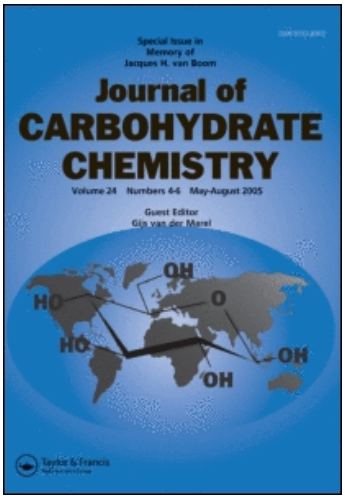

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Total Synthesis of Angucyclines. XVII. First Synthesis of Antibiotic 100-1, a Deoxydisaccharide Angucycline Antibiotic of the Urdamycinone B-Type[†]

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ABSTRACT

Two routes to the deoxydisaccharide angucycline antibiotic 100-1 (**3**) are described. Key steps comprise the regioselective oxidation/bromination of the 1,5-diacetoxy-olivose *C*-saccharide **7** to the bromoquinone **8**. Diels–Alder reaction of the bromoquinone with the diene **9** followed by HBr elimination afforded the urdamycinone B precursor **11** as a diastereomeric mixture. Selective protection as the TBDMS ether **13**, acetylation and deprotection of the silyl ether afforded the alcohol **15** which was selectively glycosylated to the α-rhamnal glycoside **17** in 72% yield (at 70% conversion) using benzoyl rhamnal (**16**) as the glycoside donor and scandium triflate as the promotor. The silyl group at C-3 of the aglycone was then transformed into a hydroxyl group. Zemplén deacylation and photooxidation of the benzylic position at C-1 then converted the two diastereoisomers into the natural product **3** and the C-3 diastereoisomer **20**. At this stage the diastereomers **3** and **20** were separated. Alternatively and more easily, the diastereomers were separated at the stage of the urdamycinone B analogues **21a** and **21b**, followed by a similar reaction sequence to the natural disaccharide **3**.

Key Words: Deoxydisaccharides; Angucycline antibiotics; *C*-glycosides; Scandium triflate.

[†]This paper is dedicated to Prof. Gérard Descotes on the occasion of his 70th birthday.

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INTRODUCTION

The angucycline antibiotics are a large group of glycosidic natural products with benzo[*a*]anthraquinone as the aglycone skeleton (reviews, see Refs. [1–3]). Typical representatives are the urdamycins[4–6] with some of their structures shown in Figure 1. The comparatively simple benzo[*a*]anthraquinone skeleton was the first angucyclinone isolated from microbial sources and named tetrangomycin.[7,8] Since the D-olivose is attached *C*-glycosidically to the quinone skeleton, the true aglycone has to be named urdamycin**one** B (**2**). This name is derived from the trisaccharide urdamycin B (**4**), first isolated by Rohr and Zeeck et al.[4,5] A disaccharide, antibiotic 100-1 (**3**), was isolated during studies on the biosynthesis of the urdamycin family from a mutant strain.[9] Remarkably, the sequence of sugars present in urdamycin B (**4**) is representative for most other related angucycline antibiotics with quite different aglycones.[1,2] Thus, D-olivose is β-*C*-glycosidically linked at C-9 of the benzo[*a*]anthraquinone, followed by an α-*O*-glycosidically attached L-rhodinose and then again by D-olivose as a β-*O*-glycoside. Accordingly, work on the glycosides, which contain the simple tetrangomycin as polyketide derived core, has model character for the entire group of angucycline antibiotics. Apart from the remarkable syntheses of the trisaccharide fragment of the antibiotic PI-080[10] and the hexasaccharide fragment of landomycin A[11] by the Sulikowski group, only three syntheses of angucycline antibiotics are known with the sugars attached to the benzo[*a*]anthraquinones (reviews on deoxyoligosaccharide synthesis, see Refs. [12,13]). In the first biomimetic-type synthesis of *ent*-urdamycinone B by Yamaguchi et al.[14] the phenolic precursor was constructed around the deoxysugar. In contrast the *C*-glycoside was prepared in a Lewis acid-promoted reaction of electron rich phenols with deoxysugars in the groups of Sulikowski[15] and Toshima.[16] This method of *C*-glycoside construction using phenols, and probably involving *O*-*C*-glycoside rearrangement, was pioneered by work of Suzuki et al.[17–19] Toshima et al. extended this method even to unprotected sugars,[20,21]

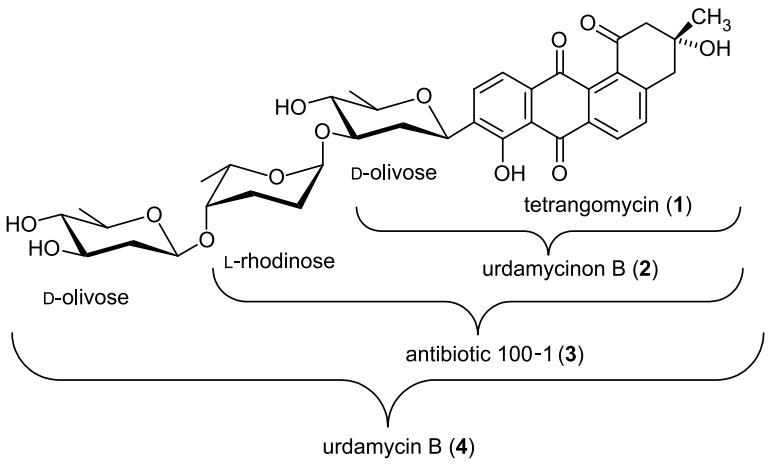


Figure 1. Structures of urdamycinones from wild strains and blocked mutants. (From Ref. [9].)

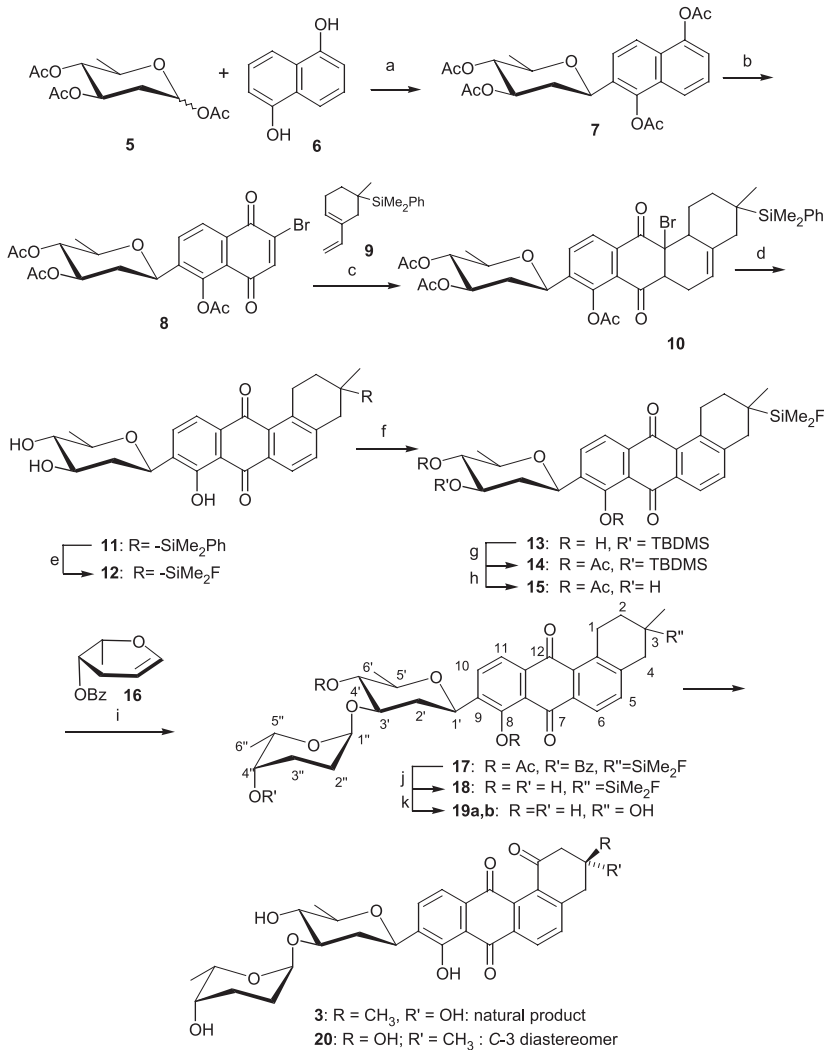
while the very simple protocol of Andrews and Larsen relied on corresponding anomeric acetates of 2-deoxy sugars.[22]

RESULTS AND DISCUSSION

We now disclose two routes to the first total synthesis of the disaccharide, antibiotic 100-1 (**3**), based on the earlier model studies on the stereoselective disaccharide deoxysugar synthesis performed on naphthol models[23] and on the tetrangomycin synthesis that relied on a Diels–Alder reaction to construct the benzo[*a*]anthraquinone skeleton.[24]

A direct electrophilic substitution of potential *C*-glycosyl donors with the electron-deficient naphthoquinones is not possible. Therefore, *C*-glycoside formation according to an electrophilic mechanism is usually performed with the corresponding eletron-rich hydroquinones or naphthols. However, to avoid the somewhat tedious preparation of the selectively protected juglone hydroquinones and the formation of possible regioisomers with less protected oligophenolic nucleophiles, we decided to start with the symmetrical 1,5-dihydroxynaphthalene, related to the first step of the Toshima urdamycinone B synthesis.[16] Thus, D-olivose acetate (**5**)[25] was reacted with a 1.6 fold excess of 1,5-dihydroxynaphthalene (**6**) and boron trifluoride etherate according to the procedure of Andersen and Larsen[22] (Scheme 1). The intermediate mono-*C*-glycoside was directly acetylated to afford the tetraacetate **7** as colorless crystals in 43% yield over the two steps. Photooxidation in the presence of oxygen of the corresponding bisphenol was performed by the group of Toshima to afford a mixture of the regioisomeric related juglone derivative in a 57:13 ratio on a small scale.[16] We anticipated that NBS bromination of **7** might selectively attack the less substituted benzene ring. Gratifyingly, our reasoning proved to be correct and the bromoquinone **8** was isolated in 86% yield in a multi-gram scale with no trace of a regioisomeric quinone detected. This reaction can be considered a breakthrough in this and all related Diels–Alder based approaches to the angucycline glycosides. The procedure is more simple than the NBS oxidation of a corresponding selectively acetylated monophenol reported by Sulikowski[15] and has a number of advantages over the reported photooxidation:[16] 1) only one regioisomer is formed and no chromatographic separation is required, 2) it can be conducted on a large scale, 3) the bromine atom on the quinone double bond directs the regiochemistry of the subsequent Diels–Alder reactions, 4) the presence of the bromine atom also facilitates the HBr elimination of the intermediate Diels–Alder adduct to afford the desired benzo[*a*]anthraquinone.

The subsequent Diels–Alder reaction of the bromoquinone **8** with the readily available known diene **9**[24,26,27] afforded the primary Diels–Alder adduct **10** with complete regioselectivity. This was in agreement with our experience that the less hindered site of dienes always adds to the sterically less hindered site of halogenated naphthoquinones such as **8**. This steric effect even dominates opposite electronic effects of the halogen atom. In the next step, as anticipated, elimination of hydrogen bromide was easily effected by treatment of bromide **10** with K_2CO_3 in methanol to yield the anthraquinone **11** in 76% yield over the two steps. The Diels–Alder products derived from the reaction of the enantiomerically pure *C*-glycoside **8** with the racemic diene **9** were a ca. 1:1 mixture of diastereoisomers that were chromatographically not separable.



Scheme 1. a) 1. CH_3CN, BF_3 Et_2O; 2. Ac_2O/py (43%). b) NBS, H_2O/CH_3CN, 86%. c) Toluene, 6 h at 70°C. d) K_2CO_3, methanol (76%, 2 steps). e) $HBF_4 \cdot Et_2O$ (60%). f) TBDMSCl/imidazole, DMF. g) Ac_2O/py. h) HF/CH_3CN (76% yield for the 3 steps). i) $Sc(OTf)_3/CH_2Cl_2$ (72% yield at 70% conversion). j) NaOMe/MeOH, (87%). k) THF/MeOH, $KHCO_3$, KF, H_2O_2. l) O_2/hν, methanol (each **3** and **20** 17% over 2 steps).

The dimethylphenylsilyl group served as a placeholder to avoid possible elimination of the tertiary hydroxyl group at C-3.[24,28] Its replacement by a hydroxyl group (with retention of stereochemistry) is usually performed in two steps: 1) protodesilylation by cleavage of the phenyl–silicon bond replacing the phenyl group by a fluoride, and 2) oxidative replacement of the dimethylfluorosilyl group by a hydroxyl group.[29] This strategy was applied previously in a number of angucyclinone

syntheses[16,24] (review, see Ref. [2]). In the first of these two steps, the fluoride **12** was obtained upon treatment of silane **11** with HBF_4 Et_2O in 60% yield.

The stage was now set to perform the selective disaccharide synthesis making use of the experience gained in our previous model studies with the bicyclic naphthol derivatives.[23] We applied a very easy and high yielding three step protection strategy. First, the slightly less hindered 3-OH of the olivose residue in **12** was selectively protected as the TBDMS ether **13**, as also performed by Suzuki et al. in the synthesis of antibiotic C-104.[30] The alcohol **13** was then acetylated to the diacetate **14**, thus protecting also the free chelated phenolic hydroxyl group. The silyl ether was then cleaved by treatment with HF/CH_3CN to afford the diacetate **15** with a free hydroxyl group at C-4 in 76% yield over the three steps. In the previous model studies, we employed scandium triflate for the first time in an α-selective *O*-glycoside synthesis.[23] According to that procedure, the alcohol **15** was treated with the L-rhodinal benzoate (**16**)[23] and scandium triflate to yield the α-*O*-gylcoside **17** selectively in 72% yield at 70% conversion as a yellow resin in addition to recovered starting *C*-glycoside **15**. Zemplén deacylation using sodium methoxide in methanol then afforded the deprotected disaccharide **18**.

It has to be remembered that up to the present stage of the synthesis, all the mono- and disaccharides with nonpolar methyl and silyl groups at C-3 were diastereoisomeric mixtures that were not separable by chromatography. Differentiation was only possible by replacing the hydrophobic silyl group with a polar hydroxyl group. This oxidative desilylation was performed according to the procedure of Chan and Nwe[29] by treating the silyl fluoride **18** with hydrogen peroxide in the presence of KF and $KHCO_3$. The crude mixture of the alcohols **19a**,**b** was then exposed to sunlight in methanol solution as described earlier by our group for C-1 oxidation of angucyclinones.[24,31] It was important to perform the photooxidation in the last step to avoid facile β-elimination of the C-3 tertiary hydroxyl group during glycosidation or deprotection steps. The products could now be separated by repeated TLC chromatography on silica gel. The less polar compound was identical in all respects to a sample kindly provided by Prof. J. Rohr, whereas the polar component was assigned the structure of the diastereoisomer **20**.

However, the separation of the isomers **3** and **20** proved to be rather difficult due to small differences in R_f. Earlier in the synthesis, we observed that the corresponding monosaccharides related to urdamycinone B were more easily separable. Thus, the diastereomeric mixture of the silyl fluorides **11** was oxidatively desilylated. Column chromatography on silica gel of the crude product with a gradient elution (CH_2Cl_2/MeOH 95:5–93:7) afforded the diastereomer **21a** corresponding to the natural configuration (23%) and the non-natural isomer **21b** (21%), both as faint yellow resins (Scheme 2). The less polar fraction was irradiated with sunlight to afford urdamycinone B (**2**), identical in all data to the natural product.[4,5,16]

The natural isomer **21a** was then transformed via **22** and **23** into the diacetate **24**, employing the three step protection procedure described for **12** (67%). The monoalcohol **24** was then glycosylated using L-rhodinal benzoate **16** and scandium triflate as promotor in analogy to the conversion of **15** into **17** to afford the disaccharide **25** (85% yield at 77% conversion) as a yellow resin and the starting monoglycoside **24**. Zemplén deacylation gave the pure diastereoisomer **19a** that was photooxidized to antibiotic 100-1 (**3**) as described above. Interestingly, the formation of the monoacetate **26** was

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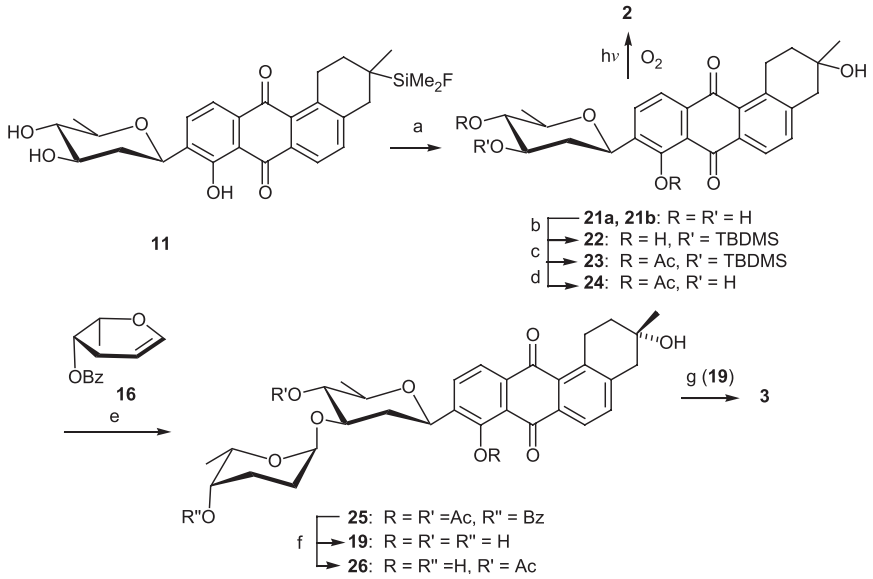

Scheme 2. a) THF/MeOH, $KHCO_3$, KF, H_2O_2 (60%), TLC separation. b–d) Steps f–h of Scheme 1 (67% for three steps). e) $Sc(OTf)_3/CH_2Cl_2$ (85% yield at 77% conversion). f) NaOMe/MeOH g) O_2/hν, methanol.

observed depending on the duration of the Zemplén saponification procedure. This compound would be ideally suited for further attachment of deoxysugars, for instance employing the selective α-glycoside synthesis using 2-deoxyglycosyl phosphates as proposed by Hashimoto[32] and recently employed by Sulikowski et al.[33]

In summary, the regioselective NBS bromination of the tetraacetate **7** allowed the large-scale preparation of the quinoid D-olivose-*C*-glycoside **8**. The aglycone was constructed by Diels–Alder reaction and the stereoselective α-L-rhodinose-*O*-glycoside by using monoalcohol **15** and L-benzoylrhodinal (**16**) and scandium triflate as the promotor. The separation of the diastereomers was more easily performed with the mono-*C*-glycoside **21a/21b** than with the disaccharides **3/20**.

EXPERIMENTAL

General remarks and instrumentation. Silica gel 60 F_{254} coated plates from Merck AG Darmstadt were used for TLC. Spots were detected by UV light (λ = 254 and 366 nm), spraying and heating with 8% ethanolic sulfuric acid or the cerium(IV)molybdato phosphoric acid reagent (Merck AG). Preparative LC was performed using silica gel plates (1 mm) from Macherey and Nagel. Melting points were recorded with a Gallenkamp Melting Point apparatus (uncorrected); IR spectra: NICOLET 510 P; optical rotations: Perkin–Elmer polarimeter 241 (589 nm); elemental analyses: Perkin–Elmer Elementar Analysator 240; mass spectra: FINNEGAN MAT 8200 and FISON MD 800, relative intensities in brackets; NMR spectra: Bruker ARX 200 (200/50 MHz) and Bruker AMX 300 (300/75 MHz) spectrometer.

1,5-Diacetoxy-2-(3,4-di-*O*-acetyl-2,6-dideoxy-β-D-*arabino*-hexopyranosyl)-naphthalene (7). A solution of 1,5-dihydroxynaphthalene **5** (2.6 g, 16.3 mmol) and D-olivose triacetate (**6**) (2.7 g, 10.1 mmol) in dry acetonitrile (60 mL) was treated dropwise at 0°C under argon with a solution of BF_3 OEt_2 (2.7 mL) in acetonitrile (10 mL). After 40 min (TLC monitoring), the reaction was quenched by addition of dry pyridine (20 mL) and acetic anhydride (9.8 mL, 100 mmol) and the solution was kept overnight at room temperature. The reaction mixture was then diluted with ethyl acetate (200 mL), washed with water (3 × 20 mL), 1 M HCl (15 mL) and saturated aqueous $NaHCO_3$ (2 × 10 mL). The organic phase was dried (Na_2SO_4), filtered, concentrated at reduced pressure and the residue purified by column chromatography on silica gel (hexane: ethyl acetate 6:4) to afford the *C*-glycoside **7** as a white foam (1.95 g, 43%). Crystallization from diethyl ether/pentane afforded colorless needles, mp 186–187°C. $[\alpha]_D^{20}$ = 12.8 (*c* 0.53, CH_2Cl_2). ^{1}H NMR: δ = 1.28 (d, $J_{5',6'}$ = 6.1 Hz, 3H, 6′-H), 1.61–2.78 (m, 2H, 2′-H_{ax}, 2′-H_{equ}), 2.03, 2.09, 2.22, 2.46 (4s, 12H, OAc), 3.60–3.84 (m, 1H, 5′-H), 4.74 (d, $J_{1',2'ax}$ = 10.5 Hz, 1H, 1′-H), 4.88 (pt, *J* = 9.4 Hz, 1H, 4′-H), 5.09–5.25 (m, 1H, 3′-H), 7.20–7.31, 7.48–7.60, 7.68–7.73, 7.80–7.91 (4m, 5H, aromatic). ^{13}C NMR: δ = 18.4 (C-6′), 21.0, 21.3 (OAc), 37.6 (C-2′), 72.5, 72.9, 75.0 (C-1′, C-3′, C-4′, C-5′), 119.3, 119.9, 120.4, 124.8, 126.9 (5 aromatic), 128.0, 128.6, 130.2, 143.6, 147.2 (5 aromatic), 169.5, 169.6, 170.6, 170.8 (4 OAc). MS (70 eV): *m*/*z* = 458.5.

Anal. Calcd for $C_{24}H_{26}O_9$: C, 62.88; H, 5.72. Found: C, 62.80; H, 5.78.

5-Acetoxy-6-(3,4-di-*O*-acetyl-2,6-dideoxy-β-D-*arabino*-hexopyranosyl)-2-bromo-[1,4]naphthoquinone (8). A solution of NBS (1.5 g, 18 mmol) in a mixture of water (50 mL) and acetic acid (25 mL) was heated to 55–60°C. A warm solution of **3** (1.1 g, 2.4 mmol) in acetic acid (25 mL) was then added dropwise to the NBS solution within 15 min at 60°C. After 45 min, the suspension was poured into ice–water (300 mL) and the mixture was extracted with CH_2Cl_2 (3 × 180 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 100 mL), water (150 mL), dried (Na_2SO_4), filtered, and concentrated at reduced pressure. The residue was purified by filtration through a short column of silica gel (hexane: ethyl acetate 6:4) to afford the bromoquinone **8** (1.05 g, 86%) as a yellow foam. ^{1}H NMR: δ = 1.28 (d, $J_{5',6'}$ = 6.2 Hz, 3H, 6′-H), 1.55–1.79 (m, 1H, 2′a-H), 2.02, 2.08, (2s, 6H, OAc), 2.44–2.59 (m, 1 H, 2′b-H), 2.47 (s, 3 H, OAc), 3.62–3.73 (m, 1H, 5′-H), 4.78 (m, 1H, 1′-H), 4.88 (pt, *J* = 9.4 Hz, *J* = 9.6 Hz, 1H, 4′-H), 5.05–5.18 (m, 1H, 3′-H), 7.36 (s, 1H, 3-H), 7.98, 8.14 (2d, $J_{7,8}$ = 8.1 Hz, 7-H, 8-H). ^{13}C NMR: δ = 18.4 (C-6′), 21.29, 21.48 (OAc), 37.65 (C-2′), 72.03, 72.22, 74.46, 75.07 (C-1′, C-3′, C-4′, C-5′), 123.1 (C-8a), 126.8 (C-8), 132.0 (C-4a), 132.9 (C-7), 138.9 (C-2), 141.9 (C-3), 142.2, 146.6 (C-5, C-6), 169.4, 170.6, 170.9 (OAc), 177.7, 181.4 (C-1, C-4). (70 eV): *m*/*z* = 509.3 (M^+).

Anal. Calcd for $C_{22}H_{21}BrO_9$: C, 51.88; H, 4.16. Found: C, 51.75; H, 4.06.

Cycloadduct 10 and Anthraquinone 11. A solution of diene **9** (750 mg, 1.75 mmol) and bromoquinone **8** (900 mg, 1.75 mmol) in dry toluene (5 mL) was kept at 70°C for 6 h. After evaporation of the solvent, the labile orange-brown adduct was used without purification for the next step. A small sample was purified by column chromatography on silica gel (1% MeOH/CH_2Cl_2). ^{1}H NMR of 10: δ = 0.32, 0.33, 0.34 (3s, 6H, $SiMe_2$), 0.78 (s, 3H, Me), 0.94–1.20 (m, 1H), 1.28 (d, $J_{5',6'}$ = 6.1 Hz, 3H, 6′-

H), 1.63–1.76 (m, 3H), 1.92–2.08 (m, 2H), 2.02, 2.08 (2s, OAc), 2.34–2.64 (m, 3H), 2.44 (m, OAc), 2.73–2.78 (m, 1H, 12b-H), 3.56–3.67 (m, 2H, 6a-H, 5′-H), 4.67–4.72 (m, 1H, 1′-H), 4.85 (t, J = 9.5 Hz, 1H, 4′-H), 5.06–5.19 (m, 1H, 3′-H), 7.32–7.35 (m, 3H, Ph), 7.43–7.53 (m, 2H, Ph), 7.90–8.01 (m, 1H, 10-H or 11-H), 8.05–8.10 (m, 1H, 10-H or 11-H).

Silyl fluoride 12. A solution of the crude Diels–Alder adduct in dry methanol (30 mL) was treated with K_2CO_3 (6.0 g) and the suspension was stirred overnight. After filtration and solvent evaporation, the residue was dissolved in CH_2Cl_2 (200 mL) and washed with brine (2 × 10 mL). The organic phase was dried (Na_2SO_4), filtered, concentrated at reduced pressure and the residue purified by column chromatography on silica gel (4% MeOH/CH_2Cl_2) to afford an orange solid **11** (755 mg, 76%). The spectral data were in agreement with those published by Toshima et al.[16] ^{13}C NMR: δ = −6.0, −5.9 ($SiMe_2$), 18.6 (C-6′), 18.9 (C-3), 19.6, 19.6 (Me), 25.2 (C-1), 29.8 (C-2′), 38.7 (C-2), 40.3 (C-4), 71.6, 73.5, 76.4, 78.4 (C-1′, C-3′, C-4′, C-5′), 115.4, 119.7, 125.0, 128.0, 129.5, 131.2, 133.1, 133.6, 134.2, 134.9, 135.7, 136.5, 137.0, 141.7, 146.1, 151.4 (aromatic), 185.2, 189.6 (C-7, C-12).

Anal. Calcd for $C_{33}H_{36}O_6Si$: C, 71.19; H, 6.52. Found: C, 71.50; H, 6.58.

Fluoride 12. A solution of the silane **11** (750 mg, 1.3 mmol) in dichloromethane was treated with HBF_4 Et_2O as described in the literature[16,24,28] to afford the fluoride **12** (390 mg, 60%). The spectral data were identical to those reported.[16] ^{13}C NMR: δ = − 4.3, − 4.0–4.04, − 3.7 ($SiMe_2$), 18.6, 19.5, 19.6 (Me, C-6′), 19.9 (C-3), 25.3, 29.5, 38.6, 39.9 (C-1, C-2, C-4, C-2′), 71.6, 73.5, 76.4, 78.4 (C-1′, C-3′, C-4′, C-5′), 115.4, 119.7, 125.3, 125.8, 129.5, 131.3, 133.3, 133.6, 134.2, 135.6, 136.6, 137.5, 141.4, 145.3 (aromatic), 158.4 (OAc), 185.2, 189.5 (C-7, C-12).

Anal. Calcd for $C_{27}H_{31}FO_6Si$: C, 65.04; H, 6.27. Found: C, 65.27; H, 6.23.

TBDMS–Ether 13. A solution of the *C*-glycoside **12** (350 mg, 0.7 mmol), imidazole (250 mg, 3.5 mmol) and TBDMSCl (270 mg, 2 mmol) in dry DMF (2.5 mL) was kept under argon for 3 h at room temperature. The reaction mixture was then poured into water (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic phase was washed with water (10 mL), dried (Na_2SO_4), filtered, and concentrated at reduced pressure. The crude silyl ether **13** was used in the next reaction. ^{1}H NMR for 13: δ = 0.11, 0.15 (2s, 6H, TBDMS), 0.22 (d, $J_{F,SiMe}$ = 8.1 Hz, 3H, SiMe), 0.26 (d, $J_{F,SiMe}$ = 7.9 Hz, 3H, SiMe), 0.90 (s, 9H, $C(CH_3)_3$), 1.03 (s, 3H, Me), 1.41 (d, $J_{5',6'}$ = 6.0 Hz, 3H, 6′-H), 1.56–1.92 (m, 3H, 2-H, 2′-H_{ax}), 2.33–2.42 (m, 2H, 2′-H_{equ}, OH), 2.62 (d, J_{gem} = 17.4 Hz, 1H, 4-H_a), 3.10 (d, J_{gem} = 17.4 Hz, 1H, 4-H_b), 3.17–3.24 (m, 1 H, 4′-H), 3.43–3.46 (m, 2H, 1-H), 3.51–3.64 (m, 1H, 3′-H), 3.75–3.87 (m, 1H, 5′-H), 4.92 (d, $J_{1',2'ax}$ = 10.8 Hz, 1H, 1′-H), 7.48 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 7.9 Hz, 1H), 8.16 (d, J = 7.9 Hz, 1H), 12.92 (s, 1H, OH).

Diacetate 14. A solution of the monosilyl ether **13** in dry pyridine (15 mL) was treated with Ac_2O (1 mL) and stirred overnight at 20°C. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with 1 M HCl (2 × 10 mL) followed by saturated aqueous $NaHCO_3$ (2 × 10 mL). The organic phase was dried (Na_2SO_4),

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filtered, concentrated at reduced pressure and the residue **14** was used without purification in the next step. ^{1}H NMR for **14**: δ = 0.10 (s, 6H, TBDMS), 0.21 (d, $J_{F,SiMe}$ = 8.1 Hz, 3H, SiMe), 0.25 (d, $J_{F,SiMe}$ = 8.0 Hz, 3H, SiMe), 0.85 (s, 9H, $C(CH_3)_3$), 1.02 (s, 3H, Me), 1.29 (d, $J_{5',6'}$ = 6.2 Hz, 3H, 6′-H), 1.60–1.92 (m, 3H, 2-H, 2′-H_{ax}), 2.11 (s, 3H, OAc), 2.22–2.37 (m, 1H, 2′-H_{equ}), 2.51 (s, 3H, OAc), 2.60 (d, J_{gem} = 17.0 Hz, 1H, 4-H_a), 3.08 (d, J_{gem} = 17.0 Hz, 1H, 4-H_b), 3.41–3.44 (m, 2H, 1-H), 3.52–3.64, 4.20–4.24 (2m, 2H, 3′-H, 5′-H), 4.64–4.79 (m, 2H, 1′-H, 4′-H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 8.20 (d, *J* = 8.2 Hz, 1H).

Alcohol 15. Hydrogen fluoride (0.2 mL, 40% in water) was added to the solution of TBDMS ether **14** in CH_3CN (7 mL). After stirring for 5 h at 20°C (TLC monitoring), the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (10 mL) and extracted with diethyl ether (3 × 50 mL). The organic phase was dried (Na_2SO_4), filtered, concentrated at reduced pressure and the residue purified by column chromatography on silica gel (3% MeOH/CH_2Cl_2) to afford **15** (310 mg, 76%) as an orange resin. ^{1}H NMR: δ = 0.21 (d, $J_{F,SiMe}$ = 8.1 Hz, 3H, SiMe), 0.25 (d, $J_{F,SiMe}$ = 8.0 Hz, 3H, SiMe), 1.02 (s, 3H, Me), 1.29 (d, $J_{5',6'}$ = 6.2 Hz, 3H, 6′-H), 1.56–1.96 (m, 3H, 2-H, 2′-H_{ax}), 2.16 (s, 3H, OAc), 2.25–2.63 (m, 2H, 4-H_a, 2′-H_{equ}), 2.51 (s, 3H, OAc), 3.07 (d, J_{gem} = 17.3 Hz, 1H, 4-H_b), 3.40–3.43 (m, 2H, 1-H), 3.57–3.73, 3.83–3.96 (2m, 2H, 3′-H, 5′-H), 4.56–4.71 (m, 2H, 1′-H, 4′-H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 8.20 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR: δ = −4.3, −4.0, −3.7 ($SiMe_2$), 18.5, 19.5 (Me, C-6′), 20.0 (C-3), 21.5, 21.7 (OAc), 25.0, 29.5, 38.4, 41.1 (C-1, C-2, C-4, C-2′), 71.9, 72.3, 74.6, 79.1 (C-1′, C-3′, C-4′, C-5′), 124.1, 125.6, 126.2, 130.5, 132.6, 134.6, 135.8, 135.4, 140.6, 140.9, 144.1, 146.2 (aromatic), 169.6. 172.3 (OAc), 182.9, 185.1 (C-7, C-12).

Anal. Calcd for $C_{31}H_{35}FO_8Si$: C, 63.90; H, 6.05. Found: C, 64.02; H, 6.13.

Disaccharide 17. A solution of *C*-glycoside **15** (150 mg, 0.25 mmol) and 4-*O*-benzoyl-L-rhodinal (16)[23] (80 mg, 0.38 mmol) in dry CH_2Cl_2 (3 mL) was treated at 0°C with $Sc(OTf)_3$ (10 mg, 0.02 mmol) and the mixture was stirred for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The organic phase was dried (Na_2SO_4), filtered, concentrated at reduced pressure and the residue purified by column chromatography on silica gel (1% MeOH/CH_2Cl_2) to yield the disaccharide **17** (104 mg, 52% yield; 72% at 70% conversion) as a yellow resin, and the starting material, *C*-glycoside 15 (45 mg). ^{1}H NMR: δ = 0.25 (d, $J_{F,SiMe}$ = 8.0 Hz, 3H, SiMe), 0.29 (d, $J_{F,SiMe}$ = 8.0 Hz, 3H, SiMe), 1.06 (s, 3H, Me), 1.25–1.34 (m, 6H, 6′-H, 6″-H), 1.52–2.11 (m, 7H), 2.17 (s, 3H, OAc), 2.34–2.50 (m, 1H), 2.57 (s, 3H, OAc), 2.57–2.68 (m, 1H, 4-H_a), 3.11 (d, J_{gem} = 17.1 Hz, 1H, 4-H_b), 3.35–3.49 (m, 2H, 1-H), 3.64–3.72 (m, 1H, 3′-H), 4.01–4.17 (m, 2H, 5′-H, 5″-H), 4.72–4.74 (m, 1H, 4″-H), 4.91 (dd, *J* = 9.4 Hz, 1H, 1′-H), 5.01 (s, 2H, 4′-H, 1″-H), 7.46–7.61 (m, 5 H), 8.00–8.16 (m, 3H), 8.24 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR: δ = −4.3, −4.0, −3.7 ($SiMe_2$), 17.7 (C-6″), 18.5 (C-6′), 19.5 (CH_3), 20.0 (C-3), 21.5, 21.8 (OAc), 23.3, 24.7, 25.4, 29.5, 37.4, 38.4 (C-1, C-2, C-4, C-2′, C-2″, C-3″), 65.9, 70.2, 72.2, 73.2, 75.1, 75.7, (C-1′, C-3′, C-4′, C-5′, C-4″, C-5″), 93.3 (C-1″), 124.1, 125.7, 126.2, 128.9, 130.1, 130.5, 130.7, 132.8, 133.5, 134.6, 135.8, 136.4, 140.6, 141.0, 144.2, 146.1 (aromatic), 166.5, 170.4 (OAc), 182.9, 185.1 (C-7, C-12).

Anal. Calcd for $C_{44}H_{49}FO_{11}Si$: C, 65.98; H, 6.17. Found: C, 66.08; H, 6.12.

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Disaccharide 18. A solution of disaccharide **17** (50 mg, 0.06 mmol) in dry methanol (5 mL) was treated with NaOMe (1 mL, 1 M in methanol) and kept for 20 h at 20°C. The solvent was removed under reduced pressure, the residue redissolved in diethyl ether (30 mL) and the solution washed with 2% HCl (10 mL) and then brine (10 mL). The organic phase was dried (Na_2SO_4), filtered, concentrated at reduced pressure and the residue purified by column chromatography on silica gel (3% MeOH/CH_2Cl_2) to afford the deacylated disaccharide **18** (33 mg, 87%) as a yellow solid. ^{1}H NMR: δ = 0.16 (m, 6 H, $SiMe_2$), 1.01 (s, 3H, Me), 1.29 and 1.40 (2d, 6H, 6′-H, 6″-H), 1.5–2.2 (m, 7H), 2.40–2.70 (m, 2H), 3.0–3.3 (m, 2H, 4-H_a, 4-H_b), 3.35–3.49 (m, 2H, 1-H), 3.65–3.80 (m, 3H, 3′-H, 5′-H, 5″-H), 4.20 and 4.42 (2m, 2H, 4′-H, 4″-H), 4.94 (d, 1H, *J* = 9.8 Hz, 1′-H), 5.06 (s, 1H, 1″-H), 7.52 (d, 1H, *J* = 8.1 Hz), 7.78 (d, 1H, *J* = 7.8 Hz), 7.92 (d, 1H, *J* = 7.8 Hz), 8.18 (d, 1H, *J* = 8.1 Hz), 12.96 (s, 1H, OH). ^{13}C NMR: δ = −5.40, −5.25 ($SiMe_2$), 17.5 (C-6″), 18.8 (C-6′), 19.4 (CH_3), 20.1 (C-3), 24.6, 25.1, 25.9, 29.5, 37.9, 38.9 (C-1, C-2, C-4, C-2′, C-2″, C-3″), 67.6, 68.0, 70.9, 71.5, 76.5, 81.6 (C-1′, C-3′, C-4′, C-5′, C-4″, C-5″), 97.9 (C-1″), 115.4, 119.8, 125.1, 132.2, 133.7, 135.7, 136.7, 141.8, 146.1, 158.4 (aromatic) 185.1, 189.7 (C-7, C-12).

Anal. Calcd for $C_{33}H_{41}FO_8Si$: C, 64.68; H, 6.74. Found: C, 64.52; H, 6.71.

Alcohol 19. From **18**: A solution of the fluoride **18** (25 mg, 0.04 mmol) in a 1:1 mixture of THF and methanol (3 mL) was treated with $KHCO_3$ (150 mg, 1.5 mmol), KF (90 mg, 1.5 mmol) and hydrogen peroxide (0.3 mL, 35% in water, 2.7 mmol).[29] The suspension was stirred for 24 h at room temperature and then quenched by addition of aqueous saturated $Na_2S_2O_3$ (5 mL) and extracted with ether (2 × 20 mL). The organic phase was dried (Na_2SO_4), filtered, concentrated at reduced pressure and the polar yellow product was used directly in the next reaction (photooxidation).

From **25**: A solution of the disaccharide **25** (100 mg, 0.14 mmol) in dry methanol (8 mL) was deacylated as described for **18** to yield **19** (52 mg, 70%) as a yellow resin. MS: *m/z* = 552.0 (M^+). ^{1}H NMR for **19**: δ = 1.25 and 1.43 (2d, 6H, 6′-H, 6″-H), 1.51 (s, 3H, Me), 1.6–2.3 (m, 7H), 2.40–2.70 (m, 2H), 3.25 (m, 2H, 4-H_a, 4-H_b), 3.4–3.6 (m, 2H, 1-H), 3.65–3.90 (m, 3H, 3′-H, 5′-H, 5″-H), 4.15 and 4.45 (2m, 2H, 4′-H, 4″-H), 4.95 (d, 1H, *J* = 9.6 Hz, 1′-H), 5.07 (s, 1H, 1″-H), 7.52 (d, 1H, *J* = 8 Hz), 7.79 (d, 1H, *J* = 8 Hz), 7.93 (d, 1H, *J* = 8 Hz), 8.22 (d, 1H, *J* = 8 Hz), 12.95 (s, 1H, OH).

Anal. Calcd for $C_{31}H_{36}O_9$: C, 67.38; H, 6.57. Found: C, 67.46; H, 6.62.

Antibiotic 100-1 (3) and the diastereomer 20. A solution of the crude disaccharide **19** from the oxidative desilylation reaction described above, in methanol (15 mL), was exposed to sunshine for 2 days, using NMR tubes as the reaction vessels. After evaporation of the solvent, the reaction mixture was separated by preparative TLC on silica (CH_2Cl_2/Et_2O/MeOH 80:20:3) to give antibiotic 100-1 (**3**) (3.5 mg, 17%) from the less polar fraction and **20** (3.5 mg, 17%) from the polar fraction, both yellow solids. The less polar compound was identical in all respects with a sample kindly provided by Prof. J. Rohr.[32]

NMR data of 3: ^{1}H NMR: δ = 1.25 and 1.38 (2d, 6H, 6′-H, 6″-H), 1.51 (s, 3H, Me), 1.2–1.9 (m, 5H, 3′-H, 2″-H, 3″-H), 2.55 (m, 1H, 3′-H), 3.0–3.4 (m, 5H, 4-H, 2-H, 5′-H), 3.5–3.8 (m, 2H, 6′-H, 4″-H), 4.0 (m, 1H, 4′-H), 4.23 (m, 1H, 5″-H), 4.92 (d, 1H, 1′-H, *J* = 10.2 Hz), 5.04 (s, 1H, 1″-H), 7.60 (d, 1H, *J* = 8 Hz), 7.74 (d, 1H, *J* = 8 Hz),

7.95 (d, 1H, J = 8 Hz), 8.36 (d, 1H, J = 8 Hz), 12.72 (s, 1H, OH). ^{13}C NMR: δ = 17.5 (C-6″), 18.8 (C-6′), 24.5, 26.2, 30.2, 38.1, 44.7, 54.4 (Me, C-2, C-4, C-2′, C-2″, C-3″), 67.6, 68.0, 71.4, 72.8, 76.7, 77.4 (C-1′, C-3′, C-4′, C-5′, C-4″, C-5″), 97.9 (C-1″), 116.0, 120.1, 129.8, 134.1, 134.3, 135.3, 137.0, 137.7, 150.2, 158.7 (aromatic) 183.6, 189.2 (C-7, C-12), 196.5 (C-1).

NMR data for diastereoisomer 20: ^{1}H NMR: δ = 1.25 and 1.38 (2d, 6H, 6′-H, 6″-H), 1.51 (s, 3H, Me), 1.2–1.9 (m, 5H, 3′-H, 2″-H, 3″-H), 2.55 (m, 1H, 3′-H), 3.0–3.4 (m, 5H, 4-H, 2-H, 5′-H), 3.5–3.8 (m, 2H, 6′-H, 4″-H), 4.0 (m, 1H, 4′-H), 4.23 (m, 1H, 5″-H), 4.92 (d, 1H, 1′-H, J = 10.2 Hz), 5.04 (s, 1H, 1″-H), 7.60 (d, 1H, J = 8 Hz), 7.74 (d, 1H, J = 8 Hz), 7.95 (d, 1H, J = 8 Hz), 8.36 (d, 1H, J = 8 Hz), 12.72 (s, 1H, OH). ^{13}C NMR: δ = 17.5 (C-6″), 18.8 (C-6′), 24.6, 26.4, 30.3, 38.1, 44.8, 54.2 (Me, C-2, C-4, C-2′, C-2″, C-3″), 67.5, 68.1, 71.4, 72.9, 76.7, 77.5 (C-1′, C-3′, C-4′, C-5′, C-4″, C-5″), 97.8 (C-1″), 116.2, 120.2, 129.8, 134.1, 134.3, 135.5, 137.0, 137.7, 150.2, 158.8 (aromatic) 183.4, 189.1 (C-7, C-12), 196.4 (C-1).

Alcohols 21a and 21b. The diastereomeric mixture of the silyl fluorides **11** (850 mg, 1.7 mmol) was oxidatively desilylated as described by Chan and Nwe[29] and applied by Toshima et al. to urdamycinone B.[16] Column chromatography on silica gel of the crude product with polarity gradient elution (CH_2Cl_2/MeOH 95:5–93:7) afforded the diastereomer **21a** corresponding to the natural configuration (170 mg, 23%) and the non-natural isomer **21b** (160 mg, 21%), both as yellow solids. For spectral data see Ref. [16].

21a: MS: m/z = 438.2 (M^+).

Anal. Calcd for $C_{25}H_{26}O_7$: C, 68.48; H, 5.98. Found: C, 68.28; H, 6.02.

21b: MS: m/z = 438.2 (M^+).

Anal. Calcd for $C_{25}H_{26}O_7$: C, 68.48; H, 5.98. Found: C, 68.34; H, 6.05.

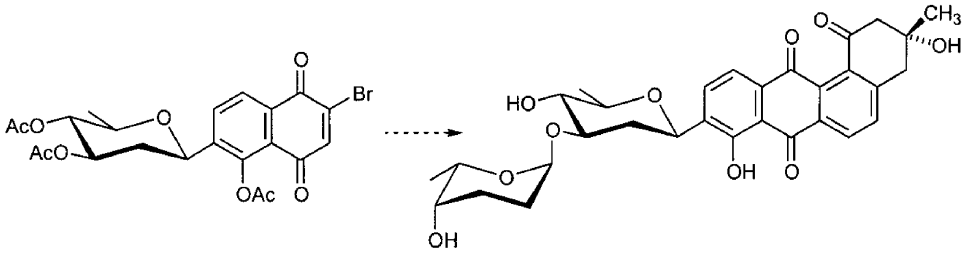
Diacetate 24. The natural isomer **21a** (170 mg, 0.37 mmol) was transformed via **22** and **23** into the diacetate **24** employing the three step protection procedure described for **12**. After column chromatography (4% MeOH/CH_2Cl_2), **24** (130 mg, 67% for three steps) was obtained as a yellow resin. MS: m/z = 522.1 (M^+). ^{1}H NMR: δ = 1.32 (d, $J_{5',6'}$ = 6.1 Hz, 3H, 6′-H), 1.41 (s, 3H, Me), 1.6–2.0 (m, 3H, 2-H, 2′-H_{ax}), 2.2 (s, 3H, OAc), 2.2–2.6 (m, 2H, 4-H_a, 2′-H_{equ}), 2.54 (s, 3H, OAc), 3.07 (d, J_{gem} = 17.3 Hz, 1H,), 3.4–3.7 (m, 4H, 1-H, 3′-H, 4-H_b), 3.9 (m, 1H, 5′-H), 4.5–4.8 (m, 2H, 1′-H, 4′-H), 7.46 (d, J = 8.0 Hz, 1H), 8.0 (d, J = 8.2 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 8.21 (d, J = 8.2 Hz, 1H). ^{13}C NMR: δ = 18.5 (C-6′), 21.5, 21.7 (OAc), 29.1 (Me) 26.9, 36.1, 42.2, 45.1 (C-1, C-2, C-4, C-2′), 59.3 (C-3) 71.8, 72.26, 74.64, 79.1 (C-1′, C-3′, C-4′, C-5′), 124.0, 125.9, 126.2, 129.4, 130.6, 134.7, 135.7, 136.0, 139.6, 140.9, 143.7, 146.2 (aromatic), 169.6, 172.4 (OAc), 182.8, 185.0 (C-7, C-12).

Anal. Calcd for $C_{29}H_{30}O_9$: C, 66.66; H, 5.79. Found: C, 66.58; H 5.84.

Disaccharide 25. A solution of *C*-glycoside **24** (110 mg, 0.23 mmol) and 4-*O*-benzoyl-L-rhodinal (**16**) (90 mg, 0.41 mmol) in dry CH_2Cl_2 (5 mL) was treated at 0°C with $Sc(OTf)_3$ (8 mg, 0.02 mmol). The mixture was stirred for 1 h and the reaction was then quenched by addition of aqueous saturated $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL). Column chromatography on silica gel (2% MeOH/CH_2Cl_2) gave

the disaccharide **25** (102 mg, 60% yield, 85% at 77% conversion) as a yellow resin and the monoglycoside **24**. (25 mg). Data of **25**: MS: m/z = 741 ($M + H^+$). ^{1}H NMR: δ = 1.2–1.3 (m, 6H, 6′-H, 6″-H), 1.42 (s, 3H, Me), 1.5–2.1 (m, 7H), 2.17 (s, 3H, OAc), 2.35–2.5 (m, 1H), 2.54 (s, 3H, OAc), 3.07 (d, J_{gem} = 17.3 Hz, 1H,), 3.4–3.75 (m, 4H, 1-H, 3′-H, 4-H), 4.0–4.25 (m, 2H, 5′-H, 5″-H) 4.72–4.74 (m, 1H, 4″-H), 4.88 (dd, J = 9.4 Hz, 1H, 1′-H), 5.08 (s, 2H, 4′-H, 1″-H), 7.46–7.6 (m, 5H), 8.00–8.16 (m, 3H), 8.24 (d, J = 8.2 Hz, 1H). ^{13}C NMR: δ = 17.7 (C-6″) 18.5 (C-6′), 21.5, 21.7 (OAc), 29.7 (Me) 23.3, 24.7, 26.9, 36.2, 37.4, 45.2 (C-1, C-2, C-4, C-2′, C-2″, C-3″), 54.1 (C-3) 65.9, 70.2, 71.8, 72.2, 73.2, 75.1, 75.7 (C-1′, C-3′, C-4′, C-5′, C-4″, C-5″), 93.3 (C-1″) 124.1, 125.9, 126.2, 128.8, 130.1, 130.6, 133.5, 134.7, 135.7, 136.4, 139.7, 141.0, 143.7, 147.0 (aromatic), 166.5, 170.4 (OAc), 182.8, 185.0 (C-7, C-12), 203.6 (C═O).

Anal. Calcd for $C_{42}H_{44}O_{12}$: C 68.10, H 5.99; Found C: 68.15, H 5.93.



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