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Synthesis Study on Marmycin A: Preparation of the C3′-Desmethyl Analogues

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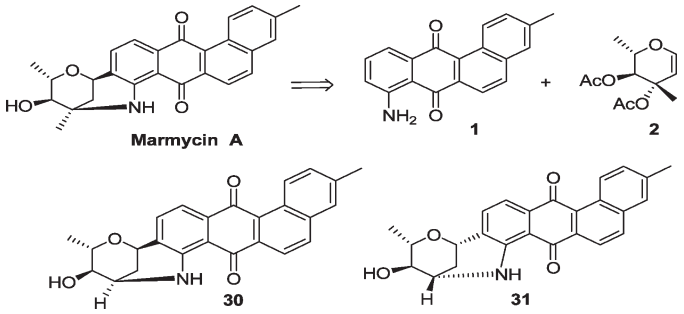

Total synthesis of natural product marmycin A was studied. An expeditious synthetic strategy for the key fragment 8-amino-3-methylbenz[*a*]anthraquinone (**1**) was established with decarboxylative alkylation, $Pd(OAc)_2$-catalyzed cyclization, aromatization, and C−N coupling as the key steps. However, final assembly of marmycin A was hampered by the failure to obtain the carbohydrate fragment **2**. Instead, a small library of desmethyl analogues of marmycin A was prepared in moderate yields by using the $InBr_3$-catalyzed *C*- and *N*-glycosidation reaction. The absolute configuration of these compounds was confirmed by comparison of their spectroscopic data with that reported for marmycin A, and by X-ray analysis.

Introduction

Angucyclines represent a relatively small class of *actinomycete bacteria*-originated natural products bearing a benz[*a*]anthracene skeleton and an *O*- or *C*-glycoside appendage (Figure 1).[1,2] Many of these compounds show good antibacterial activity along with some other biological activities, such as anticancer, antiviral, and enzyme inhibitory properties.[1,2] Such structural characteristics and multiple bioactivities have made angucyclines valuable targets for both synthetic and medicinal chemists.[2] Very recently, Fenical et al.[3] reported two new quinones of the angucycline family, marmycins A and B (Figure 1), using a bioassay-guided technique from the culture broth of a marine sediment-derived actinomycete related to the genus *Streptomyces*.

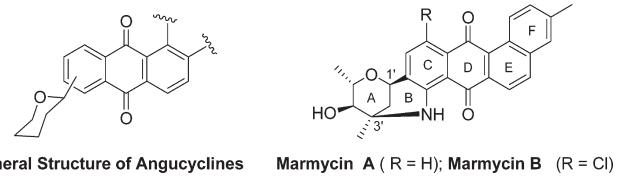

FIGURE 1. Chemical structures of angucyclines and marmycins A and B.

Compared to the general *C*-glycoside linkage in the previously reported angucyclines, marmycins A and B have unprecedented structural features containing both *C*- and *N*-glycoside bonds forming into a hexacyclic framework.

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(2) Krohn, K.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 127–195.
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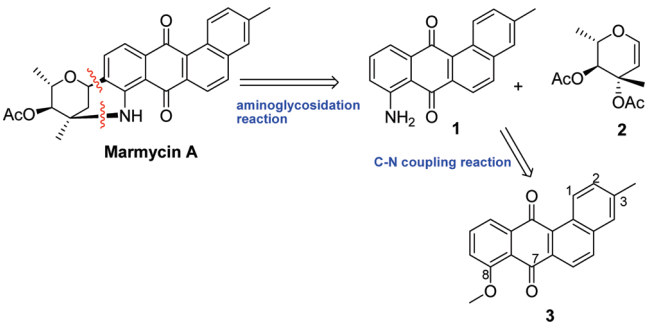


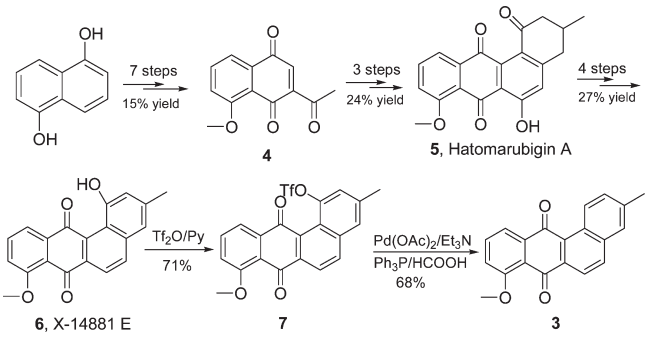
FIGURE 2. Retrosynthetic analysis of marmycin A.

More importantly, marmycin A was reported to have significant cytotoxicity against several cancer cell lines, especially human colon carcinoma cell line HCT-116 with an EC_{50} value of 60.5 nM.[3] The unusual structure features and potent cytotoxicity of marmycin A stimulated us to probe its total synthesis and that of related analogues in our drug design and discovery studies. Herein, we describe for the first time our efforts toward the total synthesis of marmycin A, and preparation of its C3′-desmethyl analogues.

Results and Discussion

The retrosynthetic analysis of marmycin A was outlined in Figure 2. The key steps include aminoglycosidation of aniline **1** and pyranose **2** to construct the *C*- and *N*-glycoside linkages in ring-B, and the C−N coupling reaction to convert intermediate **3** to aniline **1**. To determine the feasibility of this total synthesis approach, a convenient method to access anisole **3** is needed. Several approaches to construct the benzo[*a*]anthraquinone core of angucyclinone **3** have been reported, including Co^{2+}-mediated [2+2+2] cycloadditions,[4−6] Diels−Alder reactions,[7−17] anionic[18] and free radical benzannulation,[19,20] Friedel−Crafts[21,22] reactions, and rearrangement of cyclobutenones;[23] however, a practical strategy applicable to the direct synthesis of the angular skeleton of angucyclinone **3** is not available, except that early in 1995, Krohn et al.[24] reported that 8-methoxy-3-methylbenzo[*a*]anthraquinone **3** was obtained as a side product with extremely low yield during their synthesis of other angucyclinone natural products. In this regard, our first effort toward the total synthesis of marmycin A was focused on development of a convenient method for the synthesis of angucyclinone **3**.

SCHEME 1. Synthesis of 8-Methoxy-3-methylbenz-[*a*]anthraquinone 3



First, we employed a procedure reported by Parker et al.,[25] who successfully synthesized several natural antibiotics containing the angucyclinone tetracyclic nuclei (e.g., **5**, Hatomarubigin; **6**, X-14881 E). As shown in Scheme 1, acetyl naphthoquinone **4**[26,27] was prepared in seven steps from naphthalene-1, 5-diol in 15% overall yield by using a literature procedure. Michael addition of quinone **4** with 5-methyl-1,3-cyclohexandione followed by intramolecular aldol condensation provided the natural product **5**[25] in 24% overall yield. Dehydroxylation, enolation, and aromatization of quinone **5** yielded another natural antibiotic **6**[25] (X-14881 E), in 71% overall yield. Then, we developed a general procedure for conversion of natural product **6** to anisole **3**. Triflation of phenol **6** with Tf_2O and pyridine afforded triflate **7** in 71% yield, which was subsequently deoxygenated to afford 8-methoxy-3-methylbenzo[*a*]anthraquinone **3** under $Pd(OAc)_2/PPh_3/HCO_2H$ catalytic conditions[28] in 67% yield. Although this approach was straightforward and most of the chemical transformations had been reported, the long reaction sequence (16 steps from naphthalene-1,5-diol) and poor overall yield (0.47%) hampered us from collecting sufficient anthraquinone **3** for further synthetic exploration.

To find a shorter and more efficient synthetic approach for anthraquinone **3**, we decided to probe another synthetic pathway reported by Thomson et al.[29] in 1976, who successfully prepared several natural antibiotics including tetrangulol (*O*-demethylated product of **6**). Accordingly, 2-bromo-5-methoxy-1,4-naphthoquinone **10**[30] was prepared from 1, 5-diacetoxynaphthalene **8** via bromination,[31] deacetylation,

(4) Kalogerakis, A.; Groth, U. *Org. Lett.* **2003**, *5*, 843–844.
(5) Kalogerakis, A.; Groth, U. *Synlett* **2003**, 1886–1888.
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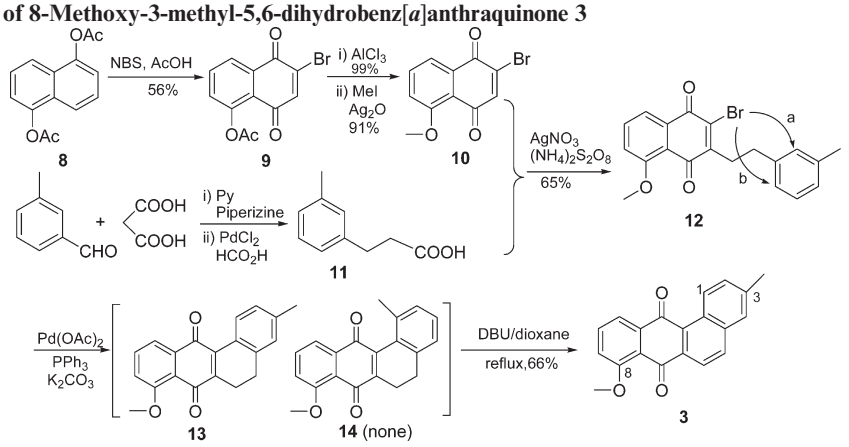
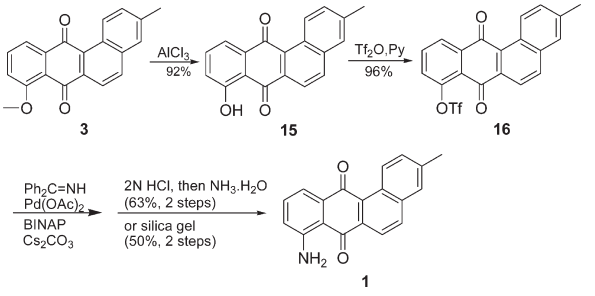
SCHEME 2. Synthesis of 8-Methoxy-3-methyl-5,6-dihydrobenz[*a*]anthraquinone 3



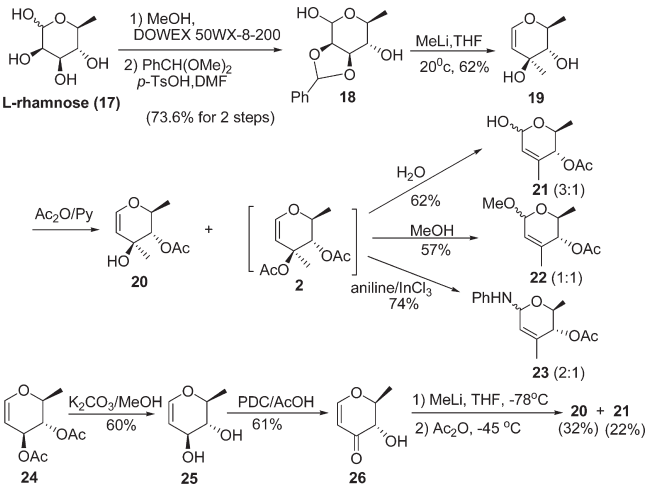
and *O*-methylation[30] in 50% overall yield, using a literature procedure (Scheme 2). *m*-Tolylpropanoic acid **11** was prepared in 91% yield by $PdCl_2$-catalyzed transfer hydrogenation[32] of (*E*)-*m*-tolylacrylic acid, which was readily prepared by Knoevenagel condensation of *m*-tolualdehyde and malonic acid in 86% yield. Following a procedure similar to that reported by Thomson,[29] treating bromide **10** and acid **11** with $AgNO_3$ and $(NH_4)_2S_2O_8$ induced a decarboxylative radical alkylation yielding the key intermediate **12**.

We initially attempted cyclization of 1,4-naphthoquinone **12** using a procedure reported by Thomson,[29] who used inorganic base (Na_2CO_3) as the promoter. However, reflux of the bromide **12** with aqueous Na_2CO_3 (2 N) only resulted a complex reaction mixture of several components probably due to the fact that cyclization of bromide **12** could occur via two regiochemically different pathways (path a and path b) potentially yielding regioisomers **13**, **14**, and/or their dehydrogenated aromatic analogues. To avoid the complexity of the cyclization and in view of the wide use of palladium catalysts in intramolecular arylation of halides,[33−36] we decided to employ $Pd(OAc)_2/PPh_3$ as the catalytic system to induce the cyclization. After several trials, we were pleased to find that treating our substrate (bromide **12**) with $Pd(OAc)_2$ (0.15 equiv), PPh_3 (0.3 equiv), and K_2CO_3 (3 equiv) in refluxing toluene for 12 h yielded the cyclization product **13** (path b) as the major product together with another minor product that was inseparable from quinone **13** by flash chromatography. This minor product was originally assumed to be the regioisomer **14** (path a), but a careful ^1H NMR examination of the mixture (4:1) indicated that it was the dehydrogenated aromatic compound, 8-methoxy-3-methylbenz[*a*]anthraquinone **3** whose H-1 proton displayed a typical chemical shift of 9.4 ppm in the 300 M ^1H NMR due to the deshielding effects of the neighboring C-12 carbonyl oxygen atom. Accordingly, the reaction mixture, without isolation, was treated directly with DBU[37] in refluxing 1,4-dioxane yielding anthraquinone **3** as the only product in 66% yield (two steps). The high regioselectivity of this cyclization is likely due to the steric effect between the methyl and carbonyl groups. Thus, by using this procedure, we succeeded in preparing compound **3** through six steps in 22% overall yield.

SCHEME 3. Synthesis of 8-Amino-3-methyl-5,6-dihydrobenz-[*a*]anthraquinone 1



SCHEME 4. Synthetic Efforts on Pyranose Diacetate 2



The conversion of anisole **3** to aniline **1** was straightforward as outlined in Scheme 3. Treating anisole **3** with $AlCl_3$[38] followed by triflation with Tf_2O and pyridine afforded triflate

(32) Arterburn, J. B.; Pannala, M.; Gonzalez, A. M.; Chamberlin, R. M. *Tetrahedron Lett*. **2000**, *41*, 7847–7849.
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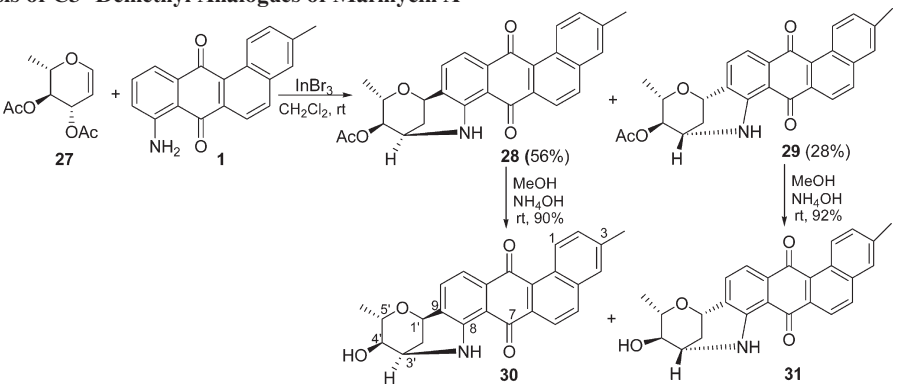
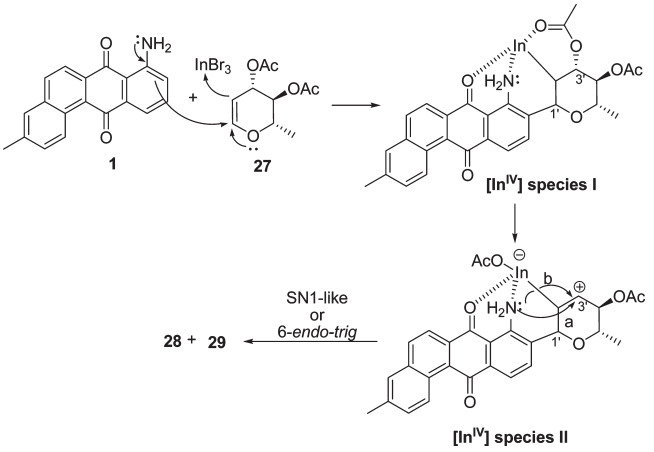
(38) Cui, J. R.; Jian, Y. J.; Wu, Y. K.; Wang, S. M. *Chin. J. Chem*. **2006**, *24*, 1163–1169.

SCHEME 5. Synthesis of C3′-Demethyl Analogues of Marmycin A



SCHEME 6. Possible Reaction Pathway



16 in 88% overall yield. $Pd(OAc)_2$-catalyzed amination of triflate **16** with benzophenone imine went smoothly,[39−41] and subsequent hydrolysis with 2 N HCl or direct treatment with silica gel provided 8-amino-3-methyl benz[*a*]anthraquinone **1** in 63% and 50% yield, respectively.

With the key intermediate **1** in hand, our next effort was directed to the synthesis of pyranose diacetate **2**, which is another key fragment for assembly of the natural product, marmycin A (Figure 1). By using a literature procedure,[42a,42b] diol **19** was prepared from L-rhamnose (**17**) in three steps with 43% overall yield (Scheme 4). The subsequent esterification was conducted by using a typical procedure (Ac_2O, Py) and two products were generated from TLC analysis. One of the products was determined as monoester **20**,[42b] which was further converted to another product by extending the reaction time (24 h). This product was assumed to be the diacetate **2**; however, its high instability made it impossible to isolate and a Ferrier-type rearrangement product was finally obtained. Interestingly, we found that the structure of the rearrangement product is dependent on the workup procedure. By using water to quench the reaction, water-involved Ferrier-rearrangement product **21** was obtained in 62% isolated yield with a α/β anomer ratio of 3:1 (determined by ^{1}H NMR). Similarly, MeO-participated rearrangement product **22** was obtained when the reaction was quenched by MeOH, a similar result reported by Parker[42c] and others.[43−46] Direct treatment of the reaction with aniline and a catalytic amount of $InCl_3$ (10%) led to a similar rearrangement product **23** in 74% yield. Alternatively, a tandem one-pot reaction of MeLi addition to ketone **26**[47a] followed by esterification was attempted by using a procedure reported by Fraser-Reid et al.[47b] Again, only monoester **20** and Ferrier-rearrangement product **21** were isolated in moderate yields, and no expected diester **2** was obtained.

In view of the instability of pyranose **2**, we decided to use the commercially available di-*O*-acetyl-L-rhamnal **27** as a replacement to explore the feasibility of construction of the *C*- and *N*-glycoside linkages in marmycin A and synthesis of a small library of desmethyl analogues for bioactivity screening.

In 2003, Yadav et al.[48] reported the first example of synthesis of heterocycles containing *C*- and *N*-glycoside linkage with the assistance of a stoichiometric amount of TMSOTf or a catalytic amount of $InBr_3$. On the basis of this result, we decided to prepare the C3′-desmethyl analogues of marmycin A by using a similar strategy.[48,49] We first used TMSOTf (1 equiv, rt) as the activator to initiate the reaction of aniline **1** and diacetate **27** (Scheme 5). To our surprise, this reaction took place very sluggishly and afforded the expected cyclization product **28** in only 7% yield after 12 h. No significant improvement was observed by extending the reaction time, and an even worse result (dark reaction mixture) was obtained when raising the reaction temperature (30−50 °C). Compared to the good yields in Yadav's reaction, the low yield in ours may be ascribed to the relatively reduced nucleophilicity of aniline **1** by the two carbonyl groups. Accordingly, a number of stronger Lewis acids were

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(40) Zhang, A.; Xiong, W.; Hilbert, J. E.; DeVita, E. K.; Bidlack, J. M.; Neumeyer, J. L. *J. Med. Chem.* **2004**, *47*, 1886–1888.
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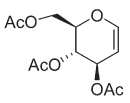
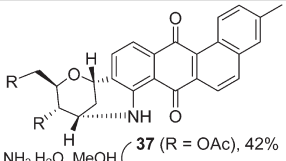
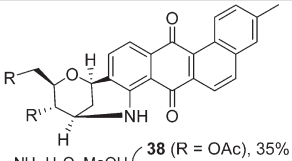
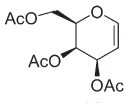
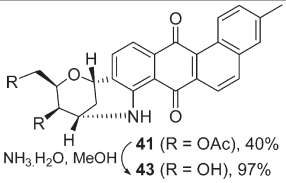
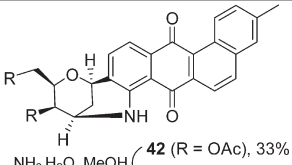
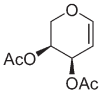
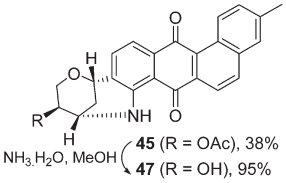
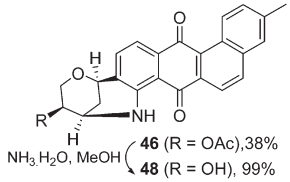
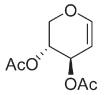
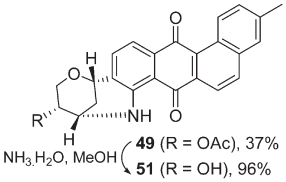
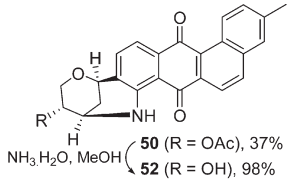
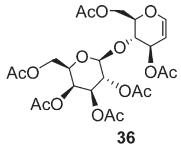
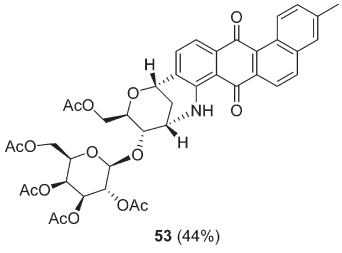
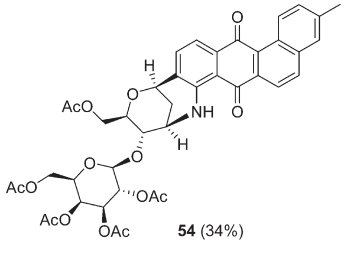
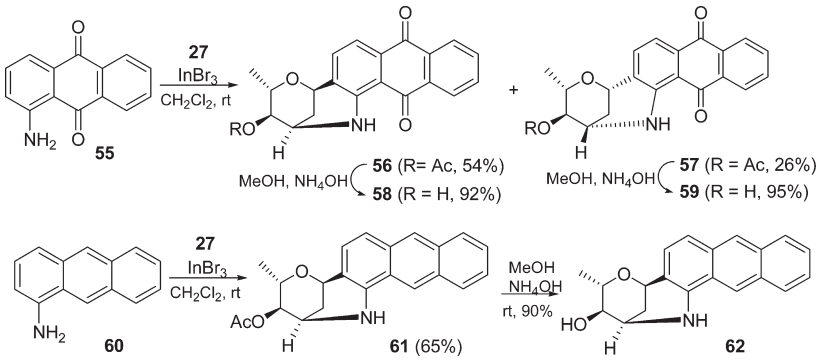
TABLE 1. Aminoglycosidation Reaction of Various Glycals 32−36 with Angucyclinone 1

Glycal	Products (yields)	
 **32**	 $NH_3.H_2O$, MeOH → **37** (R = OAc), 42%; **39** (R = OH), 96%	 $NH_3.H_2O$, MeOH → **38** (R = OAc), 35%; **40** (R = OH), 94%
 **33**	 $NH_3.H_2O$, MeOH → **41** (R = OAc), 40%; **43** (R = OH), 97%	 $NH_3.H_2O$, MeOH → **42** (R = OAc), 33%; **44** (R = OH), 98%
 **34**	 $NH_3.H_2O$, MeOH → **45** (R = OAc), 38%; **47** (R = OH), 95%	 $NH_3.H_2O$, MeOH → **46** (R = OAc),38%; **48** (R = OH), 99%
 **35**	 $NH_3.H_2O$, MeOH → **49** (R = OAc), 37%; **51** (R = OH), 96%	 $NH_3.H_2O$, MeOH → **50** (R = OAc), 37%; **52** (R = OH), 98%
 **36**	 **53** (44%)	 **54** (34%)

attempted to activate the reaction, including $CeCl_3$, $InCl_3$, $InBr_3$, $BF_3.OEt_2$, $AlCl_3$, TMSOTf, $La(OTf)_3$, and bis-(triphenyl)oxodiphosphonium trifluoromethanesulfonate (formed in situ from Ph_3PO and Tf_2O). To our delight, $InBr_3$ (10%) proved to be the best catalyst leading to a significant enhancement in production of compound **28** (56%). In addition, another steroisomer **29** was also isolated as the minor product (28%). It is of note that in Yadav's report,[48] only one product was isolated. The acetates **28** and **29** were treated with ammonia in MeOH affording angucyclines **30** and **31** in 90% and 92% yield, respectively. These two compounds can be viewed as the immediate C3′-demethyl analogues of marmycin A. The spectroscopic data of compound **30** were in agreement with those of marmycin A. In the ^1H NMR of angucycline **30**, H-1′ and H-3′ protons showed multiplicity (br s) indicating their equatorial conformations, thus the carbohydrate component was assigned as a chair conformation. The *trans*-diaxial relationship between H-4′ and H-5′ was evidenced by their coupling constant of 9.6 Hz with chemical shifts of 3.41 and 3.21 ppm, respectively. The *C*- and *N*-glycoside linkage was ascertained by the ^{13}C NMR where C-8 and C-9 chemical shifts were 148.6 and 127.7 ppm, respectively. The optical rotation ($[\alpha]^{20}_D$) of compound **30** was +553 (*c* 0.038, THF), which was similar to that reported[48] for the natural product, marmycin A ($[\alpha]^{20}_D$ +520 (*c* 0.05, THF)).

Although additional study is needed to settle the exact mechanism, a tentative reaction pathway was proposed to rationalize our results on the basis of Yadav's analysis.[48] As shown in Scheme 6, the carbonyl group would competitively interact with Yadav's [In^{III}] complex,[48] which was formed between C′3-OAc of **27** and $InBr_3$, therefore a [In^{IV}] species **I**

SCHEME 7. Reaction of Anilines 55 and 60 with Diacetate 27



may be produced in our *C*- and *N*-glycosidation reaction. The activated leaving ability of 3′-OAc in this complex may promote the formation of a carbenium ion species II. Therefore, attack of the amino group to the C3′ might occur from both α- (path b) and *β*-face (*path a*) through a S_N1-like or 6-*endo-trig* process producing two diastereomers **28** and **29**. The poor stereoselectivity in the *C*-glycosidation step may account for the low diastereomeric excess of the products. The spectroscopic data of compound **31** were similar to those of **30**. However, the CD spectrum of compound **31** showed opposite Cotton effects compared to its isomer **30** indicating the opposite stereochemistry of the two carbons (C1′, C3′) adjacent to the aromatic system (see the Supporting Information).

To extend the reaction scope and to construct a small library of desmethyl analogues of marmycin A, several different glycals including tri-*O*-acetyl-D-glucal **32**, tri-*O*-acetyl-D-galactal **33**, di-*O*-acetyl-L-arabinal **34**, di-*O*-acetyl-D-xylal **35**, and hexa-*O*-acetyl-D-lactal **36** were prepared from corresponding carbohydrates according to a literature procedure[50] and their aminoglycosidation with angucyclinone **1** was investigated. From the results summarized in Table 1, a catalytic amount of $InBr_3$ was found still to be the best activator and all reactions proceeded smoothly, affording two diastereoisomers. In all cases, the two diastereoisomers were obtained in roughly 1:1 ratios, slightly different from that observed from glycosidation of di-*O*-acetyl-L-rhamnal **27**, which gave the diastereoisomers **28** and **29** in 2:1 ratio. In the case of di-*O*-acetyl-L-arabinal **34** and di-*O*-acetyl-D-xylal **35**, the corresponding two cyclization products were obtained in 76% and 74% isolated yields, respectively, as a mixture (1:1) in which the two isomers were inseparable via flash column chromatography or preparative TLC; however, a good separation was achieved after deacetylation. In the case of hexa-*O*-acetyl-D-lactal **36**, the corresponding aminoglycosidation reaction also went smoothly and yielded the two diastereomers **53** and **54** in 44% and 34% yields, respectively. The subsequent deacetylated products were not further characterized due to the extremely poor solubility of these multihydroxyl products.

The absolute configuration of the aminoglycosidation products was further secured by the X-ray analysis of compounds **31** and **39** which were crystallized from $CHCl_3$ as reddish needle-like crystals (see the Supporting Information).

To confirm the influence of the carbonyl group in substrate **1** on the diastereoselectivity of the *C*- and *N*-glycosidation reaction, a model reaction was conducted (Scheme 7). The commercially available 1-aminoanthraquinone **55** and its reduced product **60** were used to mimic aniline **1** reacting with diacetate **27**. Similarly, $InBr_3$-catalyzed aminoglycosidation of aniline **55** with diacetate **27** under the same conditions yielded two diastereoisomers **56** and **57** in 54% and 26% yield, respectively. After *O*-deprotection, anthracyclines **58** and **59** were obtained in over 90% yields. Reduction[51] of 1-aminoanthraquinone **55** with $NaBH_4$/NaOH in *i*-PrOH afforded anthracen-1-amine **60** in 60% yield. Glycosidation of amine **60** with diacetate **27** under the same conditions provided anthracycline **61** as the only product in 65% yield, together with 25% of amine **60** recovered. Although this reaction took place somewhat slowly, no diastereoisomers were detected from TLC analysis, confirming the influence of the carbonyl group in substrates **55** and **1** on the diastereoselectivity of the glycosidation reaction.

In summary, the total synthesis of natural product marmycin A was studied. The synthesis of the key fragment, 8-amino-3-methylbenz[*a*]anthraquinone **1** was discussed, and an expeditious synthetic strategy starting from 2-bromo-5-methoxy-1,4-naphthoquinone **10** was established with decarboxylative alkylation, $Pd(OAc)_2$-catalyzed cyclization, aromatization, and C−N coupling as the key steps. However, the failure in obtaining the carbohydrate fragment, pyranose **2**, hindered our effort to directly assemble marmycin A. Instead, a series of non-methyl glycals were employed and their $InBr_3$-catalyzed Yadav's aminoglycosidation with angucyclinone **1** was conducted yielding two diastereoisomers in 2:1 to 1:1 ratios. Therefore, a small library of desmethyl analogues of marmycin A was obtained in moderate yields. The absolute configuration of these compounds was confirmed by comparison of their spectroscopic data with that reported for marmycin A, and by X-ray analysis of compounds **31** and **39**. Further efforts on development of alternative methods for the total synthesis of marmycin A, which contains a methyl-branched quaternary C3′ center as well as biological evaluation of the synthetic analogues, are underway.

Experimental Section

2-Bromo-5-methoxy-3-(3-methylphenethyl)naphthalene-1,4-dione (12). A mixture of 2-bromo-1,4-naphthoquinone **10**

(50) Shull, B. K.; Wu, Z.; Koreeda, M. *J. Carbohydr. Chem.* **1996**, *15*, 955–964.

(51) Dahan, A.; Ashkenazi, T.; Kuznetsov, V.; Makievski, S.; Drug, E.; Fadeev, L.; Bramson, M.; Schokoroy, S.; Rozenshine-Kemelmakher E, G. M. *J. Org. Chem.* **2007**, *72*, 2289–2296.

(0.637 mmol, 170 mg), phenoxyacetic acid **11** (1.0 mmol, 164 mg), and silver nitrate (0.201 mmol, 34 mg) in CH_3CN (10 mL) was heated at 80 °C under N_2. To this mixture was added dropwise within 5 min a solution of ammonium persulfate (1.34 mmol, 304 mg) in demineralized water (5 mL), and the resulting mixture was stirred at the same temperature for 1 h. The reaction was quenched with ice and extracted with CH_2Cl_2. The combined organic solution was washed with brine, dried (Na_2SO_4), and concentrated. The residue was subjected to chromatography with 25% EtOAc/petroleum ether as eluents to give the desired compound **12** as a yellow solid (159.5 mg, 65%), mp 138−141 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, 1H, J = 7.8 Hz), 7.67 (t, 1H, J = 7.8 Hz), 7.32 (d, 1H, J = 8.4 Hz), 7.18 (m, 3H), 7.03 (d, 1H, J = 6.9 Hz), 4.03 (s, 3H), 3.09 (m, 2H), 2.80 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 177.9, 159.9, 152.4, 140.7, 138.0, 136.2, 134.8, 133.2, 129.2, 128.3, 126.9, 125.4, 120.2, 119.1, 118.0, 56.5, 34.5, 33.7, 21.3; MS (EI-LR) 384 (M^+); HRMS (EI) calcd for $C_{20}H_{17}BrO_3$(M^+) 384.0361, found 384.0360.

8-Methoxy-3-methylbenz[*a*]anthraquinone (3).[24] A solution of bromide **12** (0.36 mmol, 140 mg) and $Pd(OAc)_2$ (0.054 mmol, 23 mg), PPh_3 (0.109 mmol, 28 mg), and K_2CO_3 (1.1 mol, 149 mg) in toluene (25 mL) was stirred at 80 °C for 30 min, and then refluxed for 12 h.[33−36] The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and evaporated in vacuo to afford a crude product, which was purified by chromatography to yield a mixture of **13** and **3** (78 mg) as a yellow powder. This mixture was heated (75 mg) with DBU[37] (523 mg, 3.4 mmol) in 1,4-dioxane (15 mL) for 10 h. After the solution was cooled to 0 °C, 2 N HCl (15 mL) was added. The mixture was extracted with CH_2C1_2. The combined extracts were washed with brine and dried over Na_2SO_4. Concentration in vacuo followed by purification by chromatography (hexane/EtOAc = 2:1) yielded the target compound **3**[24] as a yellow solid (60 mg, 66% yield for two steps), mp 195−198 °C (lit.[24] mp 196 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.41(d, 1H, J = 9.3 Hz), 8.24 (m, 1H), 8.01 (d, 1H, J = 8.7 Hz), 7.87 (m, 1H), 7.65 (m, 1H), 7.59 (s, 1H), 7.50 (d, 1H, J = 9.0 Hz), 7.25 (d, 1H, J = 7.8 Hz), 4.03 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.1, 183.1, 159.5, 138.6, 137.3, 136.3, 134.8, 134.4, 131.9, 128.0, 127.9, 127.6, 122.7, 120.3, 119.6, 116.9, 56.4, 21.4; MS (EI-LR) 302 (M^+).

General Procedure for $InBr_3$-Catalyzed *C*- and *N*-Glycosidation of Glycals (27 and 33−36) and Aryl Amines (1, 55, and 60). A mixture of an appropriate glycal (0.17 mmol), aniline **1** (50 mg, 0.17 mmol), and $InBr_3$ (6.2 mg, 0.017 mmol) in the dried CH_2Cl_2 (8 mL) was stirred at 27 °C under N_2 for 12 h. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography on silica gel (EtOAc/hexane 1:5) to afford the corresponding cycloadducts.

***O*-Acetyl-L-rhamnoside 28:** reddish solid (56%), mp 220 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (d, 1H, J = 3.9 Hz), 9.51 (d, 1H, J = 9.0 Hz), 8.29 (d, 1H, J = 8.4 Hz), 8.02 (d, 1H, J = 9.0 Hz), 7.60 (s, 1H), 7.50 (m, 3H), 4.79 (br s, 1H), 4.66 (dd, 1H, J = 2.7, 9.9 Hz), 4.06 (br s, 1H), 3.50 (dq, 1H, J = 5.7, 10.2 Hz), 2.51 (s, 3H), 2.34 (d, 1H, J = 12.9 Hz), 2.16 (s, 3H), 1.99 (dd, 1H, J = 3.0, 13.5 Hz), 1.12 (d, 3H, J = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.2, 185.4, 170.3, 148.5, 138.5, 136.4, 136.3, 135.9, 134.5, 134.3, 131.9, 128.5, 128.3, 128.1, 127.5, 126.9, 122.2, 115.7, 111.3, 77.2, 68.2, 65.4, 46.3, 27.6, 21.5, 21.1, 17.8; MS (EI-LR) 441 (M^+); HRMS (EI) calcd for $C_{27}H_{23}NO_5$ (M^+) 441.1576, found 441.1581.

***O*-Acetyl-L-rhamnoside 29:** reddish solid (28%), mp 210 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.06 (d, 1H, J = 4.8 Hz), 9.53 (d, 1H, J = 9.3 Hz), 8.32 (d, 1H, J = 8.7 Hz), 8.05 (d, 1H, J = 9.0 Hz), 7.63 (s, 1H), 7.51 (m, 3H), 4.94 (d, 1H, J = 3.9 Hz), 4.64 (d, 1H, J = 5.1 Hz), 3.85 (m, 2H), 2.59 (m, 1H), 2.52 (s, 3H), 2.15 (s, 3H), 1.73 (m, 1H), 1.07 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.3, 185.4, 170.2, 145.8, 138.5, 136.4, 136.3, 134.6, 134.3, 134.1, 131.9, 130.2, 128.7, 128.4, 128.2, 127.6, 122.3, 115.7, 111.9, 77.4, 67.3, 67.0, 46.5, 21.8, 21.5, 21.1, 20.0; MS (EI-LR) 441 (M^+); HRMS (EI) calcd for $C_{27}H_{23}NO_5$ (M^+) 441.1576, found 441.1582.

Di-*O*-acetyl-D-glucoside 37: reddish solid (42%), mp 185−187 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (d, 1H, J = 3.9 Hz), 9.54 (d, 1H, J = 8.7 Hz), 8.33 (d, 1H, J = 8.7 Hz), 8.08 (d, 1H, J = 8.4 Hz), 7.65 (s, 1H), 7.55 (m, 3H), 4.90 (m, 2H), 4.18 (m, 2H), 4.06 (dd, 1H, J = 2.1, 12.0 Hz), 3.61 (ddd, 1H, J = 2.4, 4.2, 10.2 Hz), 2.54 (s, 3H), 2.38 (dd, 1H, J = 1.5, 12.0 Hz), 2.16 (s, 3H), 2.06 (s, 3H), 2.01 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.2, 185.6, 170.8, 170.1, 148.3, 138.7, 136.8, 136.5, 136.2, 134.6, 134.4, 132.1, 128.7, 128.4, 128.2, 127.6, 126.1, 122.3, 115.9, 111.7, 70.7, 68.5, 67.9, 62.9, 46.2, 27.2, 21.5, 21.1, 20.8; MS (EI-LR) 499 (M^+); HRMS (EI) calcd for $C_{29}H_{25}NO_7$ (M^+) 499.1631, found 499.1639.

Di-*O*-acetyl-D-glucoside 38: reddish solid (35%), mp 171−173 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.04 (d, 1H, J = 5.4 Hz), 9.55 (d, 1H, J = 9 Hz), 8.35 (d, 1H, J = 8.7 Hz), 8.08 (d, 1H, J = 9.0 Hz), 7.66 (s, 1H), 7.55 (m, 3H), 4.99 (br s, 1H), 4.81 (br s, 1H), 3.94 (m, 3H), 3.79 (m, 1H), 2.57 (m, 4H), 2,16 (s, 3H), 1.98 (s, 3H), 1.75 (dd, 1H, J = 3.3, 13.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.3, 185.6, 170.6, 170.0, 145.7, 138.6, 136.6, 136.5, 134.8, 134.6, 134.4, 132.0, 129.2, 128.8, 128.5, 128.2, 127.7, 122.4, 115.9, 112.2, 72.3, 69.9, 67.3, 64.3, 45.8, 22.0, 21.6, 21.1, 20.8. MS (EI-LR) 499 (M^+); HRMS (EI) calcd for $C_{29}H_{25}NO_7$ (M^+) 499.1631, found 499.1637.

Di-*O*-acetyl-D-galactoside 41: reddish solid (33%), mp 220 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.90 (d, 1H, J = 5.1 Hz), 9.53 (d, 1H, J = 8.7 Hz), 8.32 (d, 1H, J = 8.1 Hz), 8.07 (d, 1H, J = 8.7 Hz), 7.65 (s, 1H), 7.58 (m, 3H), 4.93 (br s, 1H), 4.80 (br s, 1H), 4.18 (dd, 1H, J = 6.0, 11.1 Hz), 4.04 (m, 2H), 3.77 (m, 1H), 2.56 (m, 4H), 2.16 (s, 3H), 1.96 (s, 3H), 1.70 (d, 1H, J = 13.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.3, 185.7, 170.5, 170.1, 147.6, 138.7, 136.8, 136.6, 136.5, 134.5, 132.1, 128.7, 128.4, 128.2, 127.7, 126.0, 122.3, 116.0, 111.9, 69.1, 68.9, 66.7, 62.9, 45.0, 23.0, 21.5, 20.9, 20.7; MS (EI-LR) 499 (M^+); HRMS (EI) calcd for $C_{29}H_{25}NO_7$ (M^+) 499.1631, found 499.1634.

Di-*O*-acetyl-D-galactoside 42: reddish solid (40%), mp 220 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (d, 1H, J = 5.1 Hz), 9.55 (d, 1H, J = 9.0 Hz), 8.33 (d, 1H, J = 8.4 Hz), 8.07 (d, 1H, J = 9.0 Hz), 7.64 (s, 1H), 7.55 (m, 3H), 5.10 (t, 1H, J = 6.0 Hz), 4.92 (br s, 1H), 4.29 (m, 2H), 4.07 (dd, 1H, J = 4.8, 11.7 Hz), 3.77 (dd, 1H, J = 7.5, 11.7 Hz), 2.54 (s, 3H), 2.37 (dd, 1H, J = 1.8, 13.8 Hz), 2.11 (s, 3H), 1.96 (s, 3H), 1.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.3, 185.6, 170.5, 170.4, 146.3, 138.7, 136.7, 136.5, 135.1, 134.6, 134.4, 132.1, 129.0, 128.8, 128.5, 128.3, 127.6, 122.3, 115.9, 112.2, 71.1, 68.9, 66.7, 63.4, 44.2, 25.4, 21.5, 20.8, 20.7; MS (EI-LR) 499 (M^+); HRMS (EI) calcd for $C_{29}H_{25}NO_7$ (M^+) 499.1631, found 499.1635.

***O*-Acetyl-L-arabinosides 45 and 46:** reddish solid (76%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88 (d, 1H, J = 5.1 Hz, **45**), 9.82 (d, 1H, J = 3.9 Hz, for **46**), 9.53 (d, 1H, J = 9.3 Hz, for **45**), 9.51 (d, 1H, J = 8.7 Hz, for **46**), 8.30 (m, 2H, for **45**), 8.04 (m, 2H, for **46**), 7.62 (s, 2H), 7.52 (m, 6H), 5.01 (m, 1H), 4.83 (s, 1H), 4.79 (s, 1H), 4.69 (s, 1H), 4.07 (br s, 1H), 4.01 (br s, 1H), 3.79 (m, 2H), 3.54 (m, 1H), 3.20 (t, 1H, J = 11.1 Hz), 2.61 (d, 1H, J = 13.5 Hz, for **45**), 2.52 (s, 6H), 2.33 (d, 1H, J = 13.2 Hz, for **46**), 2,18 (s, 3H, for **45**), 2.12 (s, 3H, for **46**), 1.99 (m, 1H, for **46**), 1.69 (d, 1H, J = 6.0 Hz, for **45**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.3, 186.2, 185.6, 185.5, 170.3, 148.8, 147.7, 138.6, 136.7, 136.6, 136.5, 136.4, 136.2, 134.6, 134.5, 134.4, 134.3, 132.0, 128.7, 128.4, 128.2, 127.6, 126.3, 125.9, 122.3, 115.9, 115.7, 111.7, 111.4, 71.1, 69.9, 68.3, 67.6, 61.0, 59.2, 46.1, 44.6, 27.3, 23.6, 21.5, 21.2,

21.1; MS (EI-LR) 427 (M^+); HRMS (EI) calcd for $C_{26}H_{21}NO_5$ (M^+) 427.1420, found 427.1423.

***O*-Acetyl-D-xylosides 49 and 50:** reddish solid (74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.89 (d, 1H, J = 4.5 Hz, for **50**), 9.83 (d, 1H, J = 3.3 Hz, for **49**), 9.55 (d, 1H, J = 9.0 Hz, for **50**), 9.54 (d, 1H, J = 8.7 Hz, for **49**), 8.33 (d, 1H, J = 8.4 Hz, for **50**), 8.32 (d, 1H, J = 8.4 Hz, for **49**), 8.06 (d, 2H, J = 9.0 Hz), 7.64 (s, 2H), 7.53 (m, 6H), 5.01 (m, 1H), 4.84 (s, 1H), 4.80 (br s, 1H), 4.69 (br s, 1H), 4.08 (br s, 1H), 4.03 (br s, 1H), 3.80 (m, 2H), 3.54 (d, 1H, J = 12.9 Hz), 3.20 (t, 1H, J = 11.1 Hz), 2.62 (d, 1H, J = 12.6 Hz, for **50**), 2.53 (s, 6H), 2.34 (d, 1H, J = 13.2 Hz, for **49**), 2.18 (s, 3H, for **50**), 2.12 (s, 3H, for **49**), 2.00 (m, 1H, for **49**), 1.68 (d, 1H, J = 12.9 Hz, for **50**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.3, 186.2, 185.6, 185.5, 170.3, 170.2, 148.8, 147.7, 138.6, 136.7, 136.6, 136.5, 136.4, 136.1, 134.6, 134.5, 134.4, 134.3, 132.0, 128.7, 128.4, 128.2, 127.6, 126.3, 125.9, 122.3, 115.9, 115.7, 111.7, 111.4, 71.1, 69.9, 68.3, 67.6, 61.0, 59.2, 46.1, 44.6, 27.3, 23.6, 21.5, 21.2, 21.1; MS (EI-LR) 427 (M^+); HRMS (EI) calcd for $C_{26}H_{21}NO_5$ (M^+) 427.1420, found 427.1416.

Penta-*O*-acetyl-D-lactoside 53: reddish solid (44%), mp 136−138 °C; $[\alpha]^{20}_D$ −406 (*c* 0.064, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.90 (d, 1H, J = 3.6 Hz), 9.55 (d, 1H, J = 9.3 Hz), 8.34 (d, 1H, J = 9.0 Hz), 8.07 (d, 1H, J = 9.0 Hz), 7.66 (s, 1H), 7.56 (d, 2H, J = 7.5 Hz), 7.47 (d, 1H, J = 7.5 Hz), 5.47 (br s, 1H), 5.29 (m, 1H), 5.05 (m, 1H), 4.85 (br s, 1H), 4.67 (d, 1H, J = 7.8 Hz), 4.52 (d, 1H, J = 6.6 Hz), 4.34 (d, 1H, J = 6.3 Hz), 4.19 (m, 1H), 4.03 (m, 2H), 3.71 (d, 1H, J = 3.0, 9.9 Hz), 3.49 (m, 1H), 2.54 (s, 3H), 2.28 (s, 4H), 2.02 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.5, 185.0, 170.6, 170.5, 170.4, 170.1, 169.2, 148.3, 138.4, 136.8, 136.4, 136.0, 134.8, 134.4, 131.9, 128.6, 128.4, 128.2, 127.6, 125.9, 122.5, 115.3, 111.8, 101.4, 78.9, 70.9, 70.8, 68.6, 68.4, 68.3, 66.9, 63.2, 61.9, 47.1, 27.1, 21.5, 20.9, 20.8, 20.7, 20.5, 20.4; MS (EI-LR) 787 (M^+); HRMS (EI) calcd for $C_{41}H_{41}NO_{15}$ (M^+) 787.2476, found 787.2454.

Penta-*O*-acetyl-D-lactoside 54: reddish solid (34%), mp 130−133 °C; $[\alpha]^{20}_D$ +717 (*c* 0.046, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.06 (d, 1H, J = 4.8 Hz), 9.55 (d, 1H, J = 8.7 Hz), 8.31 (d, 1H, J = 8.4 Hz), 8.07 (d, 1H, J = 8.7 Hz), 7.65 (s, 1H), 7.55 (m, 2H), 7.46 (d, 1H, J = 7.8 Hz), 5.46 (d, 1H, J = 3.3 Hz), 5.27 (m, 1H), 5.03 (m, 2H), 4.61 (d, 1H, J = 8.1 Hz), 4.33 (m, 2H), 4.23 (br s, 1H), 4.08 (m, 2H), 3.74 (m, 2H), 3.61 (d, 1H, J = 5.1 Hz), 2.62 (d, 1H, J = 13.2 Hz), 2.54 (s, 3H), 2.20 (s, 6H), 2.09 (s, 3H), 2.00 (s, 6H), 1.71 (dd, 1H, J = 3.6, 14.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.2, 185.6, 170.7, 170.6, 170.2, 170.0, 169.7, 145.3, 138.6, 136.4, 136.3, 134.6, 134.4, 134.2, 132.0, 129.7, 128.8, 128.4, 128.2, 127.6, 122.2, 115.8, 112.0, 102.3, 81.8, 71.2, 70.6, 68.6, 67.6, 67.0, 64.5, 61.6, 47.6, 21.5, 21.3, 20.8, 20.7, 20.6, 20.5; MS (EI-LR) 787(M^+); HRMS (EI) calcd for $C_{41}H_{41}NO_{15}$ (M^+) 787.2476, found 787.2476.

***O*-Acetyl-L-rhamnoside 56:** reddish solid (54%), mp 155−158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.97 (d, 1H, J = 3.3 Hz), 8.27 (m, 2H), 7.76 (m, 2H), 7.62 (d, 1H, J = 7.5 Hz), 7.50 (d, 1H, J = 7.5 Hz), 4.81 (s, 1H), 4.65 (dd, 1H, J = 3.0, 9.9 Hz), 4.07 (s, 1H), 3.47 (dq, 1H, J = 6.0, 9.6 Hz), 2.35 (d, 1H, J = 13.5 Hz), 2.16 (s, 3H), 1.98 (ddd, 1H, J = 1.5, 4.5, 13.2 Hz), 1.12 (d, 3H, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.2, 183.4, 170.4, 149.4, 136.1, 134.8, 134.0, 133.2, 132.9, 127.9, 126.8, 126.7, 115.7, 112.2, 76.7, 68.3, 65.5, 46.4, 27.5, 21.2, 17.9; MS (EI-LR) 377 (M^+); HRMS (EI) calcd for $C_{22}H_{19}NO_5$ (M^+) 377.1263, found 377.1257.

***O*-Acetyl-L-rhamnoside 57:** reddish solid (26%), mp 152−154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.23 (d, 1H, J = 4.8 Hz), 8.25 (m, 2H), 7.73 (m, 2H), 7.60 (d, 1H, J = 7.5 Hz), 7.47 (d, 1H, J = 7.5 Hz), 4.94 (d, 1H, J = 4.2 Hz), 4.63 (d, 1H, J = 5.4 Hz), 3.84 (m, 2H), 2.58 (d, 1H, J = 13.5 Hz), 2.15 (s, 3H), 1.70 (m, 1H), 1.06 (d, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.1, 183.4, 170.2, 146.6, 134.7, 134.6, 134.1, 133.9, 133.1, 133.0, 131.0, 126.8, 126.7, 115.7, 112.8, 77.5, 67.4, 66.8, 46.6, 21.7, 21.1, 20.0; MS (EI-LR) 377 (M^+); HRMS (EI) calcd for $C_{22}H_{19}NO_5$ (M^+) 377.1263, found 377.1255.

***O*-Acetyl-L-rhamnoside 61:** bright orange solid (65%), mp 181−183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.30 (s, 1H), 7.98 (m, 2H), 7.46 (m, 3H), 7.00 (d, 1H, J = 8.4 Hz), 5.71 (d, 1H, J = 3.0 Hz), 5.31 (br s, 1H), 4.82 (dd, 1H, J = 4.2, 9.9 Hz), 3.65 (dq, 1H, J = 6.3, 9.6 Hz), 3.50 (br s, 1H), 2.39 (d, 1H, J = 12.9 Hz), 2.09 (s, 3H), 2.03 (m, 1H), 1.13 (d, 3H, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 137.5, 131.8, 131.4, 130.9, 128.4, 128.3, 127.8, 126.7, 125.5, 125.3, 121.3, 118.1, 117.5, 112.9, 77.4, 75.7, 65.3, 34.4, 28.4, 21.1, 17.8; MS (EI-LR) 347 (M^+); HRMS (EI) calcd for $C_{22}H_{21}NO_3$ (M^+) 347.1521, found 347.1521.

General Procedure for Deacetylation of the *C*- and *N*-Glycosidation Products. Each glycosidation cycloadduct prepared above was dissolved in a solution of $NH_3 \cdot H_2O$/MeOH (1:4) and stirred at rt overnight. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 40:1) to afford the corresponding deacetylated cycloadduct.

Angucycline 30: reddish solid (90%), $[\alpha]^{20}_D$ +553 (*c* 0.038, THF); mp 232−235 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (d, 1H, J = 4.8 Hz), 9.52 (d, 1H, J = 9.3 Hz), 8.27 (d, 1H, J = 9.3 Hz), 8.04 (d, 1H, J = 8.4 Hz), 7.64 (s, 1H), 7.54 (m, 3H), 4.79 (br s, 1H), 3.94 (br s, 1H), 3.41 (dt, 1H, J = 3.0, 9.6 Hz), 3.21 (dq, 1H, J = 9.6, 6.0 Hz), 2.54 (s, 3H), 2.28 (d, 1H, J = 13.2 Hz), 2.01 (m, 2H), 1.26 (d, 3H, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.3, 185.6, 148.7, 138.7, 136.5, 136.2, 134.6, 134.4, 132.0, 128.7, 128.5, 128.2, 127.8, 127.7, 122.3, 115.9, 111.7, 75.1, 68.8, 68.3, 49.0, 27.9, 21.6, 18.1; MS (EI-LR) 399 (M^+); HRMS (EI) calcd for $C_{25}H_{21}NO_4$ (M^+) 399.1471, found 399.1477.

Angucycline 31: reddish solid (92%), $[\alpha]^{20}_D$ −1500 (*c* 0.036, $CHCl_3/CH_3OH$ = 1:1); mp 204−206 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.10 (d, 1H, J = 4.8 Hz), 9.58 (d, 1H, J = 9.0 Hz), 8.36 (d, 1H, J = 9.0 Hz), 8. 09 (d, 1H, J = 8.7 Hz), 7.67 (s, 1H), 7.57 (d, 2H, J = 7.5 Hz), 7.45 (d, 1H, J = 7.5 Hz), 4.96 (d, 1H, J = 4.2 Hz), 3.86 (br s, 1H), 3.61 (m, 2H), 2.65 (m, 1H), 2.55 (s, 3H), 2.05 (br s, 1H), 1.72 (dd, 1H, J = 3.9, 13.5 Hz), 1.16 (d, 3H, J = 6.3 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 187.8, 186.2, 146.5, 139.6, 137.4, 137.0, 135.8, 135.4, 134.2, 132.9, 131.8, 129.7, 129.4, 128.9, 128.6, 123.1, 116.4, 112.5, 78.6, 69.1, 68.9, 50.9, 22.1, 21.7, 20.3; MS (EI-LR) 339 (M^+); HRMS (EI) calcd for $C_{25}H_{21}NO_4$ (M^+) 399.1471, found 399.1478.

Angucycline 39: reddish solid (96%), $[\alpha]^{20}_D$ −750 (*c* 0.024, CH_3CN); mp 211−214 °C dec; ^{1}H NMR (300 MHz, CD_3OD) δ 9.86 (d, 1H, J = 4.2 Hz), 9.48 (d, 1H, J = 9.0 Hz), 8.28 (d, 1H, J = 8.7 Hz), 8.05 (d, 1H, J = 8.7 Hz), 7.65 (s, 3H), 7.50 (m, 3 H), 4.82 (br s, 1H), 3.96 (br s, 1H), 3.74 (m, 3H), 3.22 (dt, 1H, J = 9.9, 3.9 Hz), 2.54 (s, 3H), 2.27 (d, 1H, J = 12.9 Hz), 2.01 (ddd, 1H, J = 1.8, 4.8, 13.2 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 186.4, 185.1, 148.5, 138.4, 136.3, 136.2, 135.8, 134.5, 134.3, 131.8, 128.4, 128.2, 127.8, 127.5, 127.0, 122.1, 115.4, 111.1, 72.3, 68.9, 68.2, 61.9, 48.8, 27.2, 21.2; MS (EI-LR) 415 (M^+); HRMS (EI) calcd for $C_{25}H_{21}NO_5$ (M^+) 415.1420, found 415.1433.

Angucycline 40: reddish solid (94%), $[\alpha]^{20}_D$ +1765 (*c* 0.017, $MeOH/CH_3CN$ = 1:10); mp 176−178 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 10.04 (d, 1H, J = 5.1 Hz), 9.51 (d, 1H, J = 9.0 Hz), 8.30 (d, 1H, J = 7.8 Hz), 8.07 (d, 1H, J = 8.4 Hz), 7.65 (s, 1H), 7.49 (m, 3H), 5.00 (br s, 1H), 3.86 (br s, 1H), 3.73 (d, 1H, J = 5.7 Hz), 3.55 (m, 4H), 3.30 (m, 1H), 2.66 (d, 1H, J = 13.8 Hz), 2.54 (s, 3H), 1.73 (dd, 1H, J = 3.3, 13.2 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 186.5, 185.3, 145.4, 138.5, 136.3, 136.1, 134.6, 134.3, 133.4, 131.9, 130.1, 128.6, 128.3, 127.9, 127.5, 122.0, 115.3, 111.5, 72.7, 72.5, 67.7, 63.0, 48.3, 21.3, 20.9; MS (EI-LR) 415 (M^+); HRMS (EI) calcd for $C_{25}H_{21}NO_5$ (M^+) 415.1420, found 415.1430.

Angucycline 43: reddish solid (98%), $[\alpha]^{20}_D$ −1095 (*c* 0.021, $CHCl_3$/MeOH = 1:1); mp 213-216 °C dec; ^{1}H NMR (300 MHz, CD_3OD) δ 9.74 (d, 1H, *J* = 4.8 Hz), 9.36 (d, 1H, *J* = 9.0 Hz), 8.17 (d, 1H, *J* = 8.4 Hz), 7.94 (d, 1H, *J* = 8.7 Hz), 7.53 (s, 1H), 7.40 (m, 3H), 4.75 (br s, 1H), 3.79 (s, 1H), 3.63 (m, 3H), 3.30 (m, 1H), 2.61 (d, 1H, *J* = 13.2 Hz), 2.41 (s, 3H), 1.51 (d, 1H, *J* = 12.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD) δ 186.4, 185.2, 148.0, 138.5, 136.3, 136.2, 136.1, 134.4, 134.3, 131.8, 128.4, 128.1, 127.8, 127.4, 126.8, 121.9, 115.4, 111.1, 69.3, 69.1, 68.9, 62.5, 47.8, 22.1, 21.1; MS (EI-LR) 415 (M^+); HRMS (EI) calcd for $C_{25}H_{21}NO_5$ (M^+) 415.1420, found 415.1417.

Angucycline 44: reddish solid (97%); $[\alpha]^{20}_D$ +800 (*c* 0.08, $CHCl_3$/MeOH = 1:1); mp 207−209 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1H), 9.29 (d, 1H, *J* = 8.7 Hz), 7.94 (d, 1H, *J* = 8.4 Hz), 7.83 (d, 1H, *J* = 8.4 Hz), 7.54 (s, 1H), 7.44 (dd, 1H, *J* = 1.2, 9.0 Hz), 7.36 (s, 2H), 4.86 (d, 1H, *J* = 3.3 Hz), 4.12 (br s, 3H), 3.71 (m, 2H), 3.52 (m, 1H), 2.52 (s, 4H), 2.27 (dd, 1H, *J* = 3.9, 13.5 Hz), 1.82 (d, 1H, *J* = 12.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD) δ 186.1, 185.1, 146.5, 138.5, 136.3, 136.2, 134.4, 134.3, 131.8, 129.8, 128.4, 128.2, 127.9, 127.5, 122.0, 115.5, 112.0, 73.5, 69.2, 66.6, 61.7, 46.2, 25.1, 21.4; MS (EI-LR) 415 (M^+); HRMS (EI) calcd for $C_{25}H_{21}NO_5$ (M^+) 415.1420, found 415.1421.

Angucycline 47: reddish solid (95%), $[\alpha]^{20}_D$ −824 (*c* 0.034, CH_3Cl/MeOH = 1:1); mp 223−225 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 9.91 (d, 1H, *J* = 4.2 Hz), 9.51 (d, 1H, *J* = 8.7 Hz), 8.33 (d, 1H, *J* = 8.4 Hz), 8.11 (d, 1H, *J* = 9.0 Hz), 7.69 (s, 1H), 7.55 (m, 3H), 4.83 (br s, 1H), 3.91 (br s, 1H), 3.67 (m, 2H), 3.51 (m, 1H), 2.77 (d, 1H, *J* = 13.2 Hz), 2.56 (s, 3H), 1.64 (d, 1H, *J* = 13.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD) δ 186.5, 185.2, 148.0, 138.4, 136.3, 136.2, 134.4, 131.7, 128.4, 128.1, 127.8, 127.4, 126.4, 126.3, 121.9, 115.4, 111.1, 68.5, 67.9, 63.3, 46.9, 22.5, 21.1; MS (EI-LR) 385 (M^+); HRMS (EI) calcd for $C_{24}H_{19}NO_4$ (M^+) 385.1314, found 385.1324.

Angucycline 48: reddish solid (99%); $[\alpha]^{20}_D$ +750 (*c* 0.028, CH_3CN); mp 235−238 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (d, 1H, *J* = 4.2 Hz), 9.42 (d, 1H, *J* = 9.0 Hz), 8.14 (d, 1H, *J* = 8.7 Hz), 7.94 (d, 1H, *J* = 8.4 Hz), 7.57 (s, 1H), 7.51 (m, 3H), 4.77 (br s, 1H), 3.89 (m, 3H), 3.04 (m, 1H), 2.51 (s, 3H), 2.27 (m, 2H), 1.97 (ddd, 1H, *J* = 1.5, 4.5, 13.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.2, 185.5, 148.9, 138.5, 136.4, 136.3, 136.2, 134.4, 131.9, 128.5, 128.3, 128.1, 127.6, 126.9, 122.1, 115.8, 111.6, 68.8, 67.4, 62.8, 48.7, 27.3, 21.5; MS (EI-LR) 385 (M^+); HRMS (EI) calcd for $C_{24}H_{19}NO_4$ (M^+) 385.1314, found 385.1316.

Angucycline 51: reddish solid (96%); $[\alpha]^{20}_D$ −778 (*c* 0.045, CH_3CN); mp 220−223 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (d, 1H, *J* = 3.9 Hz), 9.48 (d, 1H, *J* = 9.0 Hz), 8.22 (d, 1H, *J* = 8.4 Hz), 8.00 (d, 1H, *J* = 8.4 Hz), 7.61 (s, 1H), 7.53 (m, 3H), 4.77 (br s, 1H), 3.89 (m, 3H), 3.02 (t, 1H, *J* = 10.5 Hz), 2.53 (s, 3H), 2.25 (d, 1H, *J* = 12.6 Hz), 2.14 (br s, 1H), 1.98 (dd, 1H, *J* = 2.7, 13.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.3, 185.6, 148.9, 138.6, 136.5, 136.4, 136.3, 134.5, 134.4, 131.9, 128.6, 128.3, 128.1, 127.6, 126.9, 122.2, 115.9, 111.6, 68.8, 67.4, 62.8, 48.7, 27.3, 21.5; MS (EI-LR): 385 (M^+); HRMS (EI) calcd for $C_{24}H_{19}NO_4$ (M^+) 385.1314, found 385.1323.

Angucycline 52: reddish solid (98%), $[\alpha]^{20}_D$ +1020 (*c* 0.043, $CHCl_3$/MeOH = 1:1); mp 234−236 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 9.86 (d, 1H, *J* = 4.5 Hz), 9.50 (d, 1H, *J* = 9.0 Hz), 8.29 (d, 1H, *J* = 8.4 Hz), 8.05 (d, 1H, *J* = 9.0 Hz), 7.63 (s, 1H), 7.51 (m, 3H), 4.78 (br s, 1H), 3.87 (br s, 1H), 3.61 (m, 2H), 3.47 (m, 1H), 2.69 (m, 4H), 2.51 (s, 3H), 1.59 (d, 1H, *J* = 13.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD) δ 186.5, 185.5, 148.1, 138.6, 136.5, 136.4, 136.3, 134.6, 134.4, 132.0, 128.6, 128.3, 128.0, 127.6, 126.3, 122.1, 115.6, 111.3, 68.7, 68.2, 63.6, 47.1, 22.8, 21.4; MS (EI-LR) 385 (M^+); HRMS (EI) calcd for $C_{24}H_{19}NO_4$ (M^+) 385.1314, found 385.1308.

Anthracycline 58: reddish solid (92%), $[\alpha]^{20}_D$ +256 (*c* 0.085, $CHCl_3$); mp 173−176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.98 (d, 1H, *J* = 3.6 Hz), 8.16 (m, 2H), 7.71 (m, 2H), 7.55 (d, 1H, *J* = 7.2 Hz), 7.48 (d, 1H, *J* = 7.2 Hz), 4.77 (s, 1H), 3.93 (br s, 1H), 3.41(d, 1H, *J* = 7.8 Hz), 3.20 (dq, 1H, *J* = 6.0, 9.6 Hz), 2.27 (d, 2H, *J* = 13.2 Hz), 1.96 (m, 1H), 1.27 (d, 3H, *J* = 5.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.1, 183.3, 149.4, 136.2, 134.6, 134.0, 133.2, 132.9, 128.6, 126.8, 126.6, 115.8, 112.4, 75.0, 68.8, 68.3, 49.0, 27.8, 18.1; MS (EI-LR) 335 (M^+); HRMS (EI) calcd for $C_{20}H_{17}NO_4$ (M^+) 335.1158, found 335.1156.

Anthracycline 59: reddish solid (95%), $[\alpha]^{20}_D$ −557 (*c* 0.085, $CHCl_3$); mp 170−172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.27 (d, 1H, *J* = 4.2 Hz), 8.25 (m, 2H), 7.74 (m, 2H), 7.59 (d, 1H, *J* = 7.2 Hz), 7.44 (d, 1H, *J* = 7.2 Hz), 4.97 (d, 1H, *J* = 4.2 Hz), 3.85 (br s, 1H), 3.61 (m, 2H), 2.65 (m, 1H), 2.18 (br s, 1H), 1.69 (m, 1H), 1.16 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.2, 183.5, 146.4, 134.8, 134.4, 133.9, 133.5, 133.1, 131.5, 126.8, 126.6, 115.7, 112.6, 78.0, 68.5, 67.8, 49.9, 20.9, 19.8; MS (EI-LR) 335 (M^+); HRMS (EI) calcd for $C_{20}H_{17}NO_4$ (M^+) 335.1158, found 335.1156.

Anthracycline 62: bright orange solid (90%), $[\alpha]^{20}_D$ −202.7 (*c* 0.037, $CHCl_3$); mp 198−201 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.30 (s, 1H), 7.98 (m, 2H), 7.46 (m, 3H), 7.21 (d, 1H, *J* = 8.7 Hz), 5.72 (d, 1H, *J* = 3.0 Hz), 5.29 (br s, 1H), 3.60 (dt, 1H, *J* = 4.2, 9.6 Hz), 3.32 (m, 2H), 2.33 (d, 1H, *J* = 12.6 Hz), 2.07 (ddd, 1H, *J* = 1.8, 3.6, 12.6 Hz), 12.3 (d, 3H, *J* = 5.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 131.9, 131.4, 131.0, 128.3, 127.8, 126.8, 125.6, 125.4, 121.2, 118.1, 117.7, 111.9, 75.7, 68.8, 37.7, 28.8, 17.9; MS (EI-LR) 305 (M^+); HRMS (EI) calcd for $C_{20}H_{19}NO_2$ (M^+) 305.1416, found 305.1420.

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Note Added after ASAP Publication. In the version published ASAP July 17, 2009, there were errors in Scheme 7; the correct version published on the WEB August 14, 2009.

Supporting Information Available: Copies of ^{1}H, ^{13}C NMR of the final angucyclines, key intermediates, X-ray analysis, and CIF files of compounds **31** and **39**. This material is available free of charge via the Internet at http://pubs.acs.org.