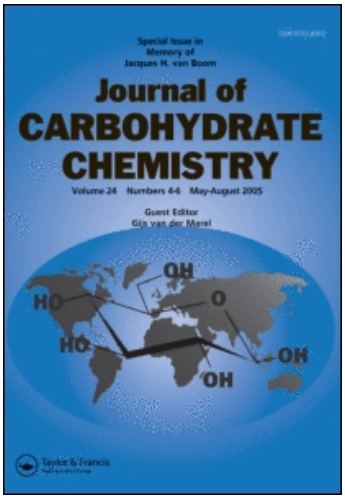

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Models for the Synthesis of Pluramycin Antibiotics. Rearrangement of Mono-Protected Aminoglycal-Substituted Cyclohexadienediols

Kathlyn A. Parker[a]; Dai-Shi Su[a]
[a] Department of Chemistry, Brown University, Providence, RI

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Models for the Synthesis of Pluramycin Antibiotics. Rearrangement of Mono-Protected Aminoglycal-Substituted Cyclohexadienediols

Kathlyn A. Parker and Dai-Shi Su

Department of Chemistry, Brown University, Providence, RI

A two-step sequence converts protected glycal-substituted quinols to aryl bis C-glycals in which one or both of the substituents is an aminoglycal. First, a lithiated glycal undergoes 1,2-addition to the carbonyl group of a protected glycal-bearing quinol, leading to a mono-protected cyclohexadienediol. Then a BF_3-etherate-catalyzed "dienol phenol-type" rearrangement converts the adduct to an aryl bis C-glycal. The glycal moiety that was originally a substituent on the quinol substrate is the substituent that migrates. The presence of the amino group does not introduce complications. This sequence provides models for the rapid access to intermediates for pluramycin synthesis.

Keywords Pluramycin, Aminoglycal, Bis-C-glycoside, Quinone, Quinol, Dienol–phenol, Rearrangement, Regiospecific, Polarity, Umplong

INTRODUCTION

Among the naturally occurring aryl C-1′-glycoside antibiotics,[1,2] the pluramycins, **1**, are particularly challenging synthetic targets because they have two aryl C-glycoside linkages on the same phenolic ring of the "aglycone." In all members of the class, the two sugar moieties are different, and they are both amino sugars (Fig. 1).[3]

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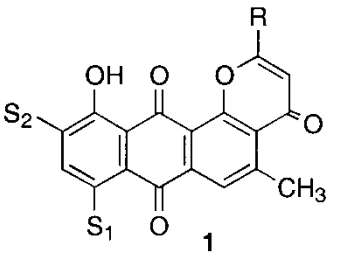
Address correspondence to Kathlyn A. Parker, State University of New York at Stony Brook, Stony Brook, NY 11794–3400, USA. E-mail: kparker@notes.cc.sunysb.edu
Dai-Shi Su, Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486.



1

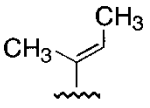
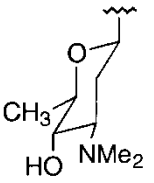
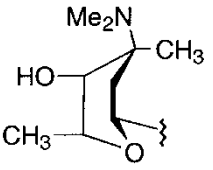
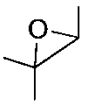
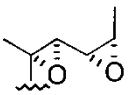
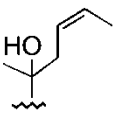
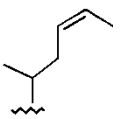
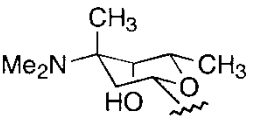
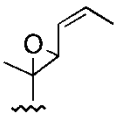
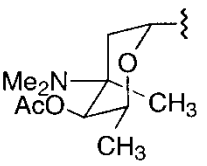
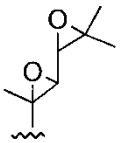
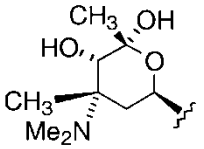
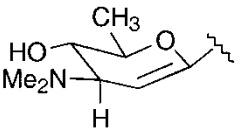
	R	S_1	S_2
1a) Kidamycin			
1b) Epoxykidamycin		"	"
1c) Hedamycin		"	"
1d) Rubiflavin E		"	"
1e) Saptomycin B		"	
1f) Pluramycin A		"	
1g) DC92-B		"	
1h) DC92-D	"		"

Figure 1: Pluramycin bis C-aryl glycosides, 1.

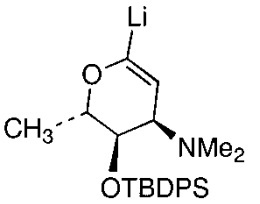
Although numerous strategies have been developed for the synthesis of aryl C-glycosides, only a few methods have been applied to a bis glycoside structural unit such as that in the pluramycins.[4] Furthermore, there is a dearth of methods for connecting amino glycoside synthons to aromatic aglycones.[5] Direct synthetic approaches to aryl C-aminoglycosides must accommodate the presence of the amino groups on the sugars.

BACKGROUND

In an effort to discover new and efficient methods of constructing C-aryl glycosides, we have examined the reduction and rearrangement chemistry of glycal-substituted quinols. Remarkably, derivatives of these complex but easy to acquire compounds can be converted to aryl C-glycals with substitution patterns representative of each of the aryl C-1′-glycoside structural classes.[4a,6]

In the previous paper in this series, we reported that the reduction of glycal-substituted quinols (Fig. 2, Equation (1)) proceeds smoothly with aminoglycal substrates to give p-hydroxyaryl aminoglycals, models for ravidomycin.[7] Our next goal was to establish that the rearrangement methodology (Fig. 2, Equation (2)), previously demonstrated only with a dihydropyran or a protected rhamnal moiety as the migrating group, could be extended to aminoglycal systems.

Using a lithiated aminoglycal reagent **2**[7] in short schemes developed with rhamnal reagent **3** for the preparation of the related deaza compounds, we have found that the aminoglycal substituent behaves well in the role of stationary appendage and in the role of migrating group. Our studies provide aryl C-aminoglycal models for the pluramycins.



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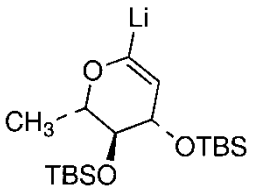


3

Models for Group 3 Aryl Bis C-Aminoglycal (Pluramycin) Synthesis

The "dienol phenol-type" rearrangement[4a] would be an especially attractive key step in a pluramycin synthesis if it could be applied directly to substrates in which at least one of the glycal substituents is an aminoglycal. In order to proceed with an efficient synthesis based on this approach, we

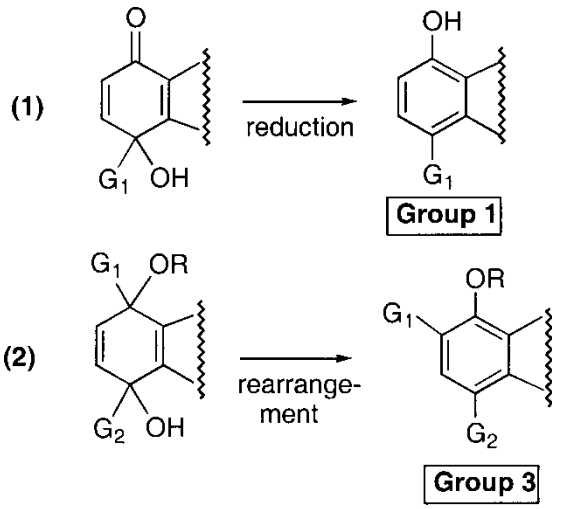


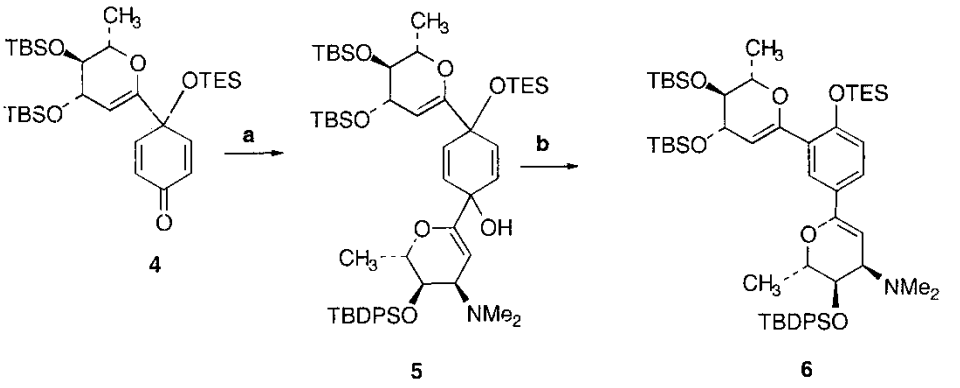
Figure 2: Substitution patterns in glycal-substituted phenol derivatives from glycal-substituted quinol substrates. G_1 and G_2 are protected glycal substituents. R = trialkylsilyl.

wished to establish (1) that an aminoglycal substituent, which was not the migrating group, would be stable to the rearrangement conditions; (2) that an aminoglycal substituent, introduced at the appropriate position, would act as the migrating substituent; (3) that modification of the substrate by the incorporation of the desired amino group(s) would not alter the regiospecificity[4a] of the rearrangement reaction; and (4) that a substrate in which both glycals were aminoglycals would undergo the rearrangement reaction. Therefore, we examined three model systems. Substrates were prepared by analogy to prior art.

The first substrate was prepared by treating protected quinol **4**[4a] with the lithiated aminoglycal reagent **2**. Treatment of substrate **5** with BF_3 etherate gave a protected phenol, assumed to be the product of migration of the glycal moiety adjacent to the silyl ether, and therefore assigned structure **6** (Sch. 1).

The second substrate was prepared from quinol **7**[7] by protection of the tertiary hydroxyl group and then introduction of the second glycal substituent by addition of the lithiated rhamnal reagent **3**. When subjected to BF_3 etherate, substrate **9** was converted to a protected phenol. This product, clearly different from the compound obtained from the regioisomeric substrate **5**, was assigned structure **10** (Sch. 2).

The third substrate, **11**, was prepared by addition of the lithiated aminoglycal reagent **2** to protected quinol **8**. Rearrangement with BF_3 etherate proceeded smoothly to provide the protected phenol **12** in high yield (Sch. 3).

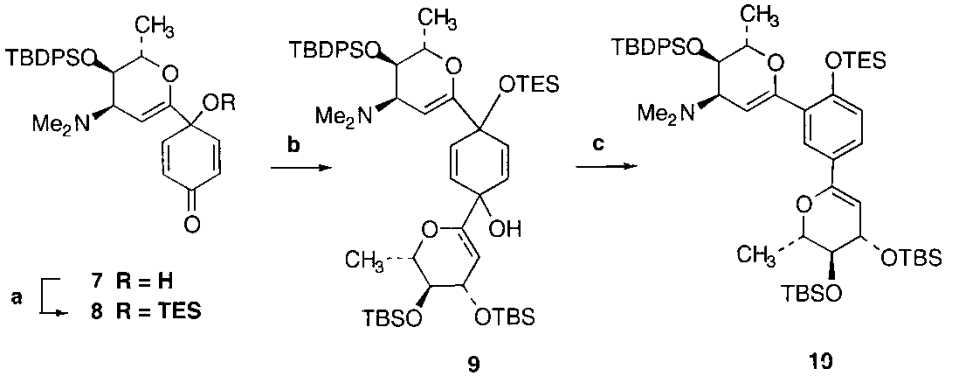


Scheme 1: Model studies for the synthesis of kidamycin: reactivity of aminoglycal-bearing substrates. Key: (a) **2**, THF, −78°C, 67%, (b) BF_3 etherate, THF, 0°C → rt, 80%.

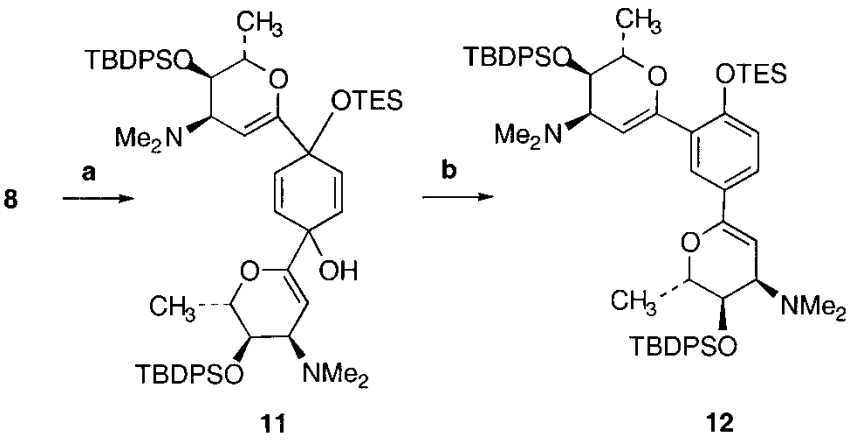
Taken together, these studies show that the aminoglycal substituent is well behaved in the "cyclohexadienol phenol-type" rearrangement, surviving the rearrangement conditions in both the migratory and nonmigratory roles. Furthermore, our results support the premise that regiochemistry in reactions of aminoglycal-containing substrates is determined by the order of introduction of the glycal substituents.

CONCLUSION

The synthesis of model compounds (**6**, **10**, and **12)** demonstrates the generality of the "reverse polarity" strategy for the preparation of aryl bis C-aminoglycosides of the pluramycin substitution pattern. The reactions are simple and easy to perform and give good yields.



Scheme 2: Model studies for the synthesis of kidamycin: migration of aminoglycal substituent. Key: (a) TESCl. Im, DMAP, DMF, rt, 94%. (b) **3**, THF, −78°C, 90% (c) BF_3 etherate, THF, 0°C → rt, 92%.



Scheme 3: Model study for the synthesis of kidamycin: a bis aminoglycal substrate. Key: (a) **2**, THF, −78°C, 61%, (b) BF_3 etherate, THF, 0°C → rt, 83%.

EXPERIMENTAL SECTION

Solvents were dried and purified by standard methods before use. Ether refers to diethyl ether. Flash chromatography was performed with silica gel (200–425 mesh).

Bisglycal 5. An 86-mg sample (0.22 mmol) of aminoglycal in 0.5 mL of THF was treated with 0.50 mL (0.68 mmol) of *t*-BuLi (1.35 M in pentane), and the resulting solution was added to 80 mg (0.14 mmol) of quinol glycal **4** in 1 mL of THF to give 91 mg (67%) of a brown oil. ^{1}H NMR ($CDCl_3$) δ 7.77 (dd, $J = 1.6$, 7.5 Hz, 2H), 7.67 (dd, $J = 1.6$, 7.5 Hz, 2H), 7.39 (m, 6H), 6.00 (dt, $J = 2.3$, 11.1 Hz, 2H), 5.74 (dt, $J = 2.3$, 11.1 Hz, 2H), 5.24 (d, $J = 2.8$ Hz, 1H), 4.91 (d, $J = 3.3$ Hz, 1H), 4.16 (dd $J = 3.0$, 6.5 Hz, 1H), 3.96 (t, $J = 6.5$ Hz, 1H), 3.76 (m, 2H), 3.44 (dd, $J = 5.6$, 7.8 Hz, 1H), 2.84 (bs, 1H), 2.38 (s, 1H), 2.19 (s, 6H), 1.18 (d, $J = 6.5$ Hz, 3H), 1.04 (s, 12H), 0.85 (m, 27H), 0.58 (m, 6H), 0.09 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 154.6, 153.0, 136.3, 136.1, 134.5, 134.1, 133.6, 131.5, 131.4, 129.5, 129.4, 127.5, 127.3, 99.3, 91.8, 75.2, 74.1, 72.5, 71.2, 71.1, 66.7, 57.0, 43.0, 27.1, 26.1, 25.9, 19.5, 18.3, 18.0, 17.8, 17.1, 6.9, 6.2, −3.5, −3.6, −4.0, −4.2; FTIR (neat): 1674, 1108 cm^{-1}.

Aryl bisglycal 6. To a solution of 14 mg (0.014 mmol) of bisglycal **5** in 0.5 mL of THF at 0°C was added 10 mL (0.082 mmol) of $BF_3 \cdot OEt_2$. After stirring at rt for 1 hr, the solution was poured into 20 mL of saturated $NaHCO_3$. Extraction with ether (4 × 15 mL) provided a combined organic solution, which was dried over $MgSO_4$ and concentrated. Flash column

chromatography (1% Et_3N in 3:1 hexanes/EtOAc) gave 11 mg (80%) of a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.79 (d, $J = 6.0$ Hz, 2H), 7.68 (d, $J = 6.5$ Hz, 2H), 7.55 (d, $J = 2.0$ Hz, 1H), 7.36 (m, 7H), 6.72 (d, $J = 8.5$ Hz, 1H), 5.14 (d, $J = 3.9$ Hz, 1H), 5.07 (d, $J = 3.2$ Hz, 1H), 4.21 (t, $J = 4.0$ Hz, 1H), 4.10 (t, $J = 6.2$ Hz, 2H), 3.87 (t, $J = 6.1$ Hz, 1H), 3.64 (t, $J = 5.0$ Hz, 1H), 2.97 (bs, 1H), 2.27 (s, 6H), 1.36 (d, $J = 6.7$ Hz, 3H), 1.06 (s, 12H), 0.89 (m, 27H), 0.76 (m, 6H), 0.09 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 153.3, 15.6, 149.2, 136.3, 136.2, 134.4, 129.5, 128.5, 127.4, 127.3, 126.5, 125.7, 119.5, 103.2, 92.1, 75.5, 74.9, 73.5, 73.3, 70.4, 57.7, 43.1, 27.1, 26.1, 26.0, 25.6, 19.6, 18.2, 17.1, 6.7, 6.6, 5.8, 5.2, −3.7, −3.9, −4.1, −4.2; FTIR (neat): 1651, 1105 cm^{-1}.

Quinol silyl ether 8. To a solution of 26 mg (0.052 mmol) of quinol glycal **7** in 1 mL of DMF was added 21 mg (0.31 mmol) of imidazole, a catalytic amount of DMAP, and 25 mL (0.15 mmol) of TESCl. The reaction mixture was stirred at rt overnight, diluted with 5 mL of ether, and poured into 20 mL of H_2O. The resulting mixture was extracted with ether (4 × 15 mL), and the combined ether solution was washed with H_2O (3 × 15 mL), dried over $MgSO_4$, and concentrated. Preparative TLC (1:9 MeOH/$CHCl_3$) gave 30 mg (94%) of a yellow-orange oil. ^{1}H NMR ($CDCl_3$) δ 7.73 (dd, $J = 1.5$, 7.6 Hz, 2H), 7.62 (dd, $J = 1.6$, 6.7 Hz, 2H), 7.36 (m, 6H), 6.74 (dd, $J = 3.0$, 10.0 Hz, 1H), 6.65 (dd, $J = 3.0$, 10.0 Hz, 1H), 6.23 (dd, $J = 1.8$, 9.9 Hz, 1H), 6.15 (dd, $J = 1.9$, 10.0 Hz, 1H), 5.26 (d, $J = 2.2$ Hz, 1H), 3.85 (q, $J = 7.0$ Hz, 1H), 3.70 (t, $J = 4.8$ Hz, 1H), 2.85 (s, 1H), 2.24 (s, 6H), 1.04 (s, 9H), 0.86 (m, 12H), 0.55 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 186.1, 151.2, 150.1, 150.0, 136.2, 136.0, 134.4, 133.8, 129.6, 129.5, 128.6, 128.5, 127.4, 127.3, 93.6, 74.8, 71.8, 71.4, 57.4, 43.0, 27.0, 26.3, 19.4, 17.2, 6.9, 6.4; FTIR ($CDCl_3$): 1674 cm^{-1}; HRMS (FAB, NaI): calcd. 640.3254, found: 640.3262 (M + Na).

Bisglycal 9. To a solution of 60 mg (0.17 mmol) of protected rhamnal glycal was added 0.31 mL (0.42 mmol) of *t*-BuLi (1.35 M in pentane) in 0.5 mL of THF at −78°C. The solution was stirred at 0°C for 1 hr, then cooled to −78°C and added via cannula to a solution of 63 mg (0.10 mmol) of protected quinol glycal **8** in 1 mL of THF at −78°C. The reaction mixture was stirred at −78°C for 4 hr and then diluted with 10 mL of ether. It was poured into 20 mL of H_2O and extracted with ether (4 × 20 mL). The ether solution was dried over $MgSO_4$ and concentrated. Preparative TLC (hexanes/EtOAc, 3:1) gave 89 mg (90%) of a brown oil. ^{1}H NMR ($CDCl_3$) δ 7.74 (dd, $J = 1.5$, 7.6 Hz, 2H), 7.64 (dd, $J = 1.5$, 7.6 Hz, 2H), 7.38 (m, 6H), 5.96 (m, 2H), 5.80 (dd, $J = 2.5$, 10.3 Hz, 1H), 5.66 (dd, $J = 1.9$, 9.8 Hz, 1H), 5.24 (d, $J = 3.2$ Hz, 1H), 4.91 (d, $J = 3.5$ Hz, 1H), 4.08 (t, $J = 3.7$ Hz, 1H), 3.96 (t, $J = 6.6$ Hz, 1H), 3.82 (t, $J = 6.2$ Hz, 1H), 3.72 (t, $J = 6.6$ Hz, 1H), 3.55 (dd, $J = 4.6$, 6.0 Hz, 1H), 2.84 (bs, 1H), 2.21 (s, 6H), 1.27 (d, $J = 6.7$ Hz, 3H), 1.04 (s, 9H), 0.88 (m, 30H), 0.59 (m, 6H), 0.08 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 154.0, 153.1,

136.2, 136.0, 134.5, 134.3, 134.2, 133.7, 131.2, 131.0, 129.6, 129.4, 127.5, 127.3, 97.6, 92.2, 75.7, 74.5, 72.3, 71.4, 69.7, 66.5, 57.2, 42.9, 27.1, 26.1, 25.8, 19.5, 18.2, 18.0, 17.4, 16.7, 7.0, 6.2, −3.8, −4.0, −4.1, −4.4; FTIR (neat): 1655, 1110 cm^{-1}.

Aryl bisglycal 10. To a solution of 25 mg (0.026 mmol) of bisglycal **9** in 1 mL of THF at 0°C was added dropwise 20 mL (0.16 mmol) of $BF_3 \cdot OEt_2$. The resulting solution was stirred at rt for 0.5 hr and then poured into 20 mL of saturated $NaHCO_3$. Extraction with ether (4 × 15 mL) gave a combined solution, which was dried over $MgSO_4$ and concentrated. Flash column chromatography (1% Et_3N in 3:1 hexanes/EtOAc) gave 23 mg (92%) of a yellow oil. ^1H NMR ($CDCl_3$) δ 7.80 (dd, $J = 1.4$, 7.9 Hz, 2H), 7.71 (dd, $J = 1.4$, 7.9 Hz, 3H), 7.64 (d, $J = 1.3$ Hz, 1H), 7.37 (m, 6H), 6.71 (d, $J = 8.4$ Hz, 1H), 5.29 (d, $J = 4.1$ Hz, 1H), 5.07 (d, $J = 3.2$ Hz, 1H), 4.27 (dd, $J = 3.3$, 5.3 Hz, 1H), 4.12 (t, $J = 7.9$ Hz, 1H), 4.02 (t, $J = 6.6$ Hz, 1H), 3.88 (t, $J = 6.2$ Hz, 1H), 3.58 (dd, $J = 5.4$, 7.4 Hz, 1H), 2.91 (t, $J = 4.8$ Hz, 1H), 2.20 (s, 6H), 1.37 (d, $J = 6.6$ Hz, 3H), 1.18 (d, $J = 6.3$ Hz, 3H), 1.07 (s, 9H), 0.90 (m, 27H), 0.68 (m, 6H), 0.09 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 153.4, 151.0, 150.0, 136.3, 136.2, 134.6, 134.5, 129.5, 129.4, 128.0, 127.4, 127.2, 126.2, 125.6, 119.2, 98.1, 97.8, 75.6, 75.4, 73.7, 73.3, 71.4, 57.9, 43.2, 27.2, 26.2, 26.0, 19.6, 18.4, 18.3, 18.1, 17.4, 6.6, 5.2, −3.5, −3.9, −4.2; FTIR (neat): 1653, 1105 cm^{-1}.

Bisaminoglycal 11. In a procedure similar to that for preparing compound **5**, a 66-mg sample (0.17 mmol) of aminoglycal was treated with 0.35 mL (0.47 mmol) of *t*-BuLi (1.35 M in pentane). The resulting solution was added to 64 mg (0.096 mmol) of quinol glycal **8** in 1 mL of THF. Isolation and chromatoraphy afforded 18 mg of recovered **8** and 42 mg (61%, calculated for 72% conversion) of **11** as a yellow oil. ^1H NMR ($CDCl_3$) δ 7.74 (dd, $J = 1.5$, 8.8 Hz, 4H), 7.67 (dd, $J = 1.5$, 8.0 Hz, 4H), 7.37 (m, 12H), 6.00 (dt, $J = 1.9$, 9.9 Hz, 2H), 5.80 (dd, $J = 2.2$, 9.7 Hz, 1H), 5.66 (dd, $J = 2.3$, 9.8 Hz, 1H), 5.23 (d, $J = 3.3$ Hz, 1H), 4.91 (d, $J = 3.3$ Hz, 1H), 3.95 (qn, $J = 6.6$ Hz, 1H), 3.79 (dd, $J = 6.3$ Hz, 2H), 3.72 (t, $J = 5.7$ Hz, 1H), 2.83 (s, 3H), 2.19 (s, 12H), 1.08 (2s, 21H), 0.89 (qn, $J = 8.6$ Hz, 12H), 0.55 (q, $J = 7.8$ Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 154.7, 153.0, 136.3, 136.2, 136.1, 136.0, 134.5, 134.3, 134.2, 133.7, 131.4, 131.0, 129.6, 129.5, 129.4, 127.5, 127.4, 127.3, 92.2, 91.9, 74.4, 74.1, 72.5, 72.2, 71.4, 66.7, 57.1, 57.0, 46.0, 43.0, 42.9, 27.1, 19.5, 17.9, 17.4, 7.0, 6.3; FTIR (neat): 3530, 1670, 1112 cm^{-1}; HRMS (FAB, NaI): calcd. 1035.5535, found: 1035.558 (M + Na).

Aryl bisglycal 12. To a solution of 13 mg (0.013 mmol) of bis aminoglycal **11** in 0.5 mL of THF at 0°C was slowly added 10 mL (0.082 mmol) of $BF_3 \cdot OEt_2$. The solution was stirred at rt for 1 hr, then poured into 15 mL of

saturated $NaHCO_3$. Extraction with ether (4×15 mL) provided a combined ether solution, which was dried over $MgSO_4$ and concentrated. Flash column chromatography (1:4 hexanes/EtOAc with 1% Et_3N) left 10 mg (83%) of a yellow oil. ^1H NMR ($CDCl_3$) δ 7.79 (m, 4H), 7.70 (m, 4H), 7.63 (s, 1H), 7.34 (m, 13H), 6.70 (d, $J = 8.5$ Hz, 1H), 5.22 (d, $J = 4.0$ Hz, 1H), 5.12 (d, $J = 3.9$ Hz, 1H), 4.11 (m, 2H), 3.88 (t, $J = 6.2$ Hz, 2H), 2.98 (bs, 1H), 2.91 (bs, 1H), 2.27 (s, 6H), 2.20 (s, 6H), 1.17 (d, $J = 6.3$ Hz, 3H), 1.06 (m, 21H), 0.91 (m, 9H), 0.66 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 153.2, 151.7, 150.1, 136.3, 136.2, 134.6, 134.5, 129.5, 129.4, 127.4, 127.3, 127.2, 125.9, 125.4, 119.2, 97.7, 92.1, 73.6, 73.4, 73.3, 60.4, 57.9, 57.8, 43.1, 43.0, 27.2, 19.6, 18.4, 18.2, 6.6, 5.2; FTIR (neat): 1653, 1104 cm^{-1}.

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