Methodology for the Regiospecific Synthesis of Bis *C*-Aryl Glycosides. Models for Kidamycins

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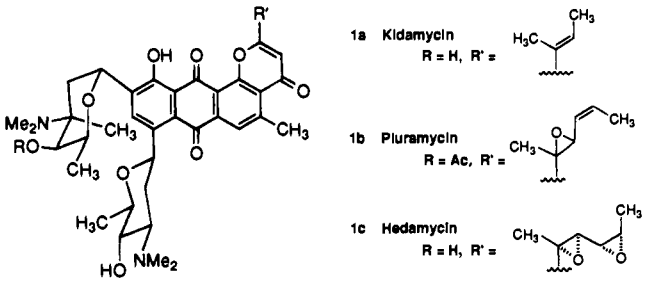
The kidamycin antibiotics[2] (also referred to as the pluramycin or anthra(1,2-*b*)pyran antibiotics) are *Streptomyces*-derived natural products. Several members of this class, including the best known examples, kidamycin (**1a**), pluramycin (**1b**), and hedamycin (**1c**), are of interest because of their antitumor activity. The mechanism of action of these compounds is believed to involve strong binding to DNA, presumably by intercalation, and, in at least some cases, a subsequent covalent bond formation which creates base-inducible single strand breaks.[3]

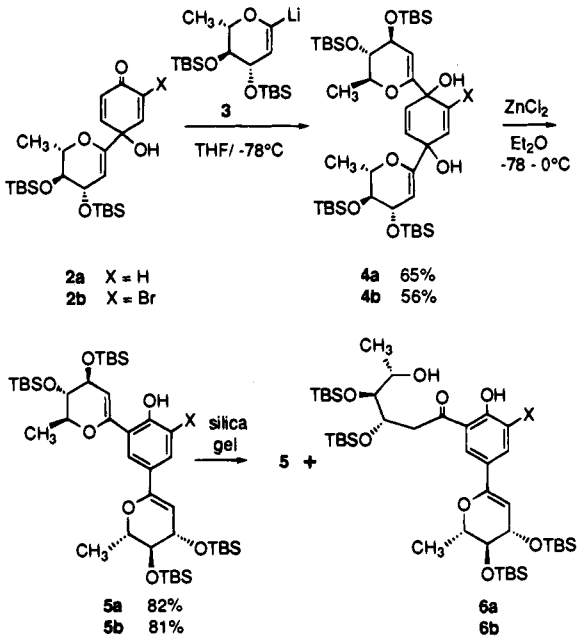


Since the appearance of a comprehensive review of the structures and the chemical, biochemical, and biological properties of the kidamycins in 1986,[2] a number of new additions to the class have been discovered.[4] Several of these exhibit much more favorable therapeutic indices than did the earlier members of the series, and these have contributed to significantly increased life spans in mice.

Previous reports of efforts focused on the synthesis of these antibiotics are limited to the synthesis of the "aglycon" of kidamycin by Hauser and Rhee[5] and a method for the preparation of bis glycals by palladium-catalyzed coupling by Dubois and Beau.[6] Aside from the latter, there is no report of an application of one of the methods for the synthesis of *C*-aryl glycosides[7] to the preparation of a bis glycoside.

In this communication, we are pleased to report a new method for the synthesis of phenolic bis glycosides of the desired substitution pattern. The key reaction is a regiocontrolled

Scheme 1



"dienone–phenol type" rearrangement[8] in which a glycal migrates in a 1,2-shift. The overall sequence promises to provide efficient access to the kidamycin bis glycosides from the corresponding quinonoid aglycons.

In an effort to expand the application of our "reverse polarity" strategy for the synthesis of *C*-aryl glycals,[9] we envisioned the Lewis acid-catalyzed rearrangement of a cyclohexadienediol substrate (e.g., **4a**,[10] prepared by addition of lithiated glycal **3** to quinol glycal **2a**[9b]) to afford a disubstituted phenol (e.g., **5a** from **4a**) (Scheme 1).

Of the Lewis acids studied,[11] $ZnCl_2$ was most efficient in inducing the desired transformation to afford bis glycal **5a**. Even more interesting was the regiospecific rearrangement of bromo substrate **4b** to bis glycal **5b**. These reactions are rapid at low temperatures in ether solution.

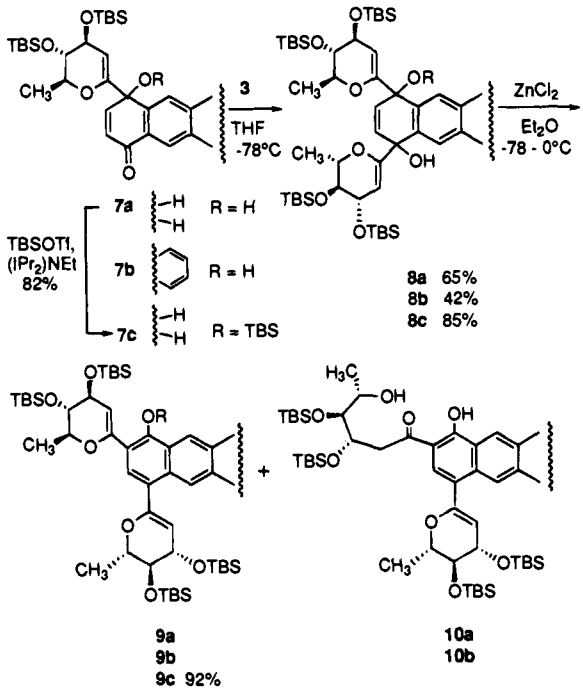
The bis glycals **5** are sensitive to acid with selective hydrolysis of the glycal substituent ortho to the phenolic hydroxyl group taking place on silica gel chromatography.[12] However, the desired bis glycals, free of the ring-opened product **6**, could be obtained in excellent yields from chromatography on neutral alumina.

Even this gentle treatment, however, was not effective for the isolation of the bis glycal products derived from naphthoquinone and 1,4-anthraquinone.[13] In these experiments (Scheme 2), isolation of the desired bis glycals **9** was complicated by

(1) Recipient of an NSF Career Advancement Award, 1992–1993.
(2) Sequin, U. *Prog. Chem. Org. Nat. Prod.* **1986**, 50, 58–122.
(3) Bennett, G. N. *Nucleic. Acids Res.* **1982**, 10, 4581–4594.
(4) (a) Uosaki, Y.; Yasazawa, T.; Hara, M.; Saitoh, Y.; Sano, H. *J. Antibiot.* **1991**, *44*, 40–44. (b) Abe, N.; Enoki, N.; Nakakita, Y.; Uchida, H.; Sato, R.; Watanabe, N. *J. Antibiot.* **1991**, *44*, 908–911. (c) Yasuzawa, T.; Saitoh, Y.; Sano, H. *J. Antibiot.* **1990**, *43*, 485–491. Takahashi, I.; Takahashi, K.-I.; Asano, K.; Kawamoto, I.; Yasuzawa, T.; Ashizawa, T.; Tomita, F.; Nakano, H. *J. Antibiot.* **1988**, *41*, 1151–1153. (d) Brill, G. M.; McAlpine, J. B.; Whittern, D. N.; Buko, A. M. *J. Antibiot.* **1990**, *43*, 229–237. Jackson, M.; Karwowski, J. P.; Theriault, R. J.; Hardy, D. J.; Swanson, S. J.; Barlow, G. J.; Tillis, P. M.; McAlpine, J. B. *J. Antibiot.* **1990**, *43*, 223–228. (e) Paschal, J. W.; Occolowitz, J. L.; Larsen, S. H.; Boeck, L. D.; Mertz, F. P. *J. Antibiot.* **1989**, *42*, 623–626. (f) Sato, Y.; Watabe, H.-o.; Nakazawa, T.; Shomura, T.; Yamamoto, H.; Sezaki, M.; Kondo, S. *J. Antibiot.* **1989**, *42*, 149–152. (g) Nadig, H.; Sequin, U. *Helv. Chim. Acta* **1987**, *70*, 1217–1228.
(5) (a) Hauser, F. M.; Rhee, R. P. *J. Am. Chem. Soc.* **1979**, 101, 1628–1629. (b) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1980**, 45, 3061–3068.
(6) (a) Dubois, E.; Beau, J.-M. *J. Chem. Soc., Chem. Commun.* **1990**, 1191–1192. (b) Dubois, E.; Beau, J.-M. *Carbohydr. Res.* **1992**, 228, 103–120.
(7) For recent reviews, see: (a) Jaramillo, C.; Knapp, S.; *Synthesis* **1994**, 1–20. (b) Suzuki, K.; Matsumoto, T. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products;* Lukacs, G., Ed.; Springer: Berlin, 1993; Vol. 2, pp 352–403.
(8) The proton acid-induced cyclohexadienediol rearrangement (or "dienone–phenol type" rearrangement) was examined by Dodge and Chamberlin: Dodge, J. A.; Chamberlin, A. R. *Tetrahedron Lett.* **1988**, 29, 4827–4830 and references cited therein.
(9) (a) Parker, K. A.; Coburn, C. A. *J. Am. Chem. Soc.* **1991**, 113, 8516–8518. (b) Parker, K. A.; Coburn, C. A. *J. Org. Chem.* **1992**, 57, 5547–5550.
(10) The coupling patterns for the vinyl protons of cyclohexadienediol **4a** (each a dd, $J = 2.1$, 10.0 Hz) were consistent with the expected cis (but not trans) stereochemistry; see: Alonso, F.; Yus, M. *Tetrahedron* **1991**, *35*, 7471–7476. The ^1H NMR spectra for lithioglycal/quinol adducts **8a** and **8b** were also consistent only with the cis products; **4b** was a mixture of two isomers, presumably both cis. Quinol TBS ethers (**7c**, **11a**, and **11b**) added lithioglycals to give both cis and trans adducts; see supplementary material.
(11) Other Lewis acids, including $HgBr_2$, $MgBr_2$, and $LiClO_4$, induced the rearrangement of **4a** to **5a**. However, $ZnCl_2$ was the easiest to handle and gave the cleanest product.
(12) This hydrolysis also took place in $CDCl_3$ solution. Therefore acetone-d_6 was used as the solvent for NMR spectroscopy.
(13) Gupta, D. N.; Hodge, P.; Khan, N. *J. Chem. Soc., Perkin Trans. 1* **1981**, 689–696.

0002-7863/94/1516-11149$04.50/0

Scheme 2



the appearance of the ring-opened byproducts **10**. We suspected that the increased sensitivity of the glycal ortho to the hydroxyl group was the result of increased hydrogen bonding in the naphthol and anthrol products (expected to be more acidic than the phenolic hydroxyl group in the simpler bis glycals **5**). Therefore we modified our procedure to remove this hydroxyl group from the scene.

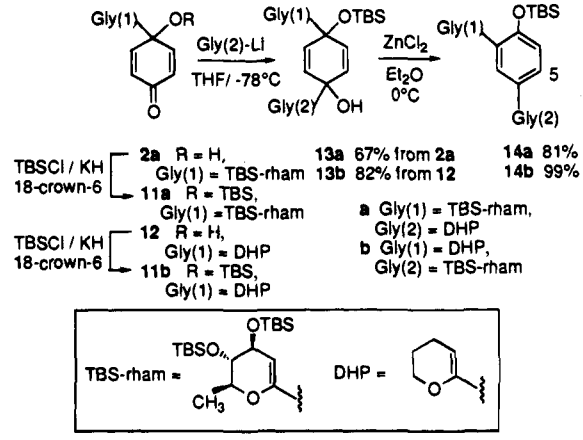
Silylation[14] of quinol glycal **7a** gave quinol silyl ether **7c**. Addition of lithiated glycal **3** produced the diadduct **8c**, which rearranged in excellent yield to bis glycal **9c** upon treatment with $ZnCl_2$. Bis glycal **9c** was stable under weakly acidic conditions, giving no sign of hydrolysis of the glycal substituent in the ortho position.

The isolation of a silyl ether rather than a phenol from the rearrangement of **8c** is consistent with a mechanism in which zinc chloride selectively chelates the hydroxyl group in the presence of the siloxy group.[15] Then formation of the cyclohexadienyl cation, migration of the glycal substituent geminal to the siloxy group, and loss of a proton (rather than the silyl moiety) from the rearranged siloxy-substituted carbonium ion lead to formation of the aromatized product **9c**.

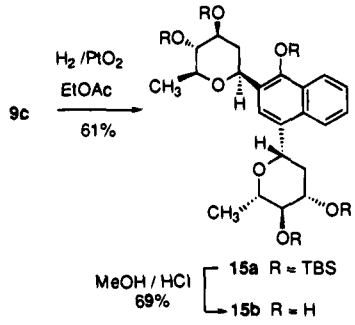
The predilection of our substrate to follow this reaction pathway implies that the regiochemistry of the product of a cyclohexadienediol rearrangement might be controlled by selective silylation of one of the two regioisomeric hydroxyl groups of an unsymmetrical substrate. This premise was tested with the two regioisomeric substrates, cyclohexadienes **13a** and **13b** (Scheme 3).

Silylation[16] of quinol glycal **2a** gave quinol silyl ether **11a** which, without purification, was transformed into diadduct **13a** upon addition of 2-lithiodihydropyran. Subsequent rearrangement of **13a** gave the expected bis glycal **14a**. On the other hand, silylation of dihydropyranyl quinol **12**[9b] gave quinol silyl ether **11b**, which was converted to diadduct **13b** by addition of

Scheme 3



Scheme 4



lithiated glycal **3**. Rearrangement of **13b** afforded **14b**. Structures of bis glycals **14a** and **14b** were confirmed with difference NOE measurements.[17] *Thus, we are able to choose which of two different glycal substituents becomes the migrating group by specifying the order of glycal introduction in the addition/silylation/addition/migration sequence.*

In order to establish the potential of the bis *C*-aryl glycals for elaboration to bis glycosides of the kidamycin type, we examined the desired conversion for model compound **9c**. Hydrogenation over PtO_2[6b] afforded bis glycoside **15a**, and desilylation proceeded smoothly to the kidamycin model **15b** (Scheme 4).

Methodology for the regiospecific synthesis of *o,p*-bis C-glycosylated phenols (kidamycin class of *C*-aryl glycosides) from quinones is therefore now available. The key step is a cyclohexadienediol rearrangement in which regiocontrol is imposed by the regiospecific modification of the substrate by monosilylation. Application of this strategy to the synthesis of kidamycin and extensions of the "reverse polarity" approach to other classes of *C*-aryl glycosides are currently being explored.

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Supplementary Material Available: Experimental procedures and ^1H NMR, ^{13}C NMR, and IR spectroscopic data for **4–6, 7b–8c, 9c–11b,** and **13–15** (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) Boschelli, D.; Takemasa, T.; Nishitani, Y.; Masamune, S. *Tetrahedron Lett.* **1985**, *26*, 5239–5242.

(15) The difference in Lewis basicities of alkyl and silyl ethers is well established; see: Sternbach, G.; Mac Diarmid, A. G. *J. Am. Chem. Soc.* **1961**, *83*, 3384–3388. West, R.; Wilson, L. S.; Powell, D. L. *J. Organomet. Chem.* **1979**, *178*, 5–9. The absence of chelation in siloxy carbonyl compounds has been observed directly and exploited in diastereoselective addition reactions; see: Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281–284. Kahn, S. D.; Keck, G. E.; Hehre, W. J. *Tetrahedron Lett.* **1987**, *28*, 279–280 and references cited therein.

(16) Braish, T. F.; Fuchs, P. L. *Synth. Commun.* **1986**, *16*, 111–115.

(17) For bis glycal **14a**, irradiation of the aromatic proton at δ 7.38 ppm (labeled 5 on the structure) led to enhancement of the enol ether proton of the dihydropyran substituent at δ 5.25. Conversely, for bis glycal **14b**, irradiation of the aromatic proton at δ 7.41 (labeled 5 on the structure) led to enhancement of the enol ether proton of the rhamnal substituent at δ 5.23.