*C*H$_3$)$_3$), 20.8 (*C*H$_3$CO), 18.3 (Si*C*), −5.3 (Si(*C*H$_3$)$_2$); ESIMS *m*/*z* 765 [M + Na]$^+$, 781 [M + K]$^+$; *anal.* C 56.49%, H 7.89%, calcd for $C_{35}H_{58}O_{13}Si_2$, C 56.58%, H 7.87%.

6,10,2′,3′,4′-Penta-*O*-acetyl-6′-*O*-*tert*-butyldimethylsilylaucubin (4). Crystallization from MeOH gave **4** as colorless crystals: mp 109 °C; $[\alpha]^{20}_D$ −121 (*c* 0.81, CH_2Cl_2); IR (NaCl film) ν_{max} 3485, 2955, 2931, 2857, 2257, 1756, 1661, 1463, 1434, 1372, 1224, 1137, 1224, 1137, 1070, 1047, 968, 913, 838, 780, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (1H, dd, $J_{3,4}$ = 6 Hz, $J_{3,5}$ = 1.5 Hz, H-3), 5.82 (1H, m, H-7), 5.28 (1H, br s, H-6), 5.21 (1H, t, $J_{3′,4′} = J_{3′,2′}$ = 9.5 Hz, H-3′), 5.12 (1H, d, $J_{1,9}$ = 4.5 Hz, H-1), 5.04 (1H, t, $J_{4′,3′} = J_{4′,5′}$ = 9.5 Hz, H-4′), 4.97 (1H, dd, $J_{3′,2′}$ = 9.5 Hz, $J_{2′,1′}$ = 8 Hz, H-2′), 4.92 (1H, dd, $J_{4,3}$ = 6 Hz, $J_{4,5}$ = 3,5 Hz, H-4), 4.83 (1H, d, $J_{1′,2′}$ = 8 Hz, H-1′), 4.73 (1H, br d, $J_{10a,10b}$ = 16 Hz, H-10a), 4.69 (1H, br d, $J_{10a,10b}$ = 16 Hz, H-10b), 3.72 (1H, dd, $J_{6′a,6′b}$ = 12 Hz, $J_{6′a,5′}$ = 2.5 Hz, H-6′a), 3.67 (1H, dd, $J_{6′b,6′a}$ = 12 Hz, $J_{6′b,5′}$ = 5 Hz, H-6′b), 3.55 (1H, ddd, $J_{5′,6′a}$ = 2.5 Hz, $J_{5′,6′b}$ = 5 Hz, $J_{5′,4′}$ = 9.5 Hz, H-5′), 3.13 (1H, m, H-9), 2.82 (1H, m, H-5), 2.02, 2.01, 1.99 (15H, 3s, (5C*H*$_3$CO)), 0.92−0.86 (9H, 3s, (C*H*$_3$)$_3$C), 0.06−0.02 (6H, 2s, (C*H*$_3$)$_2$Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 170.4, 169.4 (5 (CH$_3$*C*O)), 144.5 (C-8), 140.1 (C-3), 127.3 (C-7), 104.1 (C-4), 95.9 (C-1′), 93.8 (C-1), 82.6 (C-6), 74.9 (C-5′), 73.0 (C-3′), 70.9 (C-2′), 68.8 (C-4′), 62.2 (C-6′), 61.5 (C-10), 47.0 (C-9), 39.7 (C-5), 25.8 (C(*C*H$_3$)$_3$), 20.8 (*C*H$_3$CO), 18.4 (Si*C*), −5.3 (Si-(*C*H$_3$)$_2$); ESIMS *m*/*z* 693 [M + Na]$^+$, 709 [M + K]$^+$; *anal.* C 55.47%, H 6.98%, calcd for $C_{31}H_{46}O_{14}Si$, C 55.51%, H 6.91%.

6,2′,3′,4′,6′-Penta-*O*-acetyl-10-*O*-*tert*-butyldimethylsilylaucubin (5): colorless, amorphous solid; $[\alpha]^{20}_D$ −134 (*c* 1.02, CH_2Cl_2); IR (NaCl film) ν_{max} 2932, 2885, 2857, 1758, 1661, 1463, 1433, 1372, 1243, 1224, 1136, 1070, 1047, 968, 914, 838, 779, 733, 648 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (1H, dd, $J_{3,4}$ = 6 Hz, $J_{3,5}$ = 1.5 Hz, H-3), 5.69 (1H, br s, H-7), 5.25 (1H, m, H-6), 5.19 (1H, d, $J_{1,9}$ = 3 Hz, H-1), 5.16 (1H, t, $J_{3′,4′} = J_{3′,2′}$ = 9.5 Hz, H-3′), 5.02 (1H, t, $J_{4′,3′} = J_{4′,5′}$ = 9.5 Hz, H-4′), 4.94 (1H, dd, $J_{3′,2′}$ = 9.5 Hz, $J_{2′,1′}$ = 8 Hz, H-2′), 4.82 (1H, dd, $J_{4,3}$ = 6 Hz, $J_{4,5}$ = 3.5 Hz, H-4), 4.79 (1H, d, $J_{1′,2′}$= 8 Hz, H-1′), 4.28 (1H, br d, $J_{10a,10b}$ = 16 Hz, H-10a), 4.23 (1H, dd, $J_{6′a,6′b}$ = 12 Hz, $J_{6′a,5′}$ = 4.5 Hz, H-6′a), 4.19 (1H, br d, $J_{10a,10b}$ = 16 Hz, H-10b), 4.04 (1H, dd, $J_{6′b,6′a}$ = 12 Hz, $J_{6′b,5′}$ = 2 Hz, H-6′b), 3.67 (1H, ddd, $J_{5′,6′a}$ = 2 Hz, $J_{5′,6′b}$ = 5.5 Hz, $J_{5′,4′}$ = 9.5 Hz, H-5′), 2.99 (1H, m, H-9), 2.73 (1H, m, H-5), 2.15−1.98 (15H, 5s, C*H*$_3$CO), 0.88 (9H, 1s, (C*H*$_3$)$_3$C), 0.02 (6H, 1s, (C*H*$_3$)$_2$Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 170.6, 170.2, 169.4, 169.3 (CH$_3$*C*O), 150.0 (C-8), 139.5 (C-3), 124.3 (C7), 104.4 (C-4), 95.8 (C-1′), 93.3 (C-1), 82.6 (C-6), 72.5 (C-3′), 72.1 (C-5′), 70.7 (C-2′), 68.3 (C-4′), 61.8 (C-6′), 60.9 (C-10), 46.5 (C-9), 39.0 (C-5), 25.9 (C(*C*H$_3$)$_3$), 20.7 (*C*H$_3$CO), 18.2 (Si*C*), −5.4 (Si(*C*H$_3$)$_2$); ESIMS *m*/*z* 693 [M + Na]$^+$, 709 [M + K]$^+$; *anal.* C 55.72%, H 6.93%, calcd for $C_{31}H_{46}O_{14}Si$ C 55.51%, H 6.91%.

General Procedure for Silylether Deprotection. A solution of compound **3** (1.3 g, 1.34 mmol) in a 3:1:1 mixture of AcOH, THF, and H_2O (20 mL) was stirred at room temperature for 12 h. Toluene (20 mL) was added, and the solution was evaporated under reduced pressure. Flash chromatography (eluent: toluene/acetone, 80:20) afforded **7** (585 mg, 65%). When treated under similar conditions, **6** (1.8 g, 2.21 mmol) gave **8** (940 mg, 89.5%), isolated after purification by flash chromatography (eluent: toluene/acetone 60:40).

6,2′,3′,4′-Tetra-*O*-acetylaucubin (7). Crystallization from CH_2Cl_2 gave **7** as white crystals: mp 188 °C; $[\alpha]^{20}_D$ −134.6 (*c* 1.07, acetone); IR (NaCl film) ν_{max} 3415, 2926, 2855, 1754, 1658, 1427, 1372, 1226, 1164, 1041, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (1H, dd, $J_{3,4}$ = 6 Hz, $J_{3,5}$ = 1.5 Hz, H-3), 5.80 (1H, br s, H-7), 5.31(1H, m, H-6), 5.27 (1H, t, $J_{3′,4′} = J_{3′,2′}$ = 9.5 Hz, H-3′), 5.09 (1H, d, $J_{1,9}$ = 5.5 Hz, H-1), 5.02 (1H, t, $J_{4′,3′} = J_{4′,5′}$ = 9.5 Hz, H-4′), 4.99 (1H, dd, $J_{2′,3′}$ = 9.5 Hz, $J_{2′,1′}$ = 8 Hz, H-2′), 4.97 (1H, dd, $J_{4,3}$ = 6 Hz, $J_{4,5}$ = 3 Hz, H-4), 4.88 (1H, d, $J_{1′,2′}$ = 8 Hz, H-1′), 4.34 (1H, br d, $J_{10a,10b}$ = 14.5 Hz, H-10a), 4.22 (1H, br d, $J_{10b,10a}$ = 14.5 Hz, H-10b), 3.72 (1H, br d, $J_{6′a,6′b}$ = 12 Hz, H-6′a), 3.57 (1H, br d, $J_{6′b,6′a}$ = 12 Hz, H-6′b), 3.52 (1H, m, H-5′), 3.06 (1H, m, H-9), 2.80 (1H, m, H-5), 2.05−1.99 (12H, 4s, COC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 170.3, 170.0, 169.7 (*C*OCH$_3$), 149.5 (C-8), 140.2 (C-3), 126.2 (C-7), 104.4 (C-4), 96.3 (C-1′), 95.1 (C-1), 83.2 (C-6), 74.5 (C-5′), 72.4 (C-3′), 71.0 (C-2′), 68.7 (C-4′), 61.0 (C-6′), 60.5 (C-10), 46.1 (C-9), 40.2 (C-5), 20.8 (CO*C*H$_3$); ESIMS *m*/*z* 537 [M + Na]$^+$, 553 [M + K]$^+$; *anal.* C 53.72%, H 5.93%, calcd for $C_{23}H_{30}O_{13}$, C 53.69%, H 5.88%.

2′,3′,4′-Tri-*O*-acetylaucubin (8). Crystallization from $CHCl_3$ gave **8** as colorless crystals: mp 126 °C; $[\alpha]^{20}_D$ −131.9 (*c* 1.20, acetone); IR (NaCl film) ν_{max} 3440, 2921, 1752, 1659, 1420, 1371, 1228, 1038, 962, 761; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 6.11 (1H, dd, $J_{3,4}$ = 6 Hz, $J_{3,5}$ = 2 Hz, H-3), 5.72 (1H, m, H-7), 5.22 (1H, d, $J_{1,9}$ = 4 Hz, H-1), 5.21 (1H, t, $J_{3′,4′} = J_{3′,2′}$ = 9.5 Hz, H-3′), 4.94 (1H, d, $J_{1′,2′}$ = 8 Hz, H-1′), 4.92 (1H, t, $J_{4′,3′} = J_{4′,5′}$ = 9.5 Hz, H-4′), 4.89 (1H, dd, $J_{4,3}$ = 6 Hz, $J_{4,5}$ = 3.5 Hz, H-4), 4.86 (1H, dd, $J_{2′,3′}$ = 9.5 Hz, $J_{2′,1′}$ = 8 Hz, H-2′), 4.31 (1H, m, H-6), 4.21 (1H, br d, $J_{10a,10b}$ = 16 Hz, H-10a), 4.08 (1H, br d, $J_{10b,10a}$ = 16 Hz, H-10b), 3.72 (1H, ddd, $J_{5′,4′}$ = 9.5 Hz, $J_{5′,6′b}$ = 5.5 Hz, $J_{5′,6′a}$ = 2.5 Hz, H-5′), 3.62 (1H, dd, $J_{6′a,6′b}$ = 12 Hz, $J_{6′a,5′}$ = 2.5 Hz, H-6′a), 3.51 (1H, dd, $J_{6′b,6′a}$ = 12 Hz, $J_{6′b,5′}$ = 5.5 Hz, H-6′b), 3.04 (1H, m, H-9), 2.56 (1H, ddd, $J_{5,3}$ = 2 Hz, $J_{5,4}$ = 3.5 Hz, $J_{5,9}$ = 7 Hz, H-5), 2.00−1.90 (9H, 3s, COC*H*$_3$); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) 170.9, 170.8, 170.4 (CH$_3$*C*O), 146.8 (C-8), 139.1 (C-3), 128.4 (C-7), 105.4 (C-4), 96.2 (C-1′), 94.6 (C-1), 80.2 (C-6), 74.4 (C-5′), 72.8 (C-3′), 71.1 (C-2′), 68.9 (C-4′), 60.4 (C-6′), 59.3 (C-10), 46.2 (C-9), 42.1 (C-5), 20.1 (*C*H$_3$CO); ESIMS *m*/*z* 495 [M + Na]$^+$, 511 [M + K]$^+$; *anal.* C 53.47%, H 6.02%, calcd for $C_{21}H_{28}O_{12}$, C 53.39%, H 5.97%.

General Procedure for Mitsunobu Reaction. Anhydrous THF (10 mL) was added under Ar to an anhydrous mixture of Ph_3P (252 mg, 0.96 mmol), **7** (122 mg, 0.24 mmol), and phthalimide (106 mg, 0.72 mmol). The solution was stirred and cooled at 0 °C, and DIAD (190 μL, 0.96 mmol) was added dropwise. The reaction mixture was allowed to stand 15 min at 0 °C and at room temperature for 2.5 h. The solvent was removed in vacuo. Chromatography on silica gel (solvent: cyclohexane/EtOAc, 60:40) gave **9** (139 mg, 75%). A similar procedure applied to **8** (420 mg, 0.89 mmol) afforded **10** (403 mg, 53%) after purification by flash chromatography (solvent: toluene/acetone, 55:45).

10,6′-Diphthalimido-6,2′,3′,4′-tetra-*O*-acetyl-10,6′-dideoxyaucubin (9). Crystallization (Et_2O) gave white crystals: mp 118 °C; $[\alpha]^{20}_D$ −78.2 (*c* 1.47, CH_2Cl_2); IR (NaCl film) ν_{max} 2937, 1757, 1716, 1468, 1425, 1393, 1379, 1243, 1216, 1075, 1044, 967, 911, 728, 714 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88−7.62 (8H, 3 m, Ar-H), 6.07 (1H, dd, $J_{3,4}$ = 6 Hz, $J_{3,5}$ = 1.5 Hz, H-3), 5.57 (1H, br s, H-7), 5.21 (1H, t, $J_{3′,4′} = J_{3′,2′}$ = 9.5 Hz, H-3′), 5.16 (1H, m, H-6), 5.09 (1H, dd, $J_{2′,3′}$ = 9.5 Hz, $J_{2′,1′}$ = 8 Hz, H-2′), 5.03 (1H, t, $J_{4′,3′} = J_{4′,5′}$ = 9.5 Hz, H-4′), 4.95 (1H, d, $J_{1,9}$ = 5.5 Hz, H-1), 4.84 (1H, dd, $J_{4,3}$ = 6 Hz, $J_{4,5}$ = 3.5 Hz, H-4), 4.81 (1H, d, $J_{1′,2′}$ = 8 Hz, H-1′), 4.36 (1H, br d, $J_{10a,10b}$ = 16 Hz, H-10a), 4.23 (1H, br d, $J_{10b,10a}$ = 16 Hz, H-10b), 4.04 (1H, dd, $J_{6′a,6′b}$ = 14 Hz, $J_{6′a,5′}$ = 7 Hz, H-6′a), 3.94 (1H, ddd, $J_{5′,4′}$ = 9.5 Hz, $J_{5′,6′b}$ = 7 Hz, $J_{5′,6′a}$ = 3.5 Hz, H-5′), 3.82 (1H, dd, $J_{6′b,6′a}$ = 14 Hz, $J_{6′b,5′}$ = 3.5 Hz, H-6′b), 2.99 (1H, m, H-9), 2.74 (1H, m, H-5), 2.10−1.98 (12H, 4s, C*H*$_3$CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 170.4, 169.8, 169.3 (CH$_3$*C*O), 167.9, 167.6 (Ar-*C*O) 144.1 (C-8), 140.3 (C-3), 134.2, 132.1, 131.9 (Ar-*C*), 127.4 (C-7), 123.5 (Ar-*C*), 104.0 (C-4), 96.3 (C-1′), 94.7 (C-1), 82.9 (C-6), 72.8 (C-3′), 71.4 (C-5′), 70.9 (C-2′,C-4′), 47.3 (C-9), 40.5 (C-5), 38.9 (C-6′), 36.9 (C-10), 21.1 (COC*H*$_3$); ESIMS *m*/*z* 795 [M + Na]$^+$, 811 [M + K]$^+$; *anal.* C 60.74%, H 4.71%, calcd for $C_{39}H_{36}N_2O_{15}$, C 60.62%, H 4.70%.

(6*R*)-6,10,6′-Triphthalimido-2′,3′,4′-tri-*O*-acetyl-6,10,6′-trideoxyaucubin (10): $[\alpha]^{20}$D −33.5 (*c* 1.01, CH_2Cl_2); IR (NaCl film) ν_{max} 3420, 3058, 2223, 1757, 1716, 1591, 1484, 1468, 1437, 1394, 1246, 1220, 1192, 1119, 1071, 1039, 998, 910, 721, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.40 (12H, 3 m, Ar-H), 6.11 (1H, dd, $J_{3,4}$ = 6 Hz, $J_{3,5}$ = 2 Hz, H-3), 5.75 (1H, m, H-7), 5.34 (d, $J_{1,9}$ = 6.5 Hz, 1H, H-1), 5.26 (1H, t, $J_{3′,4′} = J_{3′,2′}$ = 9.5 Hz, H-3′), 5.23 (1H, d, $J_{6,5}$ = 9 Hz, H-6), 5.18 (1H, dd, $J_{2′,3′}$ = 9.5 Hz, $J_{2′,1′}$ = 8 Hz, H-2′), 5.10 (1H, t, $J_{4′,3′} = J_{4′,5′}$ = 9.5 Hz, H-4′), 4.88 (1H, d, $J_{1′,2′}$ = 8 Hz, H-1′), 4.61 (1H, br d, $J_{10a,10b}$ = 16 Hz, H-10a), 4.56 (1H, br d, $J_{10b,10a}$ = 16 Hz, H-10b), 4.42 (1H, dd, $J_{4,3}$ = 6 Hz, $J_{4,5}$ = 3.5 Hz, H-4), 4.16−3.96 (2H, H-6′a, H-5′), 3.83 (1H, dd, $J_{6′b,6′a}$ = 13 Hz, $J_{6′b,5′}$ = 2.5 Hz, H-6′b), 3.16 (1H, dddd, $J_{5,9}$ = 7.5 Hz, $J_{5,6}$ = 6 Hz, $J_{5,4}$ = 3.5 Hz, $J_{5,3}$ = 2 Hz, H-5), 2.82 (1H, m, $J_{1,9}$ = 6.5 Hz, $J_{5,9}$ = 7.5 Hz, H-9), 2.07−2.00 (9H, 3s, COC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 169.8, 169.2 (*C*OCH$_3$), 168.0, 167.8 (Ar-*C*O), 142.4 (C-8), 141.4 (C-3), 133.8, 133.7, 133.1, 132.3 (Ar-*C*), 127.3 (C-7), 123.4, 123.2, 123.1 (Ar-*C*), 100.4 (C-4), 98.4 (C-1′), 96.4 (C-1), 72.9 (C-3′), 71.4 (C-5′), 71.1 (C-2′,C-4′), 58.0 (C-6), 47.4 (C-9), 39.3 (C-5), 37.3 (C-6′), 37.1 (C-10), 20.8 (COC*H*$_3$); ESIMS *m*/*z* 882 [M + Na]$^+$; *anal.* C 62.93%, H 4.41%, calcd for $C_{45}H_{37}N_3O_{15}$, C 62.86%, H 4.34%.

General Procedure for Deprotection Using Hydrazine. A solution of 64% hydrazine hydrate (22 mg, 1.18 mmol) in EtOH 95% (2 mL) was added dropwise at room temperature to a stirring solution of **9** (0.44 mmol, 341 mg) in 95% EtOH (10 mL). The resulting mixture was refluxed for 1.5 h and then quenched at room temperature by addition of aqueous 10% HCl until pH 4. The solution was then filtered on Dowex 50WX8-100 (H^+ form, MeCN/H_2O, 1:1, then 0.5 N aqueous ammonia). After evaporation of the solvent, **11** (68 mg, 40%) was

isolated as a syrup. A similar procedure applied to compound **10** (180 mg, 0.21 mmol) gave **12** (30 mg, 37%), after purification on an IRC50 ion-exchange resin column ($NH_4^+Cl^-$ cycle; then elution with 1 N aqueous ammonia).

10-Amino-6′-*N*-acetylamino-10,6′-dideoxyaucubin (11): syrup, $[\alpha]^{20}_D$ −75.4 (*c* 3.57, MeOH); IR (NaCl film) ν_{max} 3359, 3298, 3099, 2916, 1726, 1649, 1561, 1480, 1432, 1374, 1243, 1080, 1046, 1016, 971, 757 cm^{-1}; ^1H NMR (400 MHz, methanol-d_4) δ 6.40 (1H, dd, $J_{3,4}$ = 6 Hz, $J_{3,5}$ = 1.5 Hz, H-3), 5.82 (1H, m, H-7), 5.20 (1H, dd, $J_{4,3}$ = 6 Hz, $J_{4,5}$ = 4 Hz, H-4), 4.73 (1H, d, $J_{1,9}$ = 8 Hz, H-1), 4.67 (1H, d, $J_{1',2'}$ = 8 Hz, H-1′), 4.48 (1H, m, H-6), 3.69 (1H, br d, $J_{10a,10b}$ = 16.5 Hz, H-10a), 3.58−3.42 (2H, m, H-6′a, H-6′b), 3.49 (1H, br d, $J_{10b,10a}$ = 16 Hz, H-10b), 3.40 (1H, t, $J_{3',4'} = J_{3',2'}$ = 9,5 Hz, H-3′), 3.29 (1H, m, H-5′), 3.24 (1H, dd, $J_{2',3'}$ = 9.5 Hz, $J_{2',1'}$ = 8 Hz, H-2′), 3.16 (1H, t, $J_{4',3'} = J_{4',5'}$ = 9.5 Hz, H-4′), 2.85 (1H, br t, $J_{9,1} = J_{9,5}$ = 8 Hz, H-9), 2.68 (1H, ddd, $J_{5,6}$ = 6.5 Hz, $J_{5,4}$ = 4 Hz, $J_{5,3}$ = 1.5 Hz, H-5), 1.96 (3H, s, (NHCOC*H*$_3$)); ^{13}C NMR (75 MHz, methanol-d_4) δ 172.6 (NHC*O*CH$_3$), 147.5 (C-8), 140.4 (C-3), 128.9 (C-7), 104.4 (C-4), 99.0 (C-1′), 97.3 (C-1), 81.8 (C-6), 76.0 (C-5′), 74.8 (C-3′), 73.6 (C-4′), 71.6 (C-2′), 47.7 (C-9), 45.5 (C-5), 41.0 (C-6′), 40.3 (C-10), 21.2 (NHCO*C*H$_3$)); ESIMS *m/z* 409 $[M + Na]^+$; HRESIMS *m/z* 386.1697 (cacld for $C_{17}H_{26}N_2O_8$, 386.1689).

6,10-Diamino-6′-*N*-acetylamino-6,10,6′-trideoxyaucubin (12): syrup, $[\alpha]^{20}_D$ −12.2 (*c* 0.97, MeOH); IR (NaCl film) ν_{max} 3345, 2928, 1649, 1565, 1433, 1378, 1297, 1220, 1071, 1021, 971 cm^{-1}; ^1H NMR (400 MHz, methanol-d_4) δ 6.61 (1H, dd, $J_{3,4}$ = 6 Hz, $J_{3,5}$ = 2 Hz, H-3), 6.01 (1H, m, H-7), 5.00 (1H, dd, $J_{4,3}$ = 6 Hz, $J_{4,5}$ = 3.5 Hz, H-4), 4.87 (1H, d, $J_{1,9}$ = 8 Hz, H-1), 4.70 (1H, d, $J_{1',2'}$ = 8 Hz, H-1′), 4.08 (1H, d, $J_{6,5}$ = 7.5 Hz, H-6), 3.89 (1H, br d, $J_{10a,10b}$ = 16 Hz, H-10a), 3.67 (1H, br d, $J_{10b,10a}$ = 16 Hz, H-10b), 3.62−3.38 (2H, m, H-6′, H-3′), 3.30 (1H, m, H-5′), 3.25 (1H, dd, $J_{2',3'}$ = 9.5 Hz, $J_{2',1'}$ = 8 Hz, H-2′), 3.20 (1H, t, $J_{4',3'} = J_{4',5'}$ = 9.5 Hz, H-4′), 3.08 (1H, m, H-5), 2.80 (1H, br t, $J_{9,1} = J_{9,5}$ = 8 Hz, H-9), 1.96 (3H, s, NHCOC*H*$_3$); ^{13}C NMR (75 MHz, methanol-d_4) δ 172.6 (NHCOCH$_3$), 145.1 (C-8), 142.9 (C-3), 130.4 (C-7), 100.5 (C-4), 99.2 (C-1′), 97.9 (C-1), 76.1 (C-5′), 75.2 (C-3′), 73.4 (C-2′), 71.7 (C-4′), 57.4 (C-6), 47.7 (C-9), 40.2 (C-6′), 40.1 (C-10), 39.0 (C-5), 21.4 (NHCO*C*H$_3$); ESIMS *m/z* 386 $[M + H]^+$, 408 $[M + Na]^+$; HRESIMS *m/z* 385.1844 (cacld for $C_{17}H_{27}N_3O_7$, 385.1849).

General Procedure for LiOH Deprotection. Compound **9** (439 mg, 0.56 mmol) was dissolved in a 1:1 mixture of CH_3CN and H_2O (100 mL). After addition of LiOH hydrate (237 mg, 5.6 mmol), the reaction mixture was stirred for 12 h at room temperature. Toluene (20 mL) was added and the mixture evaporated under reduced pressure. Chromatography on silica gel (eluent: CH_2Cl_2/MeOH, 9:1, then CH_2Cl_2/MeOH/AcOH, 80:20:0.5) gave **13** (424 mg, 78%). Under similar conditions, treatment of **10** (966 mg, 1.12 mmol) with LiOH hydrate (311 mg, 7.4 mmol) afforded **14** (455 mg, 52%) after chromatography on silica gel (eluent: CH_2Cl_2/MeOH/AcOH, 9:1:1).

10,6′-Bis(2-carboxybenzoylamino)-10,6′-dideoxyaucubin (13): colorless, amorphous solid, $[\alpha]^{20}_D$ −29.9 (*c* 2.57, MeOH); IR (NaCl film) ν_{max} 3373, 2359, 2348, 1644, 1560, 1437, 1194, 1119, 1072, 752, 721, 698 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 7.50−7.12 (8H, m, Ar-*H*), 6.22 (br d, $J_{3,4}$ = 5 Hz, 1H, H-3), 5.57 (1H, br s, H-7), 5.03 (1H, br dd, $J_{4,3}$ = 5 Hz, $J_{4,5}$ = 3 Hz, H-4), 4.90 (1H, br s, H-1), 4.65 (1H, d, $J_{1',2'}$ = 8 Hz, H-1′), 4.21 (1H, br s, H-6), 4.00 (1H, br d, $J_{10a,10b}$ = 17 Hz, H-10a), 3.84 (1H, br d, $J_{10b,10a}$ = 17 Hz, H-10b), 3.60 (1H, br d, $J_{6'a,6'b}$ = 13.5 Hz, H-6′a), 3.50−3.19 (5H, m, H-5′, H-6′b, H-3′ H-2′, H-4′), 2.86 (1H, m, H-9), 2.58 (1H, m, H-5); ^{13}C NMR (75 MHz, D_2O) δ 181.5 (*C*OOH), 172.9, 172.5 (*C*ONH), 143.4 (C-8), 140.1 (C-3), 137.8, 134.2, 134.0, 130.4 (Ar-*C*), 129.7 (C-7), 129.3, 128.1, 127.9, 127.3, 127.1 (Ar-*C*), 105.2 (C-4), 99.0 (C-1′), 97.1 (C-1), 81.0 (C-6), 75.6 (C-5′), 74.1 (C-3′), 72.8 (C-4′)*, 71.4 (C-2′)*, 47.1 (C-9), 43.9 (C-5), 40.6 (C-6′), 39.5 (C-10); ESIMS *m/z* 663 $[M + Na]^+$; HRESIMS *m/z* 640.1911 (cacld for $C_{31}H_{32}N_2O_{13}$, 640.1904).

(6*R*)-6,10,6′-Tris(2-carboxybenzoylamino)-2′,3′,4′-tri-*O*-acetyl-6,-10,6′-trideoxyaucubin (14): colorless, amorphous solid, $[\alpha]^{20}_D$ −60.9 (*c* 1.1, MeOH); IR (NaCl film) ν_{max} 3317, 1573, 1409, 1021 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 7.50−7.10 (12H, m, Ar-*H*), 6.37 (1H, br d, $J_{3,4}$ = 6 Hz, H-3), 5.72 (1H, br s, H-7), 5.09 (1H, d, $J_{1,9}$ = 7 Hz, H-1), 4.94 (1H, d, $J_{6,5}$ = 6.5 Hz, H-6), 4.93 (1H, dd, $J_{4,3}$ = 6 Hz, $J_{4,5}$ = 4 Hz, H-4), 4.74 (1H, d, $J_{1',2'}$ = 8 Hz, H-1′), 4.12 (1H, br d, $J_{10a,10b}$ = 17 Hz, H-10a), 3.90 (1H, br d, $J_{10b,10a}$ = 17 Hz, H-10b), 3.61 (1H, br d, $J_{6'a,6'b}$ = 13.5 Hz, H-6′a), 3.51−3.35 (3H, m, H-5′, H-6′b, H-3′), 3.34−3.27 (2H, m, H-4′, H-2′), 3.18 (1H, m, H-5), 2.83 (1H, br t, $J_{9,1} = J_{9,5}$ = 7 Hz, H-9); ^{13}C NMR (75 MHz, D_2O) δ 181.5 (*C*OOH), 172.2 (*C*ONH), 144.0 (C-8), 141.6 (C-3), 137.8, 133.8, 130.4, 129.2 (Ar-*C*), 127.9 (C-7), 127.5, 127.3, 127.1 (Ar-*C*), 102.8 (C-4), 99.0 (C-1′), 97.0 (C-1), 75.4 (C-5′), 74.4 (C-3′), 72.9 (C-4′)*, 70.9 (C-2′)*, 57.0 (C-6), 47.6 (C-9), 40.4 (C-6′), 39.6 (C-10), 37.9 (C-5); ESIMS *m/z* 788 $[M + H]^+$, 810 $[M + Na]^+$, 826 $[M + K]^+$; HRESIMS *m/z* 787.2231 (cacld for $C_{39}H_{37}N_3O_{15}$, 787.2225).

10,6′-Diphthalimido-10,6′-dideoxyaucubin (15). NaOMe in MeOH (1 M solution, 10 mL) was added dropwise at 0 °C under N_2 to a solution of compound **9** (165 mg, 0.21 mmol) in a 1:1 mixture of anhydrous MeOH and anhydrous CH_2Cl_2 (10 mL). The mixture was stirred for 2.5 h at room temperature and neutralized by addition of IRC50 H^+. The suspension was filtered and the solvent evaporated under reduced pressure. Chromatography on silica gel (solvent: CH_2Cl_2/MeOH, 98:2) gave **15** (97 mg, 75%) as white crystals (Et_2O): mp 137 °C; $[\alpha]^{20}_D$ −74.6 (*c* 0.71, CH_2Cl_2); IR (NaCl film) ν_{max} 3383, 2922, 1771, 1710, 1395, 1045 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 7.82−7.71 (8H, m, Ar-*H*), 6.08 (1H, dd, $J_{3,4}$ = 6 Hz, $J_{3,5}$ = 1.5 Hz, H-3), 5.55 (1H, br s, H-7), 4.91 (1H, dd, $J_{4,3}$ = 6 Hz, $J_{4,5}$ = 4 Hz, H-4), 4.64 (1H, d, $J_{1',2'}$ = 8 Hz, H-1′), 4.61 (1H, br d, $J_{1,9}$ = 7 Hz, H-1), 4.34 (1H, br d, $J_{10a,10b}$ = 16 Hz, H-10a), 4.27 (1H, br d, $J_{10b,10a}$ = 16 Hz, H-10b), 4.12 (1H, m, H-6), 4.06 (1H, dd, $J_{6'a,6'b}$ = 13.5 Hz, $J_{6'a,5'}$ = 3.5 Hz, H-6′a), 3.94 (1H, dd, $J_{6'b,6'a}$ = 13.5 Hz, $J_{6'b,5'}$ = 8 Hz, H-6′b), 3.72 (1H, ddd, $J_{5',4'}$ = 9.5 Hz, $J_{5',6'b}$ = 8.5 Hz, $J_{5',6'a}$ = 3.5 Hz, H-5′), 3.55−3.39 (3H, m, H-3′, H-4′, H-2′), 2.68 (1H, br t, $J_{9,5} = J_{9,1}$ = 7 Hz, H-9), 2.50 (1H, m, H-5); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 168.0, 167.5 (Ar-*C*O), 140.5 (C-3), 140.0 (C-8), 134.2, 134.1 (Ar-*C*), 133.0 (C-7), 132.3, 123.1, 123.0 (Ar-*C*), 104.6 (C-4), 99.3 (C-1′), 96.8 (C-1), 81.6 (C-6), 76.8 (C-3′), 73.9 (C-4′)*, 73.1 (C-2′)*, 72.8 (C-5′), 47.2 (C-9), 45.9 (C-5), 39.4 (C-6′), 37.4 (C-10); ESIMS *m/z* 627 $[M + Na]^+$, 643 $[M + K]^+$; HRESIMS *m/z* 604.1702 (cacld for $C_{31}H_{28}N_2O_{11}$, 604.1693).

10,6′-Diamino-10,6′-dideoxyaucubin (16). To a stirring solution of **15** (0.21 mmol, 180 mg) in absolute EtOH (17 mL) was added dropwise a solution of 95% hydrazine (5.5 equiv, 3 mmol, 103 mg) in absolute EtOH (5 mL) at room temperature. The resulting mixture was refluxed for 1.5 h and quenched at room temperature by addition of H_2O (5 mL). The solution was filtered over an IRC50 ion-exchange resin column, which was washed with MeCN/H_2O (1:1, 3 × 100 mL). Elution with 0.5 N aqueous ammonia followed by evaporation gave compound **16** (86.3 mg, 45%) as a white, amorphous solid: $[\alpha]^{20}_D$ −50.6 (*c* 0.57, MeOH); IR (NaCl film) ν_{max} 3352, 2920, 1655, 1584, 1439, 1367, 1227, 1083, 1046, 1017, 959, 870 cm^{-1}; ^1H NMR (400 MHz, methanol-d_4) δ 6.34 (1H, dd, $J_{3,4}$ = 6 Hz, $J_{3,5}$ = 2 Hz, H-3), 5.74 (1H, m, H-7), 5,14 (1H, dd, $J_{4,3}$ = 6 Hz, $J_{4,5}$ = 4 Hz, H-4), 4.83 (d, $J_{1,9}$ = 7.5 Hz, 1H, H-1), 4.70 (1H, d, $J_{1',2'}$ = 8 Hz, H-1′), 4.45 (1H, m, H-6), 3.52 (1H, br d, $J_{10a,10b}$ = 16 Hz, H-10a), 3.40 (1H, br d, $J_{10b,10a}$ = 16 Hz, H-10b), 3.37 (1H, t, $J_{3',4'} = J_{3',2'}$ = 9.5 Hz, H-3′), 3.33 (1H, ddd, $J_{5',4'}$ = 9.5 Hz, $J_{5',6'b}$ = 7.5 Hz, $J_{5',6a'}$ = 2.5 Hz, H-5′), 3.22 (1H, dd, $J_{2',3'}$ = 9.5 Hz, $J_{2',1'}$ = 8 Hz, H-2′), 3.16 (1H, t, $J_{4',3'} = J_{4',5'}$ = 9.5 Hz, H-4′), 3.04 (1H, dd, $J_{6'a,6'b}$ = 13.5 Hz, $J_{6'a,5'}$ = 2.5 Hz, H-6′a), 2.89 (1H, br t, $J_{9,1} = J_{9,5}$ = 7.5 Hz, H-9), 2.72 (1H, dd, $J_{6'b,6'a}$ = 13.5 Hz, $J_{6'b,5'}$ = 7.5 Hz, H-6′b), 2.64 (1H, dddd, $J_{5,9}$ = 7.5 Hz, $J_{5,6}$ = 6 Hz, $J_{5,4}$ = 4 Hz, $J_{5,3}$ = 2 Hz, H-5); ^{13}C NMR (75 MHz, methanol-d_4) δ 147.4 (C-8), 140.0 (C-3), 128.4 (C-7), 105.0 (C-4), 98.7 (C-1′), 96.7 (C-1), 81.1 (C-6), 76.4 (C-5′), 75.9 (C-3′), 73.2 (C-2′), 71.4 (C-4′), 47.0 (C-9), 44.1 (C-6′), 41.9 (C-10), 40.3 (C-5); ESIMS *m/z* 345 $[MH]^+$; HRESIMS *m/z* 345.1664 (cacld for $C_{15}H_{25}N_2O_7$, 345.1662).

(6*R*)-6,10,6′-Triamino-6,10,6′-trideoxyaucubin (17). NaOMe in MeOH (0.45 M solution, 2 mL) was added dropwise at 0 °C under argon to a solution of compound **10** (528 mg, 0.61 mmol) in anhydrous MeOH and anhydrous CH_2Cl_2 (1:1, 30 mL). The reaction mixture was stirred for 1 h at room temperature and neutralized by addition of IRC50 H^+. The resulting suspension was filtered, and the solvent was evaporated under reduced pressure. The residue (445 mg) was taken up in absolute EtOH (22 mL), and a solution of 95% hydrazine (4 equiv, 2.3 mmol, 77 mg) in absolute EtOH (3 mL) was added dropwise at room temperature. The resulting mixture was refluxed for 1.50 h and quenched by addition of H_2O (3 mL) at room temperature. The solution was filtered over a IRC50 resin column, which was washed with MeCN/H_2O (1:1 3 × 150 mL) and water (2 × 100 mL). Elution with 1 N aqueous ammonia followed by evaporation gave compound **17** (41 mg, 20%) as a whitish foam: $[\alpha]^{20}_D$ −14.6 (*c* 1.03, MeOH); IR (NaCl film) ν_{max} 3143, 1624, 1402, 1076, 970, 795, 619, 558, 462 cm^{-1}; ^1H NMR (400 MHz, methanol-d_4) δ 6.52 (1H, dd, $J_{3,4}$ = 6 Hz, $J_{3,5}$ = 2 Hz, H-3), 5.81 (1H, br s, H-7), 4.95 (1H, dd, $J_{4,3}$ = 6 Hz, $J_{4,5}$ = 4 Hz, H-4), 4.94 (1H, d, $J_{1,9}$ = 7.5 Hz, H-1), 4.73 (1H, d, $J_{1',2'}$ = 8 Hz,

H-1′), 3.89 (1H, br d, $J_{6,5}$ = 7 Hz, H-6), 3.55 (1H, br d, $J_{10a,10b}$ = 16 Hz, H-10a), 3.42 (1H, br d, $J_{10b,10a}$ = 16 Hz, H-10b), 3.38 (1H, t, $J_{3',4'} = J_{3',2'}$ = 9.5 Hz, H-3′), 3.29−3.19 (2H, m, H-5′, H-2′), 3.15 (1H, t, $J_{4',3'} = J_{4',5'}$ = 9.5 Hz, H-4′), 3.07 (1H, dd, $J_{6'b,6'a}$ = 13.5 Hz, $J_{6'b,5'}$ = 2.5 Hz, H-6′a), 2.95 (1H, m, H-5), 2.76 (1H, br t, $J_{9,1} = J_{9,5}$ = 7.5 Hz, H-9), 2.71 (1H, dd, $J_{6'b,6'a}$ = 13.5 Hz, $J_{5',6b'}$ = 7.5 Hz, H-6′b); ^{13}C NMR (75 MHz, methanol-d_4) δ 146.8 (C-8), 142.6 (C-3), 130.2 (C-7), 100.8 (C-4), 98.9 (C-1′), 97.7 (C-1), 76.6 (C-5′), 76.3 (C-3′), 73.6 (C-2′), 72.0 (C-4′), 57.6 (C-6), 47.7 (C-9) (under solvent signal), 42.3 (C-6′), 40.6 (C-10), 39.2 (C-5); ESIMS *m*/*z* 344 $[MH]^+$; HRESIMS *m*/*z* 343.1606 (cacld for $C_{15}H_{25}N_3O_6$, 343.1600).

Antimicrobial Assays. Antibacterial activities of compounds **16** and **17** against a panel of reference strains (*Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 25212, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Providencia stuartii* CIP 107808) as well as clinical wild strains of Gram + species (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Staphylococcus capitis*, *Streptococcus agalactiae*, *Enterococcus faecalis*, *Enterococcus faecium*) and Gram − species (*Escherichia coli*, *Citrobacter koseri*, *Citrobacter freundii*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Morganella morganii*, *Hafnia alvei*, *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, *Alcaligenes xylosoxidans*, *Stenotrophomonas maltophilia*, *Flavimonas oryzihabitans*) were tested using the agar dilution assay.[24] Compounds were solubilized in H_2O. Geometric dilutions were prepared to give final concentrations of 128 to 0.03 μg/mL. Streptomycin sulfate was used as a control and tested concurrently. Isolates were aseptically transferred into panel wells using an autoinoculating Steers device. Cation-adjusted Mueller-Hinton broth was used as the growth medium. Isolates were incubated 24 h at 37 °C.

References and Notes

(1) Franzyk, H. In *Fortschritte der Chemie Organischer Naturstoffe*; Herz, W., Kirby, G. W., Steglich, W., Tamm, C., Eds.; Springer-Verlag: Wien, 2000; Vol. 79, pp 1−114.
(2) Bourquelot, E.; Herissey, H. *C. R. Acad. Sci.* **1902**, *134*, 1441−1443.
(3) Mohammad-Ali, A. K.; Chan, T. H.; Thomas, A. W.; Jewett, B.; Strunz, G. M. *Can. J. Chem.* **1994**, *72*, 2137−2143.
(4) Franzyk, H.; Stermitz, F. R. *J. Nat. Prod.* **1999**, *62*, 1646−1654.
(5) Bianco, A.; Celleti, L.; Mazzei, R. A.; Umani, F. *Eur. J. Org. Chem.* **2001**, 1331−1334.
(6) Bianco, A.; Celona, D.; Di Rita, S.; Guiso, M.; Melchioni, C.; Umani, F. *Eur. J. Org. Chem.* **2001**, 4061−4066.
(7) Cachet, X.; Deguin, B.; Tillequin, F.; Rolland, Y.; Koch, M. *Helv. Chim. Acta* **2000**, *83*, 2812−2882.
(8) Naruto, M.; Ohno, K.; Naruse, N.; Takeuchi H. *Tetrahedron Lett.* **1979**, 251−254.
(9) Berkowitz, W. M.; Choudhury, S.; Hrabie, J.; Pierce, D. Sampathkumar, P. S.; Sasson, I. *Tetrahedron Lett.* **1979**, 1641−1644.
(10) Berkowitz, W. M.; Choudhury, S. *Tetrahedron Lett.* **1981**, *22*, 1075−1076.
(11) Berkowitz, W. M.; Choudhury, S.; Hrabie, J. *J. Org. Chem.* **1982**, *47*, 824−829.
(12) Tixidre, A.; Rolland, Y.; Garnier, J.; Poisson, J. *Heterocycles* **1982**, *19*, 253−256.
(13) Davini, E.; Iavarone, C.; Mataloni, F.; Trogolo, C. *J. Org. Chem.* **1988**, *53*, 2089−2091.
(14) Mouriès, C.; Deguin, B.; Lamari, F.; Foglietti, M.-J.; Tillequin, F.; Koch, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1083−1086.
(15) Mouriès, C.; Rakotondramasy, V. C.; Libot, F.; Koch, M.; Tillequin, F.; Deguin, B. *Chem. Biodiversity* **2005**, *2*, 695−703.
(16) Mouriès, C.; Deguin, B.; Koch, M.; Tillequin, F. *Helv. Chim. Acta* **2003**, *86*, 147−156.
(17) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190−6191.
(18) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99−102.
(19) Franke, F.; Guthrie, R. D. *Aust. J. Chem.* **1977**, *30*, 639−647.
(20) Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220−2222.
(21) Inouye, Y.; Onodera, K., Kitaoka, S.; Oshiai, H. *J. Am. Chem. Soc.* **1957**, *79*, 4218−4222.
(22) Hudhomme, P.; Dugay, G. *Bull. Soc. Chim. Fr.* **1991**, *128*, 760−772.
(23) Zemplèn, G., *Ber. Dtsch. Chem. Ges.* **1926**, *59B*, 1254−1266.
(24) Mitscher, L. A.; Leu, R.-P.; Bathala, M. S.; Wu, W.-N.; Beal, J. L. *Llyodia* **1972**, *35*, 157−166.

NP060368V