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Relative Reactivities of Aminoglycosides and their Synthetic Equivalents in the *C*-Glycosylation of Aromatics. Synthesis of the Pseudoaglycone (D-*C*-Glycoside) of the Benzanthrins

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Dedicated to the memory of Arthur G. Schultz, a creative chemist and a nice person

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Abstract—The pseudoaglycone of the benzanthrin antibiotics was prepared by a short sequence in which *C*-glycosylation of dehydrorabelomycin dimethyl ether served as the key step. The use of a 3-azido 2,3,6-trideoxy pyranose as an activated equivalent of a 3-dimethylamino 2,3,6-trideoxy sugar was demonstrated in this reaction.

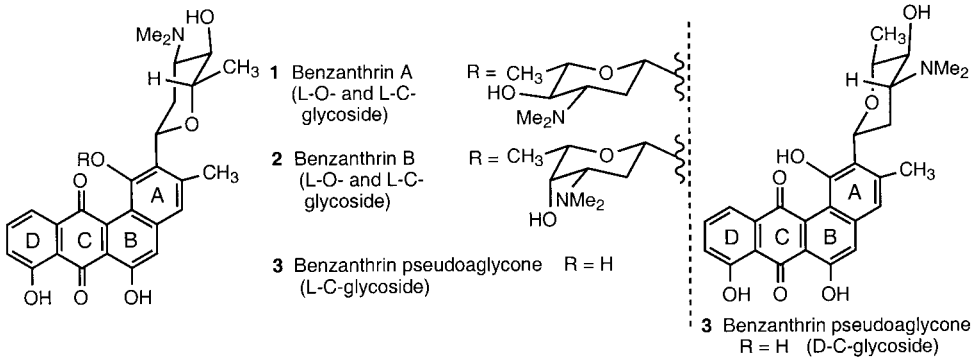
Introduction

Benzanthrins A and B are structurally novel angucyclines from *Nocardia lurida*. They exhibit strong antimicrobial activities, especially against Gram-positive bacteria[1] and are active in tumor cell lines.[2] Analysis of the spectroscopic data for benzanthrins A and B allowed assignment of structures **1** and **2**, respectively, in which relative (but not absolute) stereochemistry is designated for each of the gylcoside moieties.

Among the angucycline natural products, the structures of the benzanthrins are unusual in several respects. First and most obvious, they have four fully aromatized rings.[3] Second, in the benzanthrins, the tetracyclic nucleus bears both *O*- and *C*-glycoside appendages. Third, the *C*-glycosidic linkage is attached at C-2 in ring A rather than at C-9 in ring D as for other angucyclines. Finally, unlike other anguclycines, the benzanthrins contain amino sugars.

Retrosynthetic analysis of the structures of the benzanthrins suggested *O*-glycosylation of the pseudoaglycone **3** (L-glycoside or D-glycoside), the non-sugar hydrolysis product of benzanthrins A and B. This aryl *C*-glycoside might be available from the coupling of dehydrorabelomycin (**4a**) or one of its derivatives (e.g. **4b**) with the rare amino sugar angolosamine (**5**, drawn here as the D-sugar)[4] or its synthetic equivalent. This approach required good sources of both key intermediates (Scheme 1).

With rapid access to angucycline nuclei (including dehydrorabelomycin itself) from Michael addition chemistry,[5] we were poised to examine the *C*-glycosylation of dehydrorabelomycin derivatives. Studies focused on optimization of the coupling of **4b** and equivalents of amino pyranose **5** have now revealed the relative reactivities of 2,3-dideoxy 3-amino sugar synthons in Friedel–Crafts chemistry.[6] These results have been incorporated in the first successful synthesis of the benzanthrin pseudoaglycone (**3,** D-*C*-glycoside).



Keywords: amino sugars; glycosidation; quinones.

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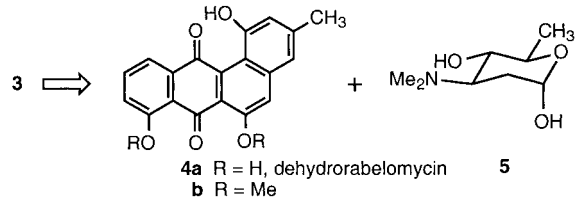


Scheme 1. Retrosynthesis of the benzanthrin pseudoaglycone 3 (D-*C*-glycoside).

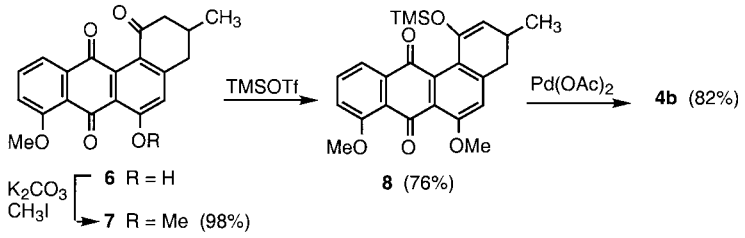
Results

Dehydrorabelomycin dimethyl ether **4b** was chosen as an appropriate tetracyclic substrate for glycosylation studies. This compound was readily available from hatamarubigin A (**6**) by methylation and application of a previously described two-step aromatization procedure (Scheme 2).[5]

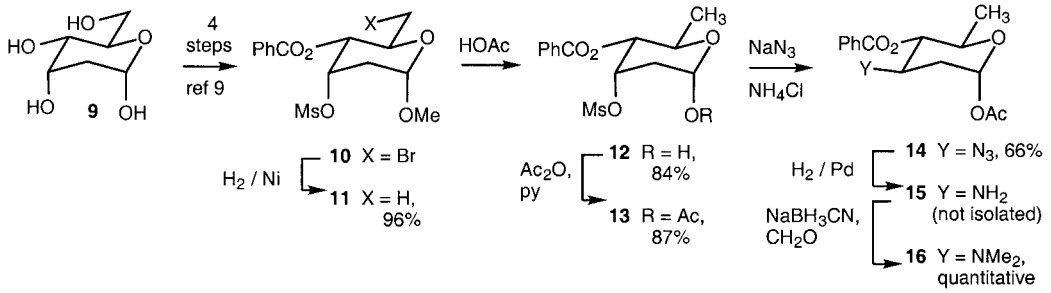
The most convergent approach to the benzanthrin pseudoaglycone would involve the direct incorporation of angolosamine itself, necessarily protected on the C-4 oxygen.[7] In our first approach, therefore, we examined the utility of the known derivative **16** which has been reported, under catalysis by TMSOTf/$AgClO_4$, to effect *C*-glycosylation of β-naphthol in excellent yield.[8] The protected and activated angolosamine **16** was prepared from the differentially functionalized **10** which had been obtained by the literature sequence.[9] Debromination of **10** was best effected by hydrogenolysis with Raney nickel (rather than with palladium), giving the known **11**[9] in quantitative yield (Scheme 3).

In our hands, activated pyranose **16** glycosylated β-naphthol in the presence of $SnCl_4$ in 86% yield, presumably via an *O*-glycosylation followed by an *O*- to *C*-glycoside migration.[10] However, this reagent did not glycosylate substrate **4b** even when extended times and higher temperatures were employed (see Scheme 4). Likewise neither catalysis by TMSOTf/$AgClO_4$ nor by $Cp_2HfCl_2/AgClO_4$, which has effected glycosylation of β-naphthol with a similar angolosamine derivative,[10] led to the formation of detectable coupling product from substrates **16** and **4b**.

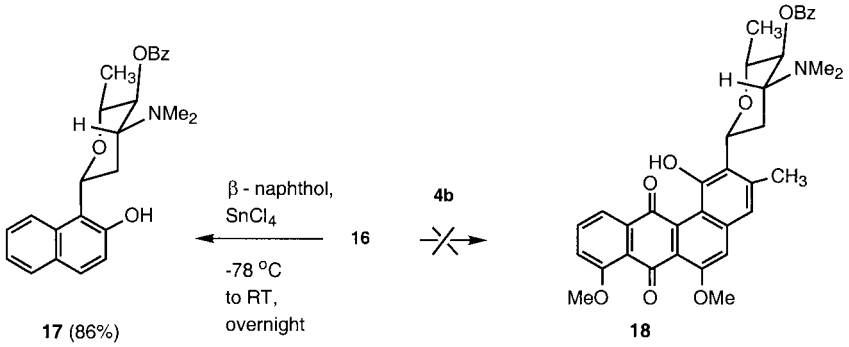
In their descriptions of studies with β-naphthol, both Suzuki and Toshima reported that amino sugars are less reactive as glycosylating agents than are 'neutral' sugars. We speculated that our benzanthrin precursor **4b** was a particularly unreactive substrate because of steric hindrance and internal



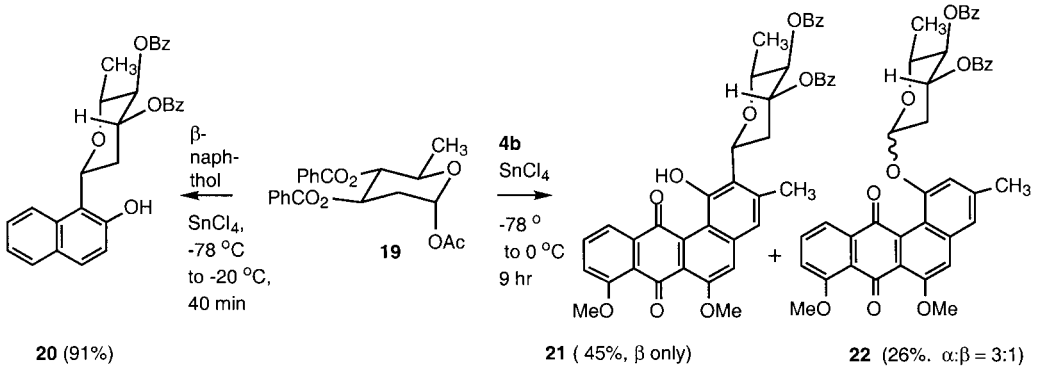
Scheme 2. Preparation of dimethyl dehydrorabelomycin **4b**.



Scheme 3. Synthesis of activated angolosamine synthons **13**, **14**, and **16**.



Scheme 4. Glycosylation experiments with angolosamine derivative **16**.



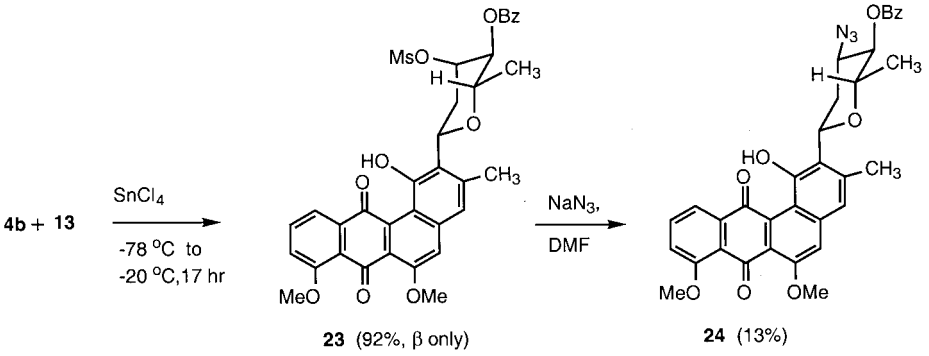
Scheme 5. Glycosylation of β-naphthol and of substrate **4b** with a 'neutral' sugar.

hydrogen bonding and we concluded that our attempts to couple **16** and **4b** were suffering from the combination of an unreactive reagent and an unreactive substrate.

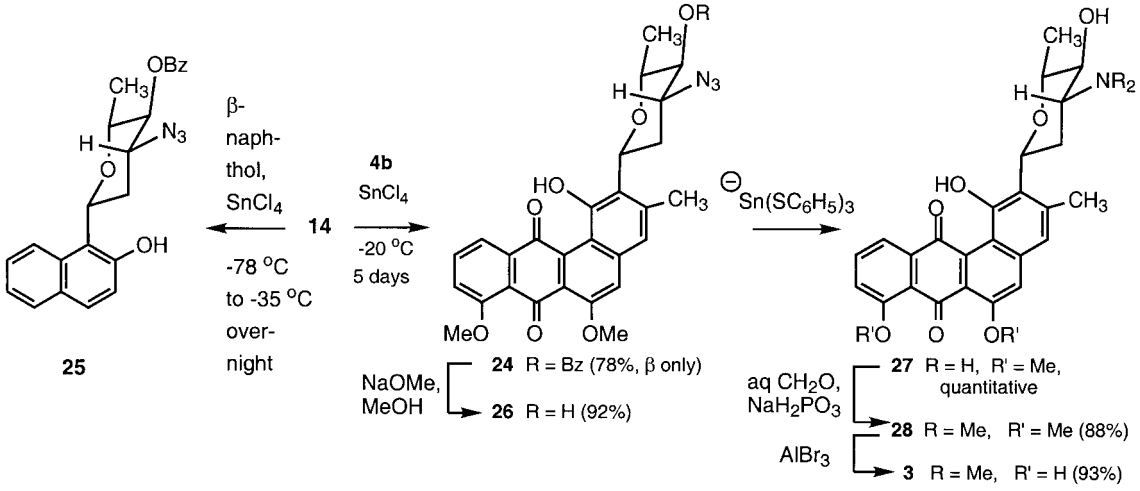
Assuming that glycosylation of **4b** with a 'neutral' sugar would be more feasible, we prepared the known olivose derivative **19**.[11] Although condensation was slow compared to that with β-naphthol (Scheme 5), this 'neutral' sugar and **4b**, in the presence of $SnCl_4$ at 0°C, afforded a relatively impressive 71% yield (total) of *C*- and *O*-glycosylation products, **21** and **22**.

The prospect of testing a synthetic equivalent of **16** in the glycosylation of **4b** then appeared particularly attractive as we had both intermediates **13** and **14** in hand. Mesylate **13** proved to be particularly reactive in coupling with substrate **4b**, providing a 92% yield of the β-*C*-glycoside in 2 h at −20° (Scheme 6). However, conversion of this product to the C-3′ azide **24** proceeded in poor yield and, although this transformation was not optimized, we regarded it as unpromising.

The desired **24** could be obtained more efficiently by the



Scheme 6. Efficient glycosylation of substrate **4b** with the mesyloxy sugar **13** and introduction of the C-3′ N by azide displacement.

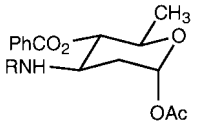


Scheme 7. Glycosylation of substrate **4b** with the azido sugar **14** and elaboration to benzanthrin pseudoaglycone **3** (D-glycoside).

direct coupling of substrate **4b** with the activated azido sugar **14** (Scheme 7). Although this glycosylation was much slower than the corresponding condensation of azido sugar **14** with β-naphthol, it afforded good yields of the advanced intermediate **24** after extended times at −25°.[12]

Completion of the synthesis of the benzanthrin pseudoaglycone **3** as the D-*C*-glycoside now required functional group manipulation. Debenzoylation was accomplished with sodium methoxide in methanol affording **26**. Successful reduction of the azide group required the testing of a number of sets of conditions[13] but was neatly accomplished with the $SnCl_2$/thiophenol/triethylamine reagent.[14] *N*,*N*-Dimethylation of the primary amine **27** with NaH_2PO_3 and aqueous formaldehyde gave the dimethylamino compound **28**. Finally, unmasking of the phenolic hydroxyl groups with aluminum bromide gave the pseudoaglycone of the benzanthrins (**3**) as the D-*C*-glycoside.

At this juncture, an observation and an final comment are appropriate. First, our studies of β-naphthol and our benzanthrin intermediate **4b** indicate the relative reactivities of the 2,3,6-trideoxy 3-amino pyranose equivalents to be **13** (3′-OMs)>**19** (3′-OBz)>**14** (3′-N_3)>**16** (3′-NMe_2). Thus 3-azido 2,3-dideoxy sugars can be considered to be reactive surrogates for 3-amino 2,3-dideoxy sugars in electrophilic susbstitution reactions. Also, in experiments with substrate **4b**, neither trifluoroacetamide **29** nor urethane **30** afforded more than trace amounts of *C*-aryl glycoside.



29 R = $COCF_3$

30 R = CO_2Me

In conclusion, benzanthrin pseudoaglycone **3**, D-*C*-glycoside, was prepared from the readily accessible hatamarubigin A dimethyl ether **4b** in 59% overall yield by a 5-step sequence in which the crucial *C*-aryl glycosylation utilized a 3-azido-2,3,6-trideoxy sugar.

Experimental

Melting points were taken on a Thomas–Hoover capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1600 series FT-IR. ^1H and ^{13}C NMR spectra were recorded on either a Bruker WM 250 or a Bruker AM 400 WB instrument. Ether refers to diethyl ether. All reactions were conducted under an atmosphere of N_2 unless otherwise indicated.

1-Hydroxy-3-methyl-6,8-dimethoxy-benz[*a*]anthracene-7,12-dione (4b). To a stirred solution of 6-*O*-methyl hatomarubigin A[5] (70 mg, 0.20 mmol) in 3 mL of methylene chloride were added at −40°C triethylamine (40 mg, 55, 0.40 mmol) and trimethylsilyl trifluoromethanesulfonate (53 mg, 46 mL, 0.26 mmol). The reaction was quenched 15 min later with the addition of saturated $NaHCO_3$ and the mixture was extracted with methylene chloride. The organic phase was dried over Na_2SO_4 and concentrated to yield a yellow solid. This material was immediately dissolved in dry acetonitrile and the solution was treated with palladium (II) acetate (54 mg, 0.24 mmol). After stirring at room temperature overnight, solvent was removed and the residue was chromatographed (2% ether/methylene chloride) to yield 57 mg (82%) of a dark red solid. IR($CHCl_3$) 1675, 1589 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44 (s, 3H), 4.03 (s, 3H), 4.04 (s, 3H), 6.95 (s, 1H), 7.01 (s, 1H), 7.26 (d, 1H, *J*=8.4 Hz), 7.49 (s, 1H), 7.63 (t, 1H, *J*=8.4 Hz), 7.75 (d, 1H, *J*=8.4 Hz), 10.96 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 56.7, 56.8, 115.3, 117.3, 117.4, 118.4, 119.5, 120.1, 123.2, 131.5, 132.7, 134.5, 136.8, 139.4, 141.6, 154.5, 155.0, 158.1, 183.4, 192.0. HRMS calcd for $C_{21}H_{16}O_5$ 348.0997, found 348.0987.

Methyl 4-*O*-benzoyl-3-*O*-methanesulfonyl-2,6-dideoxy-α-D-*ribo*-hexopyranoside (11).[9] A solution of methyl hexopyranoside **10** (4.62 g, 10.94 mmol) in methanol (120 mL) containing Raney nickel (15 mL, 50% slurry in water) and triethylamine (1 mL) was hydrogenated at room temperature for 12 h. The solid was filtered off and washed with methanol and methylene chloride. The filtrate was concentrated and the residue was partitioned between methylene chloride and water. The organic layer was dried with sodium sulfate and concentrated to give the pure product (3.62 g, 96%). ^1H NMR ($CDCl_3$) δ 1.26 (d, 3H, *J*=6.3 Hz), 2.15 (m, 1H), 2.30 (dd, 1H, *J*=15.2, 3.0 Hz), 2.96 (s, 3H), 3.39 (s, 3H), 4.40 (m, 1H), 4.75 (d, 1H, *J*=4.2 Hz), 4.81 (dd, 1H, *J*=9.8, 3.1 Hz), 5.18 (q, 1H, *J*=3.0 Hz), 7.46 (t, *J*=7.5 Hz, 2H), 7.60 (t, 1H, *J*=7.5 Hz), 8.04 (d, 2H, *J*=7.5 Hz).

4-*O*-Benzoyl-3-*O*-methanesulfonyl-2,6-dideoxy-β-D-*ribo*-hexopyranose (12). A solution of methyl hexopyranoside **11** (1.01 g, 2.94 mmol) in aqueous acetic acid (80%, 23 mL) containing 2N HCl (6 mL) was stirred at reflux for 1.5 h. The mixture was cooled and the reaction was quenched with sodium bicarbonate. The mixture was extracted with methylene chloride and the organic layer was dried with sodium sulfate and concentrated below room temperature. The residue was filtered through a short column of silica gel to yield a colorless oil (810 mg, 84%). IR ($CDCl_3$) 3356, 1725, 1602, 1452, 1365, 1265, 1179 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.43 (d, 3H, *J*=6.0 Hz), 1.6 (s, OH?), 1.91 (m, 1H), 2.40 (dm, 1H, *J*=≈12 Hz), 2.90 (s, 3H), 4.15 (m, 1H), 4.80 (dd, 1H, *J*=10.0, 3.0 Hz), 5.25 (m, 2H), 7.46 (t, 2H, *J*=7.5 Hz), 7.60 (t, 1H, *J*=7.5 Hz), 8.0 (d, 2H, *J*=7.5 Hz).

Acetyl 4-*O*-benzoyl-3-*O*-methanesulfonyl-2,6-dideoxy-β-D-*ribo*-hexopyranoside (13). Methyl hexopyranoside **11** (1.03 g) was dissolved in aqueous acetic acid (80%, 5 mL) and the mixture was stirred at reflux for 40 min. The solution was then cooled and neutralized with saturated sodium bicarbonate solution. The mixture was extracted with methylene chloride and the organic phase was dried (sodium sulfate) and concentrated to yield an off-white solid. The solid was immediately dissolved in pyridine (2.5 mL) and acetic anhydride (1 mL) was added at 0°C. The resulting mixture was stirred at 0°C for 14 h. The excess pyridine was removed at reduced pressure and the residue was subjected to column chromatography (50% ethyl acetate

in hexanes) to give 970 mg (87%) of an off-white solid. IR ($CDCl_3$) 1726 cm^{-1} ^1H NMR ($CDCl_3$) δ 1.32 (d, 3H, J=6.3 Hz), 2.13 (s, 3H), 2.10–2.20 (dm, 1H, J=≈12 Hz), 2.48 (m, 1H), 2.95 (s, 3H), 4.25 (m, 1H), 4.84 (dd, 1H, J=9.5, 9.5 Hz), 5.37 (m, 1H), 6.10 (dd, 1H, J=9.4, 2.2 Hz), 7.41 (t, 2H, J=7.5 Hz), 7.52 (t, 1H, J=7.5 Hz), 8.10 (d, 2H, J=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 17.8, 21.0, 35.4, 38.5, 69.1, 72.0, 75.3, 89.9, 128.6, 129.3, 129.7, 137.7, 165.5, 168.9. HRMS calcd for $C_{16}H_{20}SO_8$ 372.0879, found 372.0881.

Azido hexopyranoside 14. Acetyl hexopyranoside **13** (300 mg, 0.81 mmol), sodium azide (80 mg, 1.23 mmol) and DMF (3 mL) were combined and the mixture was stirred at 75°C for 34 h. The mixture was cooled and poured into water and extracted with benzene. The benzene extracts were dried with sodium sulfate and concentrated to yield a viscous oil which was passed through a short pad of silica gel (33% ethyl acetate and hexanes as eluent). Concentration of the filtrate gave a pale yellow oil (23 mg, 91%). [a]^{25}D=−26° (c=0.1, $CHCl_3$); IR ($CDCl_3$) 2103, 1762, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (d, 3H, J=6.2 Hz), 1.81 (q, 1H, J=10 Hz), 2.15 (s, 3H), 2.31 (dm, 1H, J=≈10 Hz), 3.71 (m, 1H), 4.91 (dd, 1H, J=9.6, 9.6 Hz), 5.80 (dd, 1H, J=10, 2.2 Hz), 7.45 (m, 2H), 7.58 (t, 1H, J=7.5 Hz), 8.04 (d, 2H, J=7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 17.5, 21.0, 35.0, 59.7, 72.0, 74.8, 91.4, 128.5 (2 C), 129.1, 129.8 (2 C), 133.5, 165.5, 169.0.

Dimethylamino hexopyranoside 16. To a stirred solution of the azido sugar **14** (3 mg, 9 mmol) in dry ethyl acetate (2 mL), palladium on activated carbon (10%) was added and the mixture was hydrogenated at room temperature for 30 min. The catalyst was filtered off and the filtrate was concentrated. The residue was immediately dissolved in acetonitrile (2 mL) and treated with aqueous formaldehyde (37%, 17.2 mL) and sodium cyanoborohydride (4 mg). After the mixture was stirred for 15 min, acetic acid was added to make the solution close to neutral (checking with a piece of wet pH paper). The reaction was continued for an additional 40 min and quenched with saturated sodium bicarbonate. The mixture was extracted with methylene chloride and the organic phase was dried and concentrated to yield a white crystal, 3 mg (quantitative). IR ($CDCl_3$) 1720, 1602, 1269 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (d, 3H, J=6.2 Hz), 1.52 (m, 1H), 2.05 (m, 1H), 2.14 (s, 3H), 2.27 (s, 6H), 2.90 (m, 1H), 3.60 (dd, 1H, J=9.2, 6.2 Hz), 4.90 (dd, 1H, J=9.8, 9.8 Hz), 5.78 (dd, 1H, J=9.7, 2.2 Hz), 7.42–7.48 (t, 2H, J=7.5 Hz), 7.55 (t, 1H, J=7.5 Hz), 8.02 (d, 2H, J=≈7 Hz); HRMS calcd for $C_{17}H_{23}NO_5$ 321.1576, found 321.1579.

Dimethylamino *C*-aryl glycoside 17.[8] To a stirred solution of 2-naphthol (29 mg, 0.20 mmol) in 1 mL of methylene chloride containing tin (IV) chloride (0.31 mL, 1 M solution in methylene chloride, 0.30 mmol) at −78°C, sugar **16** (32 mg, 0.1 mmol) in 0.5 mL of methylene chloride was added and the mixture was gradually warmed to rt and stirred overnight. The reaction was quenched with sat. sodium bicarbonate and the resulting mixture was extracted with methylene chloride. The solvent was removed and the residue was chromatographed (10% ether in methylene chloride) to give a viscous oil (35 mg, 86%). IR ($CDCl_3$) 3343, 1716, 1622, 1602 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.41 (d, 3H, J=6.2 Hz), 2.05 (m, 1H), 2.23 (m, 1H), 2.31 (s, 6H), 3.40 (m, 1H), 3.90 (m, 1H), 5.16 (dd, 1H, J=10, 10 Hz), 5.53 (dd, 1H, J=2, 11.4 Hz), 7.13 (d, 1H, J=8.8 Hz), 7.30 (t, 1H, J=8.7 Hz), 7.47 (t, 3H, J=≈6 Hz), 7.60 (t, 1H, J=≈6 Hz), 7.72 (t, 2H, J=9.6 Hz), 7.78 (d, 1H, J=6.9 Hz), 8.08 (d, 2H, J=≈7 Hz), 8.88 (s, 1H).

***C*-Aryl glycoside (20).** To a stirred solution of 2-naphthol (9 mg, 0.033 mmol), 4 Å molecular sieves (50 mg) and tin (IV) chloride (1 M solution in methylene chloride, 0.08 mL) at −78°C, acetyl 3,4-di-*O*-benzoyl-2,6-dideoxy-a-D-arabino-hexopyranoside **19** (11 mg, 0.028 mmol) in 1.2 mL methylene chloride was added via a syringe. The mixture was stirred for 5 min at −78°C and then the temperature was gradually increased to −20°C during 40 min. The reaction was quenched with saturated sodium bicarbonate and the mixture was extracted with methylene chloride. The organic phase was dried with sodium sulfate and concentrated to give an oil (12 mg, 91%) after column chromatography (1:2 ethyl acetate and hexanes). ^1H NMR ($CDCl_3$) δ 1.47 (d, 3H, J=6.2 Hz), 2.28 (apparent q, 1H, J=≈11 Hz), 2.70 (dm, 1H, J=≈11 Hz), 4.03 (m, 1H), 5.43 (dd, 1H, J=9.6, 9.6 Hz), 5.63 (m, 1H), 5.70 (dd, 1H, J=11.7, 2.3 Hz), 7.11 (d, 1H, J=8.6 Hz), 7.24–7.60 (m, 8H), 7.75 (m, 3H), 7.85 (d, 2H, J=8.5 Hz), 8.02 (d, 2H, J=7.5 Hz), 8.72 (s, 1H).

***C*-Glycoside 21 and *O*-glycoside 22.** To a stirred solution of the dimethyl ether of dehydrorableomycin (**4b**, 13 mg, 0.037 mmol) in methylene chloride (1 mL) containing molecular sieves (4 Å) and tin (IV) chloride (1 M solution in methylene chloride, 0.1 mL) at −78°C, hexopyranoside **19** (13 mg, 0.034 mol) in 0.5 mL methylene chloride was added via a syringe and the temperature was gradually increased to 0°C. The reaction was continued at that temperature for 9 h before it was quenched with saturated sodium bicarbonate. The mixture was extracted with methylene chloride and the organic phase was dried with sodium sulfate and concentrated to yield a dark solid, which was chromatographed (80:1 methylene chloride and ether) to afford both the *C*-glycoside (11 mg, 45%) and the *O*-glycoside (6 mg, 26%). ***C*-Glycoside 21** IR ($CHCl_3$) 3450, 1766, 1723, 1675, 1591 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.38 (d, 3H, J=6.1 Hz), 2.33–2.62 (m, 2H), 2.63 (s, 3H), 3.90 (m, 1H), 4.00 (s, 3H), 4.03 (s, 3H), 5.35 (dd, 1H, J=9.5, 9.5 Hz), 5.50 (m, 2H), 7.13 (s, 1H), 7.24–7.55 (m, 8H), 7.95 (d, 2H, J=7.0 Hz), 8.05 (d, 2H, J=7.1 Hz), 10.71(s, 1H). ^{13}C NMR ($CDCl_3$) δ 18.2, 21.3, 35.0, 56.45, 56.5, 73.2, 73.7, 75.0, 75.1, 115.4, 115.5, 117.6, 119.4, 121.6, 122.9, 123.0, 128.25–128.3 (2 C), 129.6–129.7 (2 C), 130.1, 133.0, 133.2, 134.0, 134.1, 136.8, 137.7, 139.5, 152.7, 154.7, 158.0, 165.9, 170.0, 183.0, 190.8. HRMS calcd for $C_{41}H_{34}O_{10}$ 686.2152, found 686.2148. ***O*-Glycoside 22, α- and β-anomers,** ratio ≈3: 1, IR($CHCl_3$) 1762, 1724, 1674, 1592 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.84 major and 1.15 minor (d, J=7.0 Hz and d, J=7.0 Hz, total 3H), 2.10 (m, 1H), 2.20 minor and 2.60 major (s and s, total 3H), 2.68 (m, 1H), 3.50 (m, 1H), 4.00 (m, 1H), 4.01(s, 3H), 4.02 (s, 3H), 5.10 major and 5.22 minor (bs and m, 1H total), 5.75 minor and 6.10 major (s and s, total 1H), 7.10–8.20 (m, 15H).

Methanesulfonyl *C*-aryl glycoside 23. To a stirred solution

of the aromatic compound **4b** (12 mg, 0.034 mmol), first tin (IV) chloride (1 M solution in methylene chloride, 0.12 mL, 3.5 equiv.) and then hexopyranoside **13** (18 mg, 0.034 mmol) were slowly added. The mixture was stirred at −78°C for 15 min and then it was gradually warmed to −20°C. The reaction was continued at this temperature until TLC (2.5% ether in methylene chloride) showed no aromatic starting material (17 h). The reaction was then quenched with sat. sodium bicarbonate and the mixture was extracted with methylene chloride. The organic phase was dried with sodium sulfate and concentrated to yield a dark red solid. Column chromatography (25% ether in methylene chloride) provided the *C*-glycoside (23 mg, 92%) as the β-anomer. IR($CDCl_3$) 3324, 1722, 1675, 1618, 1591, 1365, 1267 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (d, 3H, J=6.7 Hz), 2.30 (dm, 1H, J=≈12 Hz), 2.60 (s, 3H), 2.60–2.70 (m 2H), 3.05 (s, 3H), 4.10 (s, 3H), 4.11 (s, 3H), 4.20 (m, 1H), 5.03 (dd, 1H, J=10, 3 Hz), 5.41 (m, 1H), 5.78 (dd, 1H, J=11.8, 2 Hz), 7.12 (s, 1H), 7.22 (m, 1H), 7.38 (s, 1H), 7.50 (t, 2H, J=7.5 Hz), 7.60 (m, 2H), 7.65 (t, 1H, J=7.5 Hz) 8.10 (d, 2H, J=7.5 Hz), 10.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.2, 21.2, 29.3, 35.0, 38.8, 56.5, 70.4, 71.0, 73.0, 77.1, 115.3, 115.5, 117.6, 119.4, 121.5, 122.6, 122.9, 128.6, 129.3, 129.8, 130.1, 133.6, 134.0, 134.1, 136.8, 137.7, 139.5, 152.4, 154.8, 158.1, 165.7, 183.0, 190.7. HRMS calcd for $C_{35}H_{32}SO_{11}$ 660.1665, found 660.1671.

Azido *C*-aryl glycoside 24. To a stirred solution of the aromatic **4b** (15 mg, 42.5 mmol), 4 Å molecular sieves (80 mg) and tin (IV)chloride (0.15 mL, 1 M solution in methylene chloride) in 1 mL methylene chloride, acetyl azido sugar **14** in 1 mL of methylene chloride was added via a syringe. The mixture was kept at −78°C for 15 min and then gradually warmed to −20°C and then kept in the refrigerator (at approximately −20°C) for 5 days. The reaction was quenched by the addition of saturated sodium bicarbonate and the mixture was extracted with methylene chloride. The organic layer was dried with sodium sulfate and concentrated. The residue was subject to thin layer chromatography (2% ether in methylene chloride) to provide three compounds. The first component proved to be unreacted aromatic **4b** (3 mg). The second component was *C*-glycoside **24** (16 mg, 78%, dark red) and the third component was *para*-*C*-glycoside **24′** (2.4 mg, 12%, dark red). Spectra of ***ortho*-*C*-glycoside 24:** IR (CD_2Cl_2) 3333, 2104, 1727, 1678, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (d, 3H, J=6.1 Hz), 2.20–2.31 (m, 2H), 2.64 (s, 3H), 3.78 (m, 1H), 3.95 (m, 1H), 4.00 (s, 3H), 4.02 (s, 3H), 5.04 (dd, 1H, J=9.6, 9.6 Hz), 5.52 (dd, 1H, J=11.2, 2.2 Hz), 7.16 (s, 1H), 7.30 (d, 1H, J=8.3 Hz), 7.51 (s, 1H), 7.53 (m, 2H), 7.62 (m, 3H), 8.10 (d, 2H, J=7.5 Hz), 10.96 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.3, 21.5, 35.0, 56.7, 56.8, 62.4, 74.2, 75.8, 76.3, 115.7, 116.2, 118.2, 119.8, 122.1, 123.2, 123.8, 128.9. 130.0 (2 C), 130.1, 131.3 (2 C), 133.7, 133.8, 134.5, 137.1, 138.0, 140.2, 152.2, 154.9, 158.2, 166.1, 183.1, 191.5. Spectra for the ***para*-*C*-glycoside 24′** IR(CD_2Cl_2) 2103, 1727, 1676, 1588 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (d, 3H, J=6.1 Hz), 2.15 (m, 2H), 2.49 (s, 3H), 3.80 (m, 2H), 4.00 (s, 3H), 4.11 (s, 3H), 5.05 (dd, 1H, J=9.6, 9.6 Hz), 5.23 (dd, 1H, J=11.9, 2.7 Hz), 6.90 (s, 1H), 7.25 (d, 1H), 7.40 (m, 2H), 7.52 (m, 2H), 7.71 (m, 1H), 8.07 (d, 2H, J=7.5 Hz), 8.77 (s, 1H), 10.55 (s, 1H).

***C*-Glycoside 25.** To a stirred solution of 2-naphthol (4.5 mg, 30 mmol) in methylene chloride (1 mL) containing tin (IV) chloride (1 M solution in CH_2Cl_2, 45 mmol) at 78°C was hexopyranoside **14** (5 mg, 15 mmol) with 1 mL methylene chloride. The mixture was stirred at −78°C for 10 min and then the temperature was gradually increased to −35°C and kept overnight. The reaction was quenched with saturated sodium sulfate and the mixture was extracted with methylene chloride. The organic phase was dried and concentrated to yield a solid, which gave a colorless solid after column chromatography (1:3 ethyl acetate and hexanes as eluent). 6 mg, 95%. IR ($CDCl_3$) 3368, 2102, 1728, 1624, 1602, 1524, 1264 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (d, 3H, J=6.2 Hz), 2.08 (m, 1H), 2.44 (dm, 1H, J=≈12 Hz), 3.88 (m, 2H), 5.10 (dd, 1H, J=9.7, 9.7 Hz), 5.56 (dd, 1H, J=11.5, 1.7 Hz), 7.11 (d, 1H, J=8.8 Hz), 7.32 (t, 1H, J=8.0 Hz), 7.40–7.78 (m, 7H), 8.07 (d, 2H, J=8.0 Hz), 8.60 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.1, 36.0, 61.1, 75.3, 76.4, 76.5, 113.7, 113.8, 120.0, 120.3, 123.1, 127.0, 128.6, 128.8, 129.1, 129.9, 130.3, 130.6, 133.6, 153.7, 165.6.

Azido *C*-glycoside 26. To the stirred solution of product **24** (10 mg, 16.5 mmol) in a mixture of methanol and THF (4:1, 6 mL), sodium methoxide (20 mg) was added and the mixture was stirred at room temperature for 30 h. The solvent was removed at reduced pressure and the residue was partitioned between methylene chloride and diluted hydrochloric acid (0.1N). The organic phase was dried (sodium sulfate) and concentrated to give a dark solid, which was passed through a short column of silica gel to yield the pure product. IR(CD_2Cl_2) 2105, 1680, 1590, 1279 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (d, 3H, J=6.2 Hz), 2.00 (m, 2H), 2.55 (s, 3H), 3.15 (m, 1H), 3.40 (m, 1H), 3.50 (m, 1H), 3.99 (s, 3H), 4.01(s, 3H), 5.32 (dd, 1H, J=2.0, 10.5 Hz), 7.13 (s, 1H), 7.27 (m, 1H), 7.41 (s, 1H), 7.64 (m, 2H), 10.58 (s, 1H); ^{13}C ($CDCl_3$) δ 18.4, 21.3, 34.8, 56.7, 56.8, 64.9, 74.4, 76.3, 77.3, 115.4, 115.6, 118.0, 119.4, 121.7, 123.4 (2 C), 130.5, 134.5 (2 C), 137.3, 138.0, 139.8, 152.3, 155.0, 158.3, 182.9, 190.9; HRMS calcd for $C_{27}H_{25}N_3O_7$ 503.1625, found 503.1627.

Amino *C*-glycoside 27. A solution of azido *C*-glycoside **26** (6 mg, 0.012 mmol) in 0.5 mL tin (II) chloride solution (prepared by dissolving 285 mg $SnCl_2$, 0.62 mL thiophenol and 0.62 mL triethylamine in 10 mL THF) was stirred at room temperature for 20 min before another 0.30 mL of the tin (II) chloride solution was added. The reaction was continued for another 50 min before it was quenched with 1N NaOH solution. The pH was adjusted to 9.5 with 0.5N HCl solution and the mixture was extracted with methylene chloride. The organic phase was dried with sodium sulfate and concentrated to yield a dark solid, which was passed through a short silica gel column, eluted first with methylene chloride to get rid of the thiophenol and then with 15% methanol in methylene chloride to give a dark solid (5.7 mg, 98%). IR ($CDCl_3$) 3295, 1673, 1619, 1591, 1382, 1277, 1235, 1075 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (d, 3H, J=6.0 Hz), 2.1 (m, 2H), 2.40 (s, 3H), 3.10 (m, 1H), 3.20 (dd, 1H, J=9.7, 8.9 Hz), 3.52 (m, 1H), 4.10 (s, 3H), 4.11 (s, 3H), 5.24 (d, 1H, J=9.6 Hz), 7.10 (s, 1H), 7.20 (d, 1H, J=8.2 Hz), 7.30 (s, 1H), 7.50 (m, 2H); ^{13}C ($CDCl_3$) δ 19.1, 21.4, 40.4, 55.3, 56.6, 56.7, 75.7, 77.8, 112.9, 114.5, 116.5, 117.6, 119.7, 121.6, 122.6, 127.6, 133.2, 134.8,

136.5, 136.6, 137.9, 151.1, 153.6, 156.8, 180.7, 187.6. HRMS calcd for $C_{27}H_{27}NO_7$ 477.1788, found 477.1782.

Dimethylamino *C*-glycoside 28. The above primary amine **27** (6 mg, 0.0123 mmol) was dissolved in 1,4-dioxane (0.5 mL) and treated with formaldehyde (20 mL) and an aqueous solution of NaH_2PO_3 (1N, 0.5 mL). The mixture was stirred at 60°C for 5 h and the reaction was quenched with 0.5N NaOH solution. The mixture was extracted with methylene chloride and the organic phase was dried with sodium sulfate and then concentrated. The residue was passed through a short column of silica gel and washed with 15% methanol in methylene chloride to give a dark orange solid (5.3 mg, 88%) IR ($CDCl_3$) 3294, 1674, 1621, 1591, 1278, 1074 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (d, 3H, J=6.0 Hz), 1.92 (m, 2H), 2.30 (d, 1H, OH, J=8.5 Hz), 2.42 (s, 6H), 2.53 (s, 3H), 2.80 (m, 1H), 3.30 (dd, 1H, J_1=9.5 Hz, J_2=9.0 Hz), 3.51 (m, 1H), 4.01 (s, 3H), 4.07 (s, 3H), 5.27 (dd, 1H, J_1=10.0, 3.3 Hz), 7.10 (s, 1H), 7.24 (d, 1H, J=8 Hz), 7.34 (s, 1H), 7.60 (dd, 1H, J=8.0, 7.9 Hz), 7.67 (d, 1H, J=7.9 Hz), 10.37 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.7, 21.1, 25.9, 40.3, 56.4, 56.5, 67.7, 71.4, 75.5, 77.2, 78.2, 114.2, 114.4, 115.4, 117.3. 118.9, 121.1, 123.0, 129.1, 134.1, 134.9, 137.1, 137.6, 138.9, 152.1, 154.8, 158.1, 182.8, 190.1; HRMS calcd for $C_{29}H_{31}NO_7$ 505.2101, found 505.2108.

Benzanthrin pseudoaglycone (3, D-*C*-glycoside). Dimethylamino *C*-glycoside **28** (6 mg, 0.012 mmoL) was treated with aluminum bromide (0.25 mL, 1 M solution in CH_2Br_2) solution at 0°C. The mixture was stirred at 0°C for 1 h and the reaction was quenched with saturated sodium bicarbonate. The mixture was extracted with methylene chloride (9 times). The organic phase was dried with sodium sulfate and concentrated to yield a dark green solid (5.3 mg, 93%). IR ($CDCl_3$) 1630, 1606, 1457.8, 1277 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (d, 3H, J=6.2 Hz), 2.00 (m, 2H), 2.35 (s, 6H), 2.53 (s, 3H), 2.70 (m, 1H), 3.20 (dd, 1H, J=10, 10 Hz), 3.42 (m, 1H), 5.20 (dd, 1H, J=9.7, 2.5 Hz), 7.00 (s 1H), 7.20 (m, 1H), 7.35 (s, 1H), 7.60 (m, 2H), 9.85 (s, 1H), 11.71 (s, 1H), 11.86 (s, 1H). HRMS calcd for $C_{27}H_{27}NO_7$ 477.1788, found 477.1782.

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2. Benzanthrin A was inactive in animal models for sarcoma, leukemia and lung tumors. See Ref. 1b above.

3. Only antibiotic C104 shares this structural feature. See Matsumoto, T.; Yamaguchi, H.; Suzuki, K. *Tetrahedron* **1997**, *53*, 16533–16544 and references therein.

4. For convenience, we have employed D-sugars in our synthetic studies.

5. See the previous paper in this series.

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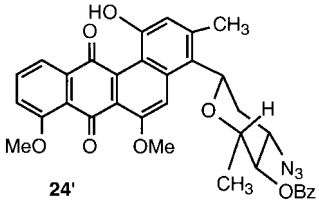
12. In this reaction, a small amount of the *para*-substituted *C*-glycoside **24′** was recovered along with traces of the tetracyclic starting material. Higher temperature (0°C) resulted in the production of larger amounts of 24′ and also decomposition products.



24'

13. (a) Chromium (II) chloride: Kondo, J.; Nakai, H.; Goto, T. *Tetrahedron*, **1973**, **29**, 1801. We had successfully employed this reagent for the reduction of the β-naphthol *C*-glycoside. However, with **26**, chromium (II) chloride reduces the quinone to hydroquinone and further reduction is sluggish. (b) Triphenyl phosphine, aqueous THF: Vaultier, M. Knouzi, N.; Carrie, R. *Tetrahedron Lett.* **1983**, *24*, 763–764. This reaction was slow and afforded numerous products. (c) Transfer hydrogenation over 5% Pd/C: Gartiser, T.; Selve, C.; Delpuech, J. J. *Tetrahedron Lett.* **1983**, *24*, 1609–1610. These conditions gave an unidentified product. (d) Hydrogenation over Lindlar catalyst: Corey, E. J.; Nicolaou, K. C.; Balanson, R. D.; Machida, Y. *Synthesis*, **1975**, 590–591. The reduction followed by *N*,*N*-dimethylation with formaldehyde and NaH_2PO_3 afforded 20% of the desired **28**.

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