Application of Substituent-Controlled Oxidative Coupling of Glycals in a Synthesis and Structural Corroboration of Ciclamycin 0: New Possibilities for the Construction of Hybrid Anthracyclines

Koji Suzuki, Gary A. Sulikowski, Richard W. Friesen, and Samuel J. Danishefsky*

Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06511-8118. *Received February 8, 1990*

Abstract: A synthesis of ciclamycin 0 (**1**) has been achieved. The required trisaccharide glycal **14** was assembled by substituent-directed iodinative coupling of glycals (see **2** + **3** → **5** and **2** + **7** → **8**). The key anthracycline–trisaccharide attachment was effected by iodinative coupling of ϵ-pyrromycinone (**15**) with **14**. In addition to the expected diaxial product, **16** this reaction gave rise to considerable amounts of the axial glycoside–equatorial iodide product **17** as well as traces of 1,2-diequatorial product. The two major series converged upon de-iodination leading to ciclamycin 0. By employing a similar iodinative coupling of daunomycinone **21** and **14**, this time with improved diaxial stereoselectivity, the ciclamycin–daunomycin hybrid **26** was eventually synthesized.

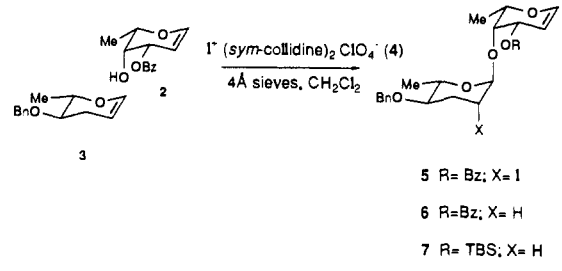
Background and Scope of the Investigation

The ciclamycin complex of antibiotics produced by *streptomyces capoamus* possesses highly inhibitory in vitro activity against experimental tumors[1] and is claimed to be of value against human neoplasia.[2] The antibiotics are apparently largely or entirely composed of η- and ϵ-pyrromycinone aglycones, joined at carbon 7 by glycosidic linkages to variously permuted carbohydrate domains.[3,4] Recently, small amounts of several homogeneous components of the complex were isolated and their structures assigned.[5] One such component, of particularly difficult availability, is ciclamycin 0.[6] Its structure was formulated to be **1**. No intact trisaccharide fragment had been retrieved from hydrolysis of ciclamycin 0. Similarly, no fragments containing a glycosidic bond to the ϵ-pyrromycinone skeleton could be isolated by partial hydrolysis. The structure assigned to ciclamycin 0 is thus based on spectroscopic arguments alone. Our interest in the ciclamycin family arises from ongoing involvements in the chemistry of anthracyclines[7] and in the field of oligosaccharide synthesis.[8]

Extensive research in the bioorganic and biophysical chemistry of anthracycline antibiotics has been directed toward the aglycone sectors and to their interaction with oligonucleotides.[9] However, it is clear that the carbohydrate domains are crucial in endowing the systems with clinically useful activity.[10] Whether the carbohydrate ensembles are required solely for biotransport or whether they also provide contacts for interaction with nucleic acids is an unresolved question.[11] Synthesis could well play a useful role in addressing such issues. Since appropriate aglycones can be secured by total synthesis[12] or by deglycosylation of readily available antibiotics (vide infra), we chose to focus our study on the elaboration of a suitable trisaccharide[13-15] and to use it to glycosylate an appropriate aglycone available by other means.

A synthesis of the carbohydrate sector of ciclamycin 0 posed an interesting challenge from several standpoints. There would be required a strategy and supporting technology for generating a keto group, specifically at $C_{4''}$ (cinerulose sector). Since our goal in this investigation was the synthesis of the entire ciclamycin 0 drug, the particular target carbohydrate system to be assembled would have to be selected with particular care. The carbohydrate sector must be appropriate for glycosylation. Moreover, all resident protecting groups must be dischargeable in a fashion which would allow for retrieval of the intact target molecule.

Scheme I



(1) De Lima, V. Q. G.; Albert, C. A.; De Lima, O. G. *An. Acad. Bras. Cienc.* **1964**, *36*, 317.

(2) Afora, J. J.; Santana, C. F.; De Lima, O. G. *Ann. XVIIth Int. Congr. of Hematology and Hemotherapy*, Paris, 1978, p. 165.

(3) (a) Da Lima, O. G.; Monache, F. D.; D'Albuquerque, I. L. Marini-Bettôlo, G. B. *Tetrahedron Lett.* **1969**, 471. (b) Bieber, L. W.; Da Silva Filho, A. A.; De Mello, J. F.; Von Der Saal, W.; De Lima, O. G. *Rev. Inst. Antibiot. (Recife)* **1982-1983**, *21*, 27.

(4) Oki, T. *Anthracycline Antibiotics* [*Pap. Symp. on Anthracyclines, Aug 24-25, 1981, New York*[; Khakeme, E. Ed.; Academic Press: New York, 1982; p 75.

(5) (a) Bieber, L. W.; Da Silva Filho, A. A.; De Mêllo, J. F.; De Lima, O. G.; Do Nascimento, M. S.; Veith, H. J.; Von Der Saal, W. *J. Antibiot.* **1987**, *40*, 1335. (b) The optical rotation of naturally derived ciclamycin 0 was not provided and could not be measured from the trace sample available to us.

(6) For other examples of anthracyclines which do not contain aminodeoxysugars see: Oki, T. *Jpn. J. Antibiot.* **1977**, *30*, (suppl) S-70. Matsuzawa, Y.; Yoshimoto, A.; Shibamoto, N.; Tobe, H.; Oki, T.; Naganawa, H.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1981**, *34*, 959.

(7) Sulikowski, G.; Turos, E. Unpublished results, Yale University.

(8) (a) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656. (b) Friesen, R. W.; Danishefsky, S. J. *Tetrahedron* **1990**, *46*, 103.

(9) See: Lown, J. W. *Anthracycline and Anthracenedione—Based Anticancer Agents*; 1988; Section 2 (*Bioact. Mol.* **1988**, *6*).

(10) (a) Arcamone, F.; Bargiotti, A.; Cassinelli, G.; Redaelli, S.; Hanessian, S.; Di Marco, A.; Casazza, A. M.; Dasdia, T.; Necco, A.; Reggiani, P.; Supino, R. *J. Med. Chem.* **1976**, *19*, 733. (b) Acton, E. M.; Tong, G. L.; Taylor, D. L.; Streeter, D. G.; Filppi, J. A.; Wolgemuth, R. L. *J. Med. Chem.* **1986**, *29*, 2074. (c) Israel, M.; Murray, R. J. *J. Med. Chem.* **1982**, *25*, 24.

(11) (a) Williams, L. D.; Egli, M.; Gho, Q.; Bash, P.; van Der Marel, G. A.; van Boom, J. H.; Rich, A.; Frederick, C. A. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 2225. (b) Quigley, G. J.; Wang, A. H.-J.; Ughetto, G.; van Der Marel, G.; van Boom, J. H.; Rich, A. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 7204. (c) Wang, A. H.-J.; Ughetto, G.; Quigley, G. J.; Rich, A. *Biochemistry* **1987**, *26*, 1152.

(12) Krohn, K. *Tetrahedron* **1990**, *46*, 291.

(13) Syntheses of trisaccharides relevant to anthracyclines have been elegantly accomplished by the Thiem[14] and Monneret[15] groups. We have not found at this writing an example where a fully synthetic oligosaccharide has been used to glycosylate an anthracyclinone en route to a naturally occurring anthracycline antibiotic.

(14) For a definitive paper setting forth the concepts of the Thiem school in the synthesis of oligosaccharides of anthracyclines and other antibiotics, see: (a) Thiem, J. *Trends in Synthetic Carbohydrate Chemistry*; Horton, D.; Hawkins, L. D.; McGarvey, G. J. Eds. ACS Symposium Series 386, American Chemical Society: Washington, DC, 1989; Chapter 8. See also: (b) Thiem, J.; Klaffke, W. *Carbohydr. Res.* **1988**, *174*, 201. (c) Heyns, K.; Feldmann, J.; Hadamczyk, D.; Schwentner, J.; Thiem, J. *Chem. Ber.* **1981**, *114*, 232. (d) Thiem, J.; Springer, D. *Carbohydr. Res.* **1985**, *136*, 325.

(15) For a definitive paper describing the Monneret contributions, see: (a) Monneret, C.; Martin, A.; Pais, M. *J. Carbohydr. Chem.* **1988**, *7*, 417. For related papers, see: (b) Abbaci, B.; Florent, J. C.; Monneret, C. *J. Chem. Soc., Chem. Commun.* **1989**, 1896.

0002-7863/90/1512-8895$02.50/0

Given our findings in the assembly of oligosaccharides terminating in glycals at their "reducing" termini, it was natural to explore the possibility of synthesizing a trisaccharide glycal as a glycosyl donor with respect to a suitable anthracyclinone "acceptor". In so doing, we hoped to learn more about the applicability of a recently disclosed strategy for the iodinative coupling of two glycals[16] wherein the sense of coupling is controlled by the nature of the resident substituents of the glycals.[8,17] Not infrequently a total synthesis is a particularly informative setting for evaluating the usefulness of new methodology.

As will be shown, success was realized through the specific trisaccharide **14** (vide infra). After achieving the synthesis of compound **14**, its coupling to ε-pyrromycinone and the deprotection of the adduct to provide **1** were accomplished. The structure of ciclamycin 0 was thus established and the methodology was extended to the synthesis of the daunomycin–ciclamycin hybrid **26**.

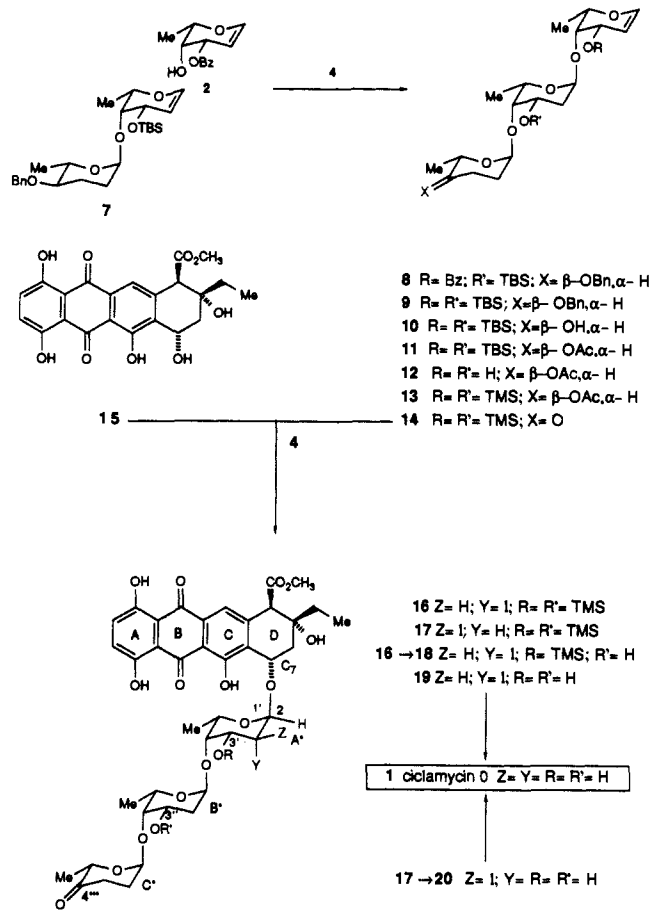
Discussion of Results

While at the outset of the investigation it was not possible for us to identify the specific trisaccharide glycal goal system, it seemed that the generalized matrix we had in mind might be assembled from the known L-fucal derivative **2**[18] and the known 3,6-dideoxy-L-glycal system **3**.[19] As matters transpired, glycal **2** was used at two stages of the synthesis.

Treatment of **2** and **3** in methylene chloride with **4**[20] gave an iododisaccharide **5**, which on reduction with Ph_3SnH afforded **6** (57% overall yield for coupling and reduction) (Scheme I). In line with previous trends,[8a] the benzoyloxy group at C_3 of glycal **2** had apparently deactivated this system relative to **3** with respect to attack by I^+. *The roles of* **2** and **3** *were thus defined to be those of glycosyl acceptor and glycosyl donor, respectively.* After reduction with LAH and reprotection with TBSCl (50% overall) glycal **7** was obtained.[21] The choice of a silyl protecting group at $C_{3''}$ was dictated by the need to clearly distinguish that center from $C_{4'''}$ (bearing a benzyl ether) which was destined to become the sole ketone in the carbohydrate sector. The TBS version of silyl protection was selected with a view to its survival during a metal–ammonia-induced debenzylation at a crucial stage (vide infra). Glycal **7** was to serve as the glycosyl donor in the next iteration with **2**.

Indeed, coupling of **7** with **2** (via **4**) followed by reduction with Ph_3SnH afforded **8** (54%) (Scheme II). Some functional group adjustments were necessary to establish a productive context for the final glycosylation-deblocking phase of the venture. Reduction of **8** with LAH (to remove the benzoyl group) was followed by reprotection to afford the bis TBS derivative **9**. Again a TBS group had been selected for protection at $C_{3'}$ in the hope that it would survive the transformation of the $C_{4'''}$ benzyl ether to the unique ketone function. Given the complex chemistry arising upon two electron reduction of anthracycline antibiotics, any scheme to remove the $C_{4'''}$ benzyl group by reductive methods would have to be implemented before the glycoside attachment was forged.

Scheme II



In the event, the two TBS groups installed at $C_{3'}$ and $C_{3''}$ did indeed prove to be equal to the task. Treatment of **9** with sodium in liquid ammonia provided compound **10** which was converted by Ac_2O–DMAP to **11** (analyzed as its monohydrate), containing a unique acetate in the trideoxy L-gluco ring.

While the TBS versions of the silyl protecting groups had served well to this point, further explorations[21b] indicated that it would not be possible to use them throughout the synthesis. More precisely, there arose severe complications in deprotecting several TBS-protected alcohols after the glycoside bond to the anthracyclinone had been established. Given the results in these probe experiments, it was decided to change the OTBS groups at $C_{3'}$ and $C_{3''}$ to (trimethylsilyl)oxy functions. The TMS ethers were expected to be more readily deprotected (post glycosylation) allowing survival of the fragile anthracyclinone–carbohydrate glycosidic bond. Accordingly, **11** was subjected to the action of TBAF in tetrahydrofuran. Compound **12** thus obtained was re-silylated (TMSCl–DMAP) to afford **13**. The yield of **13** from **8** was 65%. Fortunately the TMS ethers proved to be sufficiently stable to the two steps ((i) LAH–ether| (ii) Dess–Martin periodinane[22] in methylene chloride) required for transformation of **13** → **14**; consequently the stage for the final oxidative coupling was set.

Treatment of **14** and ε-pyrromycinone (**15**)[23] with **4**[20] provided a three component mixture. Each of the two major products, **16** (35%) and **17** (25%), contained the required axial (α) glycosidic

(16) For previous papers in the haloglycosylation of glycals with non glycal glycosyl acceptors, see: (a) reference 14. (b) Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696. (c) Lemieux, R. U.; Fraser-Reid, B. *Can. J. Chem.* **1964**, *42*, 532. For a recent report of the synthesis of 2-deoxy-β-glycosides from glycals, see: Ramesh, S.; Kaila, N.; Gewal, G.; Franck, R. W. *J. Org. Chem.* **1990**, *55*, 5.

(17) An important finding, wherein the glycosyl-donating and glycosyl-accepting role of *n*-pentenyl glycoside can be controlled by the nature of the resident group at the C_2 oxygen was recently reported in several disclosures from Fraser–Reid and co-workers; see: (a) Mootoo, D. R.; Konradsson, P.; Ododong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583. (b) Mootoo, D. R.; Konradsson, P.; Fraser-Reid, B. *Ibid.* **1989**, *111*, 8540. The factors at work in the glycal case are rather more subtle than in the *n*-pentenyl glycoside case wherein the C_2-protecting groups apparently served as an on-off control mechanism. In our work, all of the glycals employed in ref 8 are attacked by the iodonium oxidant. The issue is purely one of competitive rate vis-à-vis the iodonium equivalent reagent **4**. (c) Veeneman, G. H.; van Boom, J. H.; *Tetrahedron Lett.* **1990**, 275.

(18) Compound **2** is prepared by the selective benzoylation of L-fucal derived from the corresponding diacetate: Whistler, R. C.; Wolfrom, M. L. *Methods in Carbohydrate Chemistry*; 1963; Vol. II, 457.

(19) Compound **3** is prepared by benzylation (NaH; BnBr) of the corresponding alcohol, see: Martin, A.; Pais, M.; Monneret, C. *Carbohydr. Res.* **1983**, *113*, 21.

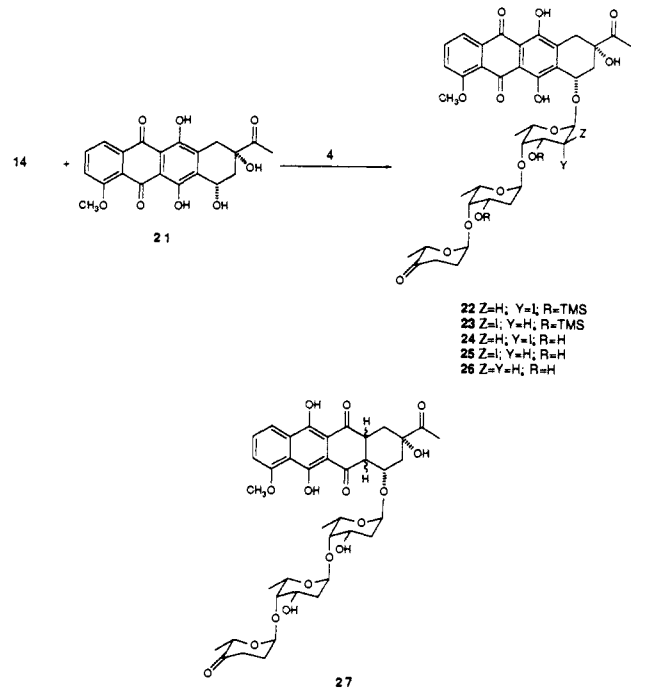
(20) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190.

(21) (a) The low yield for this two-step process is partly attributed to an approximate 10% contamination of an L-fucose derived byproduct from the preceding iodoglycosylation step. (b) Friesen, R. W. Unpublished results, Yale University.

(22) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(23) The aglycone which we used was obtained by removal of the oligosaccharide from the bohemic acid complex; see: Nettleton, D. E.; Bradner, W. T.; Bush, J. A.; Coon, A. B.; Moseley, J. E.; Myllymaki, R. W.; O'Herron, F. A.; Schreiber, R. H.; Vulcano, A. L. *J. Antibiot.* **1977**, *30*, 525.

Scheme III



linkage to the C_7 oxygen, but differed in the stereochemistry of the iodo substituent.[24,25] A third product, not shown here (9%), is one in which the aglycone and iodine functions are equatorial. Compounds **16** and **17** were each converted to ciclamycin 0. Reaction of **16** with methanolic acetic acid led to cleavage of the B′ ring silyl ether, affording **18**. The A′ alcohol was deprotected (TBAF–THF) to afford **19** (54% from **16**). Finally, deiodination of **19** (excess Ph_3SnH; AIBN–benzene)[26] gave a 97% yield of ciclamycin 0 (**1**). The ^1H NMR spectrum at 500 MHz was indistinguishable from that measured for the trace specimen sample provided by Professor Bieber. The melting point of our synthetic sample mp 165.5–166.0 °C, agrees well with the literature value (mp 165–167 °C),[5] and the chromatographic mobilities are in similar accord. The optical rotation of synthetic ciclamycin was $[\alpha]_D = +64.8°$ (*c* 0.29, $CHCl_3$).[5b] The conversion of **17** → **1** was more straightforward in that both of the OTMS groups could be cleaved in a single step (AcOH, THF–MeOH) to afford **20** (83%). Deiodination of the latter (Ph_3SnH, AIBN, benzene) afforded ciclamycin 0 in 79% yield. *There can be no doubt that the structure of ciclamycin had been correctly assigned.*

While the ciclamycins are a promising group of compounds, antibiotics derived from daunomycinone and adriamycinone skeleta have already had wide clinical usage.[9] Accordingly we wondered whether the trisaccharide glycal could be appended to daunomycinone to create a potential hybrid antibiotic. Conceivably such systems might show activity against tumor lines which are resistant to natural anthracyclines. We set compound **26** as our goal. This synthesis would provide an additional opportunity and challenge to study the stereoselectivity of the glycosylation step with **14** and a different sensitive aglycone. Similarly, the final deiodination step would be evaluated in a different setting.

Oxidative coupling of daunomycinone (**21**)[25] with **14** mediated by iodinium salt **4** was carried out in methylene chloride at 0 °C in the presence of molecular sieves (Scheme III). There was obtained a 59% combined yield of glycosides which could be separated into three components. The major product (39%) was the diaxial isomer **22**. The next isomer most prevalent, **23** (16%), has the axial glycoside–equatorial iodide arrangement. A third compound (not shown here), obtained in 5% yield, was presumed to have the glycosidic and iodide bonds diequatorial. Two fold desilylation was achieved in each instance with HF–pyridine to afford **24** (66%) and **25** (60%), respectively. Each of these compounds suffered deiodination with triphenyltin hydride to afford the common ciclamycin–daunomycin hybrid **26** (65% from **24** and 45% from **25**).[26] From this reaction there was also obtained compound **27** (10% from **24** and 15% from **25**) wherein the quinone ring had also undergone reduction.[27] This result is consonant with the work of Koch[28] in that when rapidly followed by tautomerization to ring B diketonic forms, the dihydro product is stabilized vis ā vis elimination of the C_7 glycosidic bond.

Summary

The trisaccharide glycal **14** has been successfully attached to aglycones **15** and **21**. In each case the coupling was far from stereospecific, though with **21** some diaxial selectivity was realized. The factors which cause the erosion of the diaxial selectivity remain to be identified. Post-glycosidation functional group manipulations led to a natural anthracycline antibiotic **1** and to a hybrid structure **26**. To our knowledge the synthesis of **1** is the first recorded case wherein a natural anthracycline containing a trisaccharide domain has been assembled via a fully synthetic glycal as a trisaccharide glycosylating agent.[29,30] Having accomplished this goal, albeit with complications, one is in a better position to consider designing anthracyclines (or other drugs) with extended oligosaccharide domains. Such compounds might be useful in achieving more favorable pharmacological performance than the natural products.

Experimental Section

General. The solvents used in the following experimentals were, unless otherwise indicated, freshly distilled under dry nitrogen according to the following protocols: Tetrahydrofuran and ether were distilled from deep blue solutions of benzophenone ketyl. Benzene was distilled from calcium hydride. Dichloromethane was distilled from phosphorus pentoxide. All reactions requiring anhydrous conditions were conducted under a blanket of dry nitrogen in flame- or oven-dried glassware. Column chromatography was carried out on silica gel 60 (E. Merck 9285, 230–400 mesh). Thin-layer chromatographic analysis was conducted on 0.25-mm silica gel plates with a 254-nm ultraviolet indicator (E. Merck silica gel 60 F-254). Spectroscopic analysis was carried out on the following instruments: IR, Perkin-Elmer 1420; UV-vis, Cary 219; NMR, 500 MHz, Brucker WM500; NMR, 250 MHz, Brucker WM 250. High-resolution (EI, CI, and FAB) mass spectrometric analyses were conducted on a Kratos MS 80 RFA. Low-resolution mass spectrometric analyses were conducted on a Hewlett-packard 5985 mass spectrometer. Melting points were taken on Thomas Hoover apparatus and are uncorrected. Optical rotations were taken on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by Oneida Research Services, Inc.

1,5-Anhydro-3-*O*-benzoyl-2,6-dideoxy-L-*lyxo*-hex-1-enitol (2).[18] A solution of 2,6-diacetoxy-1,5-anhydro-L-*lyxo*-hex-1-enitol (506 mg, 2.36 mmol) in methanol (106 mL) was treated with potassium carbonate (33 mg, 0.236 mmol). The resulting mixture was stirred for 3 h at room temperature. Evaporation of the solvent afforded crude product as a slightly yellow oil. This was purified by flash chromatography (98:2 chloroform–methanol) to give diol (297 mg, 97%) as colorless needles: mp 71–72 °C; $[\alpha]^{22}_D = +18.0°$ (*c* 0.77, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 6.38 (dd, *J* = 1.4, 6.2 Hz, 1 H), 4.67 (dt, *J* = 2.0, 6.2 Hz, 1 H), 4.37 (m, 1 H), 4.04 (q, *J* = 6.5 Hz, 1 H), 3.71 (m, 1 H), 2.31 (d, *J* =

(24) When the iodoglycosylation reaction is slow as in the case of the reaction of **14** and **15** there seems to be a serious loss of stereospecificity. The origin of compound **17**, the apparent product of cis iodoglycosylation, has not been established. It could well be the result of anomerization of the trans diequatorial product. If so, it is a fortunate result since it allows one to convert the otherwise useless diequatorial product to the ciclamycin series. An alternative explanation invokes cationic character at C-1 of the α-iodonium intermediate, see: Kessler, H.; Kling, A.; Kottewhuhn, M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 425.

(25) For reports on iodoglycosylation of adriamycinone derivatives with glycals of monosaccharides, see: (a) Horton, D.; Priebe, W.; Varela, O. *Carbohydr. Res.* **1984**, *130*, C_1. (b) Horton, D.; Priebe, W. *Ibid.* **1985**, *136*, 391. (c) Reference 14.

(26) cf. Horton, D.; Priebe, W.; Sznaidman, M. *Carbohydr. Res.* **1989**, *187*, 149.

(27) The stereochemistry of the ring fusion of **27** is unassigned.

(28) Bird, D. M.; Boldt, M.; Koch, T. H. *J. Am. Chem. Soc.* **1989**, *111*, 1148.

(29) For a report describing an iodoglycosylation of an anthracyclinone monosaccharide with a glycal to produce an anthracyclinone disaccharide, see: Thiem, J.; Klaffke, W. *J. Org. Chem.* **1989**, *54*, 2006.

(30) For the attachment of a trisaccharide, obtained by degradation to an anthracycline to create a hybrid, see: Tanaka, H.; Yoshioka, T.; Shimauchi, Y.; Matsushita, Y.; Matsuzawa, Y.; Oki, T.; Ishikura, T. *J. Antibiot.* **1982**, *35*, 312.

9.5 Hz, 1 H), 1.99 (d, J = 8.4 Hz, 1 H), 1.38 (d, J = 6.5 Hz, 3 H); IR ($CHCl_3$) 3490, 2960, 1615, 1360, 1213, 1060 cm^{-1}.

A solution of diol (2.0 g, 15.4 mmol) in dichloromethane (100 mL) and triethylamine (10.4 mL, 74.6 mmol) was treated with benzoyl chloride (4.3 g, 30.6 mmol). The resulting mixture was stirred at room temperature for 4 h. At that time excess benzoyl chloride was quenched by the addition of methanol (1 mL). Saturated sodium bicarbonate solution (200 mL) was then added. The resulting mixture was extracted (3 × 200 mL) with dichloromethane. The combined organic extracts were washed with brine and dried over anhydrous magnesium sulfate. Filtration and concentration in vacuo followed by flash chromatography (95:5 hexane–ethyl acetate) afforded 805 mg (16%) of 3,4-dibenzoate, 2.80 g (78%) of 3-benzoate **2**, and 210 mg (6%) of 4-benzoate, as colorless oils. Compound **2**: $[\alpha]^{22}_D$ = +86.3° (c 0.54, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 8.07 (d, J = 8.5 Hz, 2 H), 7.62–7.43 (m, 3 H), 6.54 (dd, J = 1.6, 6.3 Hz, 1 H), 5.69 (m, 1 H), 4.78 (dt, J = 1.9, 6.3 Hz, 1 H), 4.19 (q, J = 6.6 Hz, 1 H), 4.11 (m, 1 H), 1.99 (d, J = 7.0 Hz, 1 H), 1.43 (d, J = 6.6 Hz, 3 H); IR ($CHCl_3$) 3000, 1721, 1640, 1448, 1270, 1110, 1082, 1066 cm^{-1}; HRMS m/e 234.0887 (M^+), calcd for $C_{13}H_{14}O_4$ 234.0892.

1,5-Anhydro-4-*O*-benzyl-2,3,6-trideoxy-L-*erythro*-hex-1-enitol (3).[19] To a cold (0 °C) solution of 1,5-anhydro-4-*O*-hydroxy-2,3,6-trideoxy-L-*erythro*-hex-1-enitol (597 mg, 5.30 mmol) in tetrahydrofuran (20 mL) was added solid sodium hydride (60% in oil, 314 mg, 7.85 mmol). After the solution was stirred for 30 min, benzyl bromide (0.93 mL, 7.8 mmol) was then added. This mixture was stirred at room temperature for 14 h. At that time excess sodium hydride was quenched by addition of water (50 mL). The resulting mixture was then extracted (3 × 100 mL) with ether. The combined ethereal extracts were washed with brine and dried over anhydrous magnesium sulfate. Filtration and concentration furnished the crude benzyl ether. The residue was purified by flash chromatography (25:1 hexane–ether). The benzyl ether was further purified by fractional distillation under vacuum (130–140 °C, 15 mmHg) to afford pure benzyl ether **3** (902 mg, 96%) as a colorless oil: $[\alpha]^{23}_D$ = −120.0° (c 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.33 (m, 5 H), 6.29 (distorted d, J = 6 Hz, 1 H), 4.67 (d, J = 11.8 Hz, 1 H), 4.62 (m, 1 H), 4.54 (d, J = 11.8 Hz, 1 H), 3.86 (dq, J = 5.6, 6.3 Hz, 1 H), 3.40 (dt, J = 5.6, 7.9 Hz, 1 H), 2.37 (ddd, J = 1.6, 7.9, and 16.6 Hz, 1 H), 2.06 (ddt, J = 2.5, 7.9, and 16.6 Hz, 1 H), 1.35 (d, J = 6.3 Hz, 3 H); IR ($CHCl_3$) 3062, 3015, 3006, 2930, 2905, 2870, 1656, 1455, 1350, 1240, 1135, 1100, 1066 cm^{-1}; HRMS m/e 204.1166 (M^+), calcd for $C_{13}H_{16}O_2$ 204.1151.

1,5-Anhydro-3-*O*-benzoyl-4-*O*-(4-*O*-benzyl-2,3,6-trideoxy-α-L-*arabino*-hexapyranosyl)-2,6-dideoxy-L-*lyxo*-hex-1-enitol (6). To a solution of glycal **3** (7.0 g, 34.3 mmol) and alcohol **2** (8.85 g, 37.8 mmol) in dichloromethane (600 mL) was added 4-Å sieves (12.0 g). The resulting mixture was stirred at room temperature for 30 min, cooled to 0 °C in an ice bath and stirred for an additional 30 min. The cold reaction mixture was then treated with I(*sym*-collidine)$_2$ClO$_4$ (**4**) (90%, 23.3 g, 44.5 mmol). After the solution was stirred at 0 °C for 30 min, 10% sodium thiosulfate solution (200 mL) was added and the mixture filtered through Celite. The two-phase mixture was then extracted (3 × 500 mL) with dichloromethane, and the organic phases were combined, dried ($MgSO_4$), and concentrated. Flash chromatography (9:1 hexane–ethyl acetate) afforded the iodide **5** (12.8 g). Without further purification the iodide **5** was dissolved in benzene (500 mL) and treated with triphenyltin hydride (9.55 g, 27.2 mmol) and azobis(isobutyronitrile) (120 mg, 0.73 mmol). The mixture was then heated at reflux for 30 min. Evaporation of the solvent provided crude product which was purified by flash chromatography (9:1 hexane–ethyl acetate) to furnish benzoate **6** (8.51 g, 57%) as a colorless oil: $[\alpha]^{23}_D$ = +43.9° (c 0.46, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 8.08 (d, J = 8.0 Hz, 2 H), 7.57–7.22 (m, 8 H), 6.42 (dd, J = 1.1, 6.1 Hz, 1 H), 5.65 (t, J = 4.2 Hz, 1 H), 4.93 (dd, J = 4.2, 6.1 Hz, 1 H), 4.89 (d, J = 2.0 Hz, 1 H), 4.56 (d, J = 11.8 Hz, 1 H), 4.40 (d, J = 11.8 Hz, 1 H), 4.38 (m, 1 H), 4.27 (t, J = 4.2 Hz, 1 H), 3.87 (dq, J = 6.2, 9.2 Hz, 1 H), 3.00 (dt, J = 3.9, 9.2 Hz, 1 H), 1.96–1.65 (m, 4 H), 1.48 (d, J = 6.7 Hz, 3 H), 0.96 (d, J = 6.2 Hz, 3 H); IR ($CHCl_3$) 3060, 3030, 3010, 2940, 2880, 1722, 1644, 1455, 1280, 1250, 1120, 1078 cm^{-1}; HRMS m/e 438.2029 (M^+), calcd for $C_{26}H_{30}O_6$ 438.2043.

1,5-Anhydro-4-*O*-(4-*O*-benzyl-2,3,6-trideoxy-α-L-*arabino*-hexopyranosyl)-3-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-L-*lyxo*-hex-1-enitol (7). A solution of benzoate **6** (5.26 g, 12.0 mmol) in tetrahydrofuran (250 mL) was cooled to 0 °C in an ice bath and treated with lithium aluminum hydride (1 M solution in ether, 24.7 mL, 24.7 mmol), which was added in a dropwise manner. The mixture was stirred at 0 °C for 30 min. Saturated ammonium chloride solution (2 mL) and anhydrous magnesium sulfate were then added and the resulting mixture filtered, and concentrated in vacuo to afford a slightly yellow oil. Flash chromatography (9:1 hexane–ether) provided the corresponding alcohol (2.98 g, 75%) as a colorless oil: $[\alpha]^{23}_D$ = −85.6° (c 1.08, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.34 (m, 5 H), 6.26 (dd, J = 2.0, 6.2 Hz, 1 H), 4.92 (s, 1 H), 4.68 (dt, J = 2.0, 6.2 Hz, 1 H), 4.66 (d, J = 11.6 Hz, 1 H), 4.55 (d, J = 11.6 Hz, 1 H), 4.40 (m, 1 H), 4.14 (q, J = 6.6 Hz, 1 H), 4.07 (d, J = 10.1 Hz, 1 H), 4.00 (dq, J = 6.3, 9.2 Hz, 1 H), 3.74 (m, 1 H), 3.12 (dt, J = 3.8, 9.2 Hz, 1 H), 2.07–1.68 (m, 4 H), 1.33 (d, J = 6.6 Hz, 3 H), 1.27 (d, J = 6.3 Hz, 3 H); IR ($CHCl_3$) 3360, 3012, 3005, 1643, 1455, 1385, 1120, 1100, 1072, 1040, 1005 cm^{-1}; HRMS m/e 334.1782 (M^+), calcd for $C_{19}H_{26}O_5$ 334.1781.

A solution of the alcohol (3.38 g, 10.1 mmol) in dichloromethane (300 mL) was treated with *tert*-butyldimethylsilyl chloride (6.1 g, 40.5 mmol) and imidazole (4.13 g, 60.7 mmol). The mixture was then heated at reflux for 29 h and concentrated in vacuo to afford crude product. The residue was purified by flash chromatography (95:5 hexane–ethyl acetate) to afford ether **7** (3.21 g, 80%) as a colorless oil: $[\alpha]^{23}_D$ = −39.9° (c 0.72, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.33 (m, 5 H), 6.23 (d, J = 6.1 Hz, 1 H), 4.92 (d, J = 2.8 Hz, 1 H), 4.73 (dd, J = 4.8, 6.1 Hz, 1 H), 4.67 (d, J = 11.9 Hz, 1 H), 4.48 (d, J = 11.9 Hz, 1 H), 4.38–4.26 (m, 2 H), 3.95 (t, J = 4.1 Hz, 1 H), 3.91 (m, 1 H), 3.08 (dt, J = 4.0, 10.0 Hz, 1 H), 2.04–1.69 (m, 4 H), 1.39 (d, J = 6.8 Hz, 3 H), 1.25 (d, J = 6.2 Hz, 3 H), 0.91 (s, 9 H), 0.12 (s, 3 H), 0.11 (s, 3 H); IR ($CHCl_3$) 3018, 3010, 1648, 1460, 1390, 1360, 1255, 1130, 1110, 1080 cm^{-1}; HRMS m/e 449.2706 ((M + H)$^+$), calcd for $C_{25}H_{41}O_5Si$ 449.2724.

1,5-Anhydro-3-*O*-benzoyl-4-*O*-[4-*O*-(4-*O*-benzyl-2,3,6-trideoxy-α-L-*arabino*-hexopyranosyl)-3-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl]-2,6-dideoxy-L-*lyxo*-hex-1-enitol (8). To a solution of glycal **7** (338 mg, 0.753 mmol) and alcohol **2** (194 mg, 0.828 mmol) in dichloromethane (20 mL) was added 4-Å sieves (300 mg). The mixture was stirred at room temperature for 30 min, cooled to −78° in a dry ice–acetone bath, and stirred for an additional 30 min. The cold reaction mixture was then treated with I(*sym*-collidine)$_2$ClO$_4$ (**4**) (90%, 510 mg, 0.979 mmol). After the solution was stirred at −78 °C for 30 min, 10% sodium thiosulfate solution (20 mL) was added and the mixture filtered through Celite. The resulting two-phase mixture was then extracted (3 × 30 mL) with dichloromethane, and the organic phases were combined, dried ($MgSO_4$), and concentrated. Flash chromatography (95:5 hexane–ethyl acetate) afforded the iodide (332 mg, 54%) as a colorless oil: $[\alpha]^{22}_D$ = −8.7° (c 0.31, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 8.03 (d, J = 7.4 Hz, 2 H), 7.59–7.40 (m, 3 H), 7.32 (m, 5 H), 6.44 (d, J = 6.0 Hz, 1 H), 5.62 (t, J = 4.5 Hz, 1 H), 4.90 (dd, J = 5.5, 6.0 Hz, 1 H), 4.68 (br s, 1 H), 4.65 (d, J = 11.9 Hz, 1 H), 4.48 (d, J = 11.9 Hz, 1 H), 4.41 (m, 1 H), 4.27 (br s, 1 H), 4.06 (t, J = 3.3 Hz, 1 H), 3.75–3.50 (m, 2 H), 3.04 (m, 1 H), 2.15–1.45 (m, 7 H), 1.21 (d, J = 6.1 Hz, 3 H), 1.16 (br s, 3 H), 0.87 (br s, 12 H), 0.02 (br s, 6 H); IR ($CHCl_3$) 3018, 2985, 2940, 2870, 1718, 1648, 1458, 1390, 1280, 1120, 1080 cm^{-1}. Anal. Calcd for $C_{38}H_{53}O_9ISi$: C, 56.95; H, 6.69. Found: C, 56.43, H, 6.61.

A solution of iodide (279 mg, 0.345 mmol) in benzene (10 mL) was treated with triphenyltin hydride (145 mg, 0.413 mmol) and azobis(isobutyronitrile) (10 mg, 0.06 mmol). The mixture was then heated at reflux for 30 min. The reaction mixture was then cooled to room temperature and concentrated to afford crude product. Flash chromatography (95:5 hexane–ethyl acetate) afforded benzoate **8** (220 mg, 93%) as a colorless glass: $[\alpha]^{23}_D$ = −30.0° (c 0.24, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 8.04 (d, J = 7.1 Hz, 2 H), 7.58–7.42 (m, 3 H), 7.32 (m, 5 H), 6.41 (d, J = 6.1 Hz, 1 H), 5.60 (t, J = 4.8 Hz, 1 H), 5.05 (d, J = 2.2 Hz, 1 H), 4.92 (t, J = 5.5 Hz, 1 H), 4.83 (d, J = 2.6 Hz, 1 H), 4.64 (d, J = 11.8 Hz, 1 H), 4.47 (d, J = 11.8 Hz, 1 H), 4.41 (q, J = 6.5 Hz, 1 H), 4.26 (t, J = 4.5 Hz, 1 H), 4.16 (dq, J = 6.2, 9.6 Hz, 1 H), 4.03 (d, J = 10.9 Hz, 1 H), 3.92 (q, J = 6.7 Hz, 1 H), 3.50 (br s, 1 H), 3.02 (dt, J = 4.3, 9.6 Hz, 1 H), 2.11 (dt, J = 3.7, 12.3 Hz, 1 H), 2.04–1.55 (m, 5 H), 1.51 (d, J = 6.7 Hz, 3 H), 1.20 (d, J = 6.2 Hz, 3 H), 1.05 (d, J = 6.5 Hz, 3 H), 0.80 (s, 9 H), −0.06 (s, 3 H), −0.08 (s, 3 H); IR ($CHCl_3$) 3020, 2962, 2942, 2870, 1719, 1650, 1460, 1380, 1340, 1280, 1255, 1116, 1083, 1014 cm^{-1}. Anal. Calcd for $C_{38}H_{54}O_9Si$: C, 65.58; H, 7.70. Found: C, 66.83; H, 7.97.

1,5-Anhydro-4-*O*-[4-*O*-(4-*O*-benzyl-2,3,6-trideoxy-α-L-*arabino*-hexopyranosyl)-3-*O*-(*tert*-butyldimethylsilyl)-α-L-*lyxo*-hexopyranosyl]-3-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-L-*lyxo*-hex-1-enitol (9). A solution of benzoate **8** (1.70 g, 2.49 mmol) in ether (120 mL) was cooled to 0 °C in an ice bath and treated with lithium aluminum hydride (1 M solution in ether, 2.5 mL, 2.5 mmol), which was added in a dropwise manner. The mixture was stirred at 0 °C for 1.5 h. Saturated ammonium chloride solution (0.5 mL) and anhydrous magnesium sulfate were then added, and the resulting mixture was filtered and concentrated in vacuo to afford crude alcohol. The alcohol was dissolved in dimethylformamide (50 mL), and *tert*-butyldimethylsilyl chloride (1.12 g, 7.43 mmol) and imidazole (678 mg, 9.96 mmol) were added. The mixture was then heated to 50 °C for 4 h. Water (200 mL) was added, and the mixture was extracted (3 × 100 mL) with benzene. The combined

organic extracts were then washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography (95:5 hexane–ethyl acetate) furnished silyl ether **9** (1.37 g, 79%) as a colorless oil: $[\alpha]^{23}_D = -89.6°$ (*c* 0.43, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.34 (m, 5 H), 6.22 (d, *J* = 6.2 Hz, 1 H), 5.07 (d, *J* = 2.0 Hz, 1 H), 4.93 (d, *J* = 2.6 Hz, 1 H), 4.67 (d, *J* = 11.9 Hz, 1 H), 4.66 (dd, *J* = 1.5 and 6.2 Hz, 1 H), 4.49 (d, *J* = 11.9 Hz, 1 H), 4.30–4.23 (m, 4 H), 4.17 (q, *J* = 6.7 Hz, 1 H), 3.86 (t, *J* = 4.0 Hz, H), 3.64 (br s, 1 H), 3.06 (dt, *J* = 4.0, 10.0 Hz, 1 H), 2.12 (dt, *J* = 3.3, 12.0 Hz, 1 H), 2.07–1.58 (m, 5 H), 1.38 (d, *J* = 6.8 Hz, 3 H), 1.24 (d, *J* = 6.2 Hz, 3 H), 1.21 (d, *J* = 6.7 Hz, 3 H), 0.92 (s, 9 H), 0.91 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 6 H), 0.07 (s, 3 H); IR ($CHCl_3$) 3020, 2965, 2940, 2870, 1648, 1476, 1469, 1390, 1368, 1260, 1112, 1080, 1010 cm^{-1}. Anal. Calcd for $C_3{}_-H_{64}O_8Si_2$: C, 64.29; H, 9.44. Found: C, 64.12; H, 9.31.

4-*O*-[4-*O*-(4-*O*-Acetoxy-2,3,6-trideoxy-α-L-*arabino*-hexopyranosyl)-3-*O*-(*tert*-butyldimethylsilyl)-α-L-*lyxo*-hexopyranosyl]-1,5-anhydro-3-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-L-*lyxo*-hex-1-enitol (11). Liquid ammonia (ca. 130 mL) was collected via a dry ice condenser in a 500-mL three-necked flask cooled to −78 °C in a dry ice–acetone bath and sodium metal (445 mg, 19.35 mmol) was added. To the resulting dark blue solution was then added a solution of silyl ether **9** (1.34 g, 1.93 mmol) in tetrahydrofuran (60 mL). After the solution was stirred for 10 min, solid ammonium chloride was added at which time the solution became colorless. The dry ice condenser and dry ice–acetone bath were removed and the liquid ammonia was allowed to evaporate as the mixture slowly warmed to room temperature. The resulting slurry was diluted with chloroform (200 mL) and dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford crude alcohol **10**. The alcohol **10** was then dissolved in dichloromethane (100 mL) and treated with triethylamine (1.35 mL, 9.69 mmol), 4-(dimethylamino)-pyridine (47 mg, 0.385 mmol), and acetic anhydride (0.92 mL, 9.75 mmol). The resulting mixture was stirred at room temperature for 12 h. Saturated sodium bicarbonate solution (100 mL) was then added, and the mixture was extracted (3 × 150 mL) with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to provide crude acetate **11**. Flash chromatography (95:5 hexane–ethyl acetate) furnished acetate **11** (1.09 g, 87%) as a colorless oil: $[\alpha]^{22}_D = -67.8°$ (*c* 0.18, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 6.22 (d, *J* = 6.5 Hz, 1 H), 5.08 (d, *J* = 3.0 Hz, 1 H), 4.97 (d, *J* = 2.8 Hz, 1 H), 4.67 (dd, *J* = 4.1, 6.5 Hz, 1 H), 4.47 (m, 1 H), 4.38–4.14 (m, 5 H), 3.86 (t, *J* = 4.5 Hz, 1 H), 3.67 (br s, 1 H), 2.13 (dt, *J* = 2.2, 12.6 Hz, 1 H), 2.06–1.75 (m, 5 H), 2.04 (s, 3 H), 1.38 (d, *J* = 7.0 Hz, 3 H), 1.21 (d, *J* = 6.9 Hz, 3 H), 1.11 (d, *J* = 6.2 Hz, 3 H), 0.93 (s, 9 H), 0.91 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 6 H), 0.07 (s, 3 H); IR ($CHCl_3$) 2938, 2918, 2840, 1720, 1632, 1247, 1100, 1069, 1015, 1000 cm^{-1}. Anal. Calcd for $C_{32}H_{60}O_9Si_2 \cdot 1H_2O$: C, 57.97; H, 9.43; Si, 8.47. Found: C, 58.13; H, 9.34; Si, 8.73.

4-*O*-[4-*O*-(4-*O*-Acetyl-2,3,6-trideoxy-α-L-*arabino*-hexopyranosyl)-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl]-1,5-anhydro-2,6-dideoxy-L-*lyxo*-hex-1-enitol (12). A solution of silyl ether **11** (2.90 g, 4.50 mmol) in tetrahydrofuran (200 mL) was cooled to 0 °C in an ice bath. To this cooled solution was added tetrabutylammonium fluoride (1 M solution in tetrahydrofuran, 18.0 mL, 18.0 mmol). The resulting mixture was stirred at room temperature for 5 h. Evaporation of the solvent afforded crude product which was purified by flash chromatography (9:1 hexane–ethyl acetate) to furnish diol **12** (1.87 g, 100%) as a colorless oil: $[\alpha]^{22}_D = -119.5°$ (*c* 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 6.26 (dd, *J* = 2.3, 6.4 Hz, 1 H), 5.13 (d, *J* = 3.6 Hz, 1 H), 4.82 (s, 1 H), 4.66 (dt, *J* = 1.9, 6.4 Hz, 1 H), 4.56 (m, 1 H), 4.38 (m, 1 H), 4.23 (q, *J* = 6.8 Hz, 1 H), 4.13 (dd, *J* = 2.8, 6.7 Hz, 1 H), 4.19–4.02 (m, 2 H), 4.06 (d, *J* = 10.4 Hz, 1 H), 3.88 (d, *J* = 9.8 Hz, 1 H), 3.73 (d, *J* = 4.3 Hz, 1 H), 3.61 (d, *J* = 2.5 Hz, 1 H), 2.07 (s, 3 H), 2.06–1.85 (m, 6 H), 1.35 (d, *J* = 6.8 Hz, 3 H), 1.22 (d, *J* = 7.0 Hz, 3 H), 1.19 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 170.4, 143.6, 102.8, 99.7, 99.4, 82.7, 77.7, 72.7, 72.6, 68.7, 67.5, 65.4, 65.0, 34.6, 28.8, 23.7, 21.1, 17.6, 17.0, 16.8; IR ($CHCl_3$) 3380, 2961, 2910, 1721, 1632, 1368, 1240, 1110, 1090, 1035, 1030, 1014, 995 cm^{-1}. Anal. Calcd for $C_{20}H_{32}O_9$: C, 57.68; H, 7.75. Found: C, 57.42; H, 7.74.

4-*O*-[4-*O*-(4-*O*-Acetyl-2,3,6-trideoxy-α-L-*arabino*-hexopyranosyl)-2,6-dideoxy-3-*O*-(trimenthylsilyl)-α-L-*lyxo*-hexopyranosyl]-1,5-anhydro-2,6-dideoxy-3-*O*-(trimethylsilyl)-L-*lyxo*-hex-1-enitol (13). A solution of diol **12** (590 mg, 1.42 mmol), triethylamine (1.19 mL, 8.54 mmol), and 4-(dimethylamino)pyridine (17.3 mg, 0.142 mmol) in dichloromethane (60 mL) was cooled to 0 °C in an ice bath. The cooled solution was treated with trimethylsilyl chloride (0.72 mL, 5.67 mmol) which was added in a dropwise manner. The mixture was stirred at 0 °C for 30 min. Water (50 mL) was then added and resulting mixture was extracted (3 × 100 mL) with dichloromethane. The combined organic extracts were then dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to furnish crude product. Flash chromatography (9:1 hexane–ethyl acetate) afforded silyl ether **13** (785 mg, 99%) as a colorless oil: $[\alpha]^{22}_D = -164.2°$ (*c* 0.19, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 6.26 (dd, *J* = 1.3, 6.2 Hz, 1 H), 5.10 (d, *J* = 3.2 Hz, 1 H), 4.88 (d, *J* = 2.8 Hz, 1 H), 4.60 (dd, *J* = 1.0, 6.2 Hz, 1 H), 4.54–4.38 (m, 3 H), 4.28 (q, *J* = 6.7 Hz, 1 H), 4.20–4.13 (m, 2 H), 3.79 (dd, *J* = 2.1, 4.5 Hz, 1 H), 3.64 (d, *J* = 2.6 Hz, 1 H), 2.12 (dt, *J* = 3.5, 12.2 Hz, 1 H), 2.05 (s, 3 H), 2.10–1.75 (m, 5 H), 1.54 (d, *J* = 6.7 Hz, 3 H), 1.18 (d, *J* = 6.7 Hz, 3 H), 1.12 (d, *J* = 5.7 Hz, 3 H), 0.15 (s, 9 H), 0.14 (s, 9 H); IR ($CHCl_3$), 2938, 1720, 1632, 1249, 1100, 1020, 1000 cm^{-1}; HRMS *m/e* 583.2774 ((M + Na)$^+$), calcd for $C_{26}H_{48}O_9NaSi_2$ 583.2735.

1,5-Anhydro-2,6-dideoxy-4-*O*-[4-*O*-(2,3,6-trideoxy-α-L-*glycero*-hexopyranosid-4-ulosyl)-2,6-dideoxy-3-*O*-(trimethylsilyl)-α-L-*lyxo*-hexopyranosyl]-3-*O*-(trimethylsilyl)-L-*lyxo*-hex-1-enitol (14). A solution of acetate **13** (726 mg, 1.29 mmol) in tetrahydrofuran (76 mL) was cooled to 0 °C in an ice bath. The solution was treated with lithium aluminum hydride (1 M solution in ether, 0.97 mL, 0.97 mmol) which was added in a dropwise manner. The resulting mixture was stirred at 0 °C for 30 min. Saturated ammonium chloride solution (0.5 mL) and anhydrous magnesium sulfate were added. The mixture was then filtered and concentrated in vacuo to afford crude product. Flash chromatography (3:1 hexane–ethyl acetate) provided the corresponding alcohol (614 mg, 82%) as a colorless glass: $[\alpha]^{22}_D = -123.6°$ (*c* 0.28, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 6.25 (dd, *J* = 1.0, 6.1 Hz, 1 H), 5.10 (d, *J* = 3.1 Hz, 1 H), 4.86 (d, *J* = 2.4 Hz, 1 H), 4.61 (dd, *J* = 3.0, 6.1 Hz, 1 H), 4.39 (m, 1 H), 4.27 (q, *J* = 6.6 Hz, 1 H), 4.28–4.12 (m, 4 H), 3.79 (dd, *J* = 1.9, 4.7 Hz, 1 H), 3.64 (d, *J* = 2.8 Hz, 1 H), 3.24 (m, 1 H), 2.11 (dt, *J* = 3.6, 12.5 Hz, 1 H), 2.05–1.61 (m, 5 H), 1.34 (d, *J* = 7.0 Hz, 3 H), 1.23 (d, *J* = 6.1 Hz, 3 H), 1.18 (d, *J* = 6.6 Hz, 3 H), 0.15 (s, 18 H); IR ($CHCl_3$) 3365, 2938, 1632, 1244, 1110, 1096, 1063, 1040, 1012, 992 cm^{-1}. Anal. Calcd for $C_{24}H_{46}O_8Si_2$: C, 55.56; H, 8.94. Found: C, 55.44; H, 9.03.

A solution of alcohol (300 mg, 0.578 mmol) in dichloromethane (45 mL) was treated with sodium bicarbonate (1.75 g, 20.8 mmol) and the Dess-Martin periodinate (590 mg, 1.39 mmol).[22] The mixture was stirred at room temperature for 50 min, 10% sodium thiosulfate solution (50 mL) and saturated sodium bicarbonate solution (50 mL) were then added. The resulting biphasic mixture was stirred for an additional 30 min. The mixture was then extracted (3 × 100 mL) with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford crude ketone. Flash chromatography (9:1 hexane–ethyl acetate) furnished ketone **14** (286 mg, 95%) as a colorless solid. Recrystallization from ethanol–H_2O gives colorless needles: mp 104–105 °C; $[\alpha]^{2\infty}_D = -271.4°$ (*c* 0.28, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 6.24 (dd, *J* = 1.6, 6.2 Hz, 1 H), 5.12–5.06 (m, 2 H), 4.90 (q, *J* = 6.6 Hz, 1 H), 4.60 (dd, *J* = 3.0, 6.2 Hz, 1 H), 4.40 (br s, 1 H), 4.33 (q, *J* = 6.7 Hz, 1 H), 4.28–4.15 (m, 1 H), 4.15 (q, *J* = 6.7 Hz, 1 H), 3.78–3.70 (m, 2 H), 2.69 (dt, *J* = 7.7, 15.7 Hz, 1 H), 2.42 (dt, *J* = 6.3, 15.7 Hz, 1 H), 2.28–2.17 (m, 2 H), 2.06 (dt, *J* = 3.6, 13.5 Hz, 1 H), 1.76 (dd, *J* = 4.2, 13.5 Hz, 1 H), 1.33 (d, *J* = 6.7 Hz, 3 H), 1.26 (d, *J* = 6.7 Hz, 3 H), 1.22 (d, *J* = 6.6 Hz, 3 H), 0.16 (s, 9 H), 0.13 (s, 9 H); IR ($CHCl_3$) 2960, 2920, 1714, 1632, 1245, 1160, 1100, 1018 cm^{-1}. Anal. Calcd for $C_{24}H_{44}O_8Si_2$: C, 55.78; H, 8.58; Si, 10.87. Found: C, 55.72; H, 8.69; Si, 11.24.

Reaction of ϵ-Pyrromycinone (15) and Trisaccharide 14. To a solution of ϵ-pyrromycinone (**15**) (886 mg, 2.07 mmol) and ketone **14** (1.07 g, 2.07 mmol) in dichloromethane (200 mL) was added 4-Å sieves (1.5 g). The mixture was stirred at room temperature for 30 min, cooled to 0 °C in an ice bath, and stirred for an additional 30 min. The cold reaction mixture was then treated with I(*sym*-collidine)$_2ClO_4$ (90%, 1.40 g, 2.69 mmol). After the solution was stirred at 0 °C for 20 min, 10% sodium thiosulfate solution (200 mL) was added and the mixture was filtered through Celite. The resulting mixture was then extracted (3 × 200 mL) with dichloromethane, and the organic phases were combined, dried ($MgSO_4$), and concentrated. Flash chromatography on 2% KH_2PO_4–silica gel (8:2 hexane–ethyl acetate) furnished 208 mg (9%) of 2′-epi **17**, 562 mg (25%) of **17**, and 770 mg (35%) of **16**.

7-*O*-[4-*O*-[4-*O*-(2,3,6-Trideoxy-α-L-*glycero*-hexopyranosid-4-ulosyl)-2,6-dideoxy-3-*O*-(trimethylsilyl)-α-L-*lyxo*-hexopyranosyl]-2,6-dideoxy-2-Iodo-3-*O*-(trimethylsilyl)-β-L-galactopyranosyl]-ϵ-pyrromycinone: mp 159.5–160 °C dec; $[\alpha]^{2\infty}_D = +208.90$ (*c* 0.27, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 9.81 (s, 1 H), 9.31 (s, 1 H), 9.10 (s, 1 H), 7.71 (s, 1 H), 7.31 (d, *J* = 9.5 Hz, 1 H), 7.27 (d, *J* = 9.5 Hz, 1 H), 5.59 (d, *J* = 1.5 Hz, 1 H), 5.05 (t, *J* = 3.4 Hz, 1 H), 4.99 (d, *J* = 9.1 Hz, 1 H), 4.93 (br s, 1 H), 4.84 (q, *J* = 6.6 Hz, 1 H) 4.24 (s, 1 H), 4.25–4.10 (m, 1 H), 4.15 (s, 1 H), 3.99 (dd, *J* = 9.1, 10.5 Hz, 1 H), 4.78–4.65 (m, 3 H), 3.66 (s, 3 H), 3.59 (q, *J* = 6.2 Hz, 1 H), 3.45 (d, *J* = 2.7 Hz, 1 H), 2.71–2.15 (m, 6 H), 2.01 (dt, *J* = 3.1, 10.2 Hz, 1 H), 1.80–1.46 (m, 3 H), 1.22 (d, *J* = 6.6 Hz, 3 H), 1.19 (d, *J* = 6.2 Hz, 3 H), 1.16 (d, *J* = 6.6 Hz, 3 H), 1.10 (t, *J* = 7.3 Hz, 3 H), 0.24 (s, 9 H), 0.08 (s, 9 H); IR ($CHCl_3$) 3490, 2928, 1718, 1590, 1442, 1290, 1248, 1152, 1096, 1010,

1002, 900, 890, 840 cm^{-1}. Anal. Calcd for $C_{46}H_{63}O_{17}ISi_2$: C, 51.58; H, 5.93; Si, 5.24. Found: C, 50.99; H, 5.87; Si, 5.28.

7-*O*-[4-*O*-[4-*O*-(2,3,6-Trideoxy-α-L-*glycero*-hexopyranosid-4-ulosyl)-2,6-dideoxy-3-*O*-(trimethylsilyl)-α-L-*lyxo*-hexopyranosyl)]-2,6-dideoxy-2-iodo-3-*O*-(trimethylsilyl)-α-L-galactopyranosyl]-ε-pyrromycinone (17): $[\alpha]^{22}_D$ = +125.9 (*c* 0.54, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 9.74 (s, 1 H), 9.08 (s, 1 H), 9.01 (s, 1 H), 7.74 (s, 1 H), 7.31 (d, *J* = 9.5 Hz, 1 H), 7.27 (d, *J* = 9.5 Hz, 1 H), 5.60 (d, *J* = 3.1 Hz, 1 H), 5.38 (br s, 1 H), 5.06 (t, *J* = 3.7 Hz, 1 H), 4.99 (d, *J* = 1.2 Hz, 1 H), 4.85 (q, *J* = 6.7 Hz, 1 H), 4.29–4.11 (m, 6 H), 4.17 (s, 1 H), 3.80–3.62 (m, 2 H), 3.68 (s, 3 H), 2.74–2.16 (m, 6 H), 2.02 (dt, *J* = 3.4, 11.8 Hz, 1 H), 1.86–1.45 (m, 3 H), 1.27 (d, *J* = 6.7 Hz, 3 H), 1.24 (d, *J* = 6.7 Hz, 3 H), 1.20 (d, *J* = 6.5 Hz, 3 H), 1.08 (t, *J* = 7.2 Hz, 3 H), 0.15 (s, 18 H); IR ($CHCl_3$) 3480, 2930, 1718, 1590, 1443, 1310, 1285, 1245, 1150, 1110, 1095, 1000, 900, 870, 840 cm^{-1}. Anal. Calcd for $C_{46}H_{62}O_{17}ISi_2$: C, 51.58; H, 5.93; Si, 5.24. Found: C, 51.80; H, 6.07; Si, 5.30.

7-*O*-[4-*O*-[4-*O*-(2,3,6-Trideoxy-α-L-*glycero*-hexopyranosid-4-ulosyl)-2,6-dideoxy-3-*O*-(trimethylsilyl)-α-L-*lyxo*-hexopyranosyl]-2,6-dideoxy-2-iodo-3-*O*-(trimethylsilyl)-α-L-talopyranosyl]-ε-pyrromycinone (16): mp 156–157 °C; $[\alpha]^{22}_D$ = −6.1° (*c* 0.44, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 9.76 (s, 1 H), 9.13 (s, 1 H), 9.04 (s, 1 H), 7.75 (s, 1 H), 7.36 (d, *J* = 9.0 Hz, 1 H), 7.32 (d, *J* = 9.0 Hz, 1 H), 5.91 (br s, 1 H), 5.30 (br s, 1 H), 5.11 (t, *J* = 3.6 Hz, 1 H), 4.95–4.78 (m, 2 H), 4.48 (br s, 2 H), 4.21–4.10 (m, 1 H), 4.14 (s, 1 H), 3.98 (br s, 1 H), 3.80–3.60 (m, 1 H), 3.78 (d, *J* = 2.7 Hz, 1 H), 3.71 (s, 3 H), 3.33 (br s, 1 H), 2.70 (dt, *J* = 7.3, 15.9 Hz, 1 H), 2.58–2.18 (m, 6 H), 2.06 (dt, *J* = 4.1, 11.4 Hz, 1 H), 1.85–1.43 (m, 3 H), 1.32 (br s, 3 H), 1.27 (d, *J* = 6.6 Hz, 3 H), 1.22 (d, *J* = 6.2 Hz, 3 H), 1.10 (t, *J* = 7.4 Hz, 3 H), 0.17 (s, 9 H), 0.12 (br s, 9 H); IR ($CHCl_3$) 3495, 2960, 2930, 1720, 1591, 1445, 1396, 1310, 1290, 1248, 1156, 1120, 1100, 1010, 979 cm^{-1}. Anal. Calcd for $C_{46}H_{63}O_{17}ISi_2$: C, 51.58; H, 5.93; Si, 5.24. Found: C, 51.51; H, 5.92; Si, 5.17.

7-*O*-[4-*O*-[4-*O*-(2,3,6-Trideoxy-α-L-*glycero*-hexopyranosid-4-ulosyl)-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl]-2,6-dideoxy-β-L-*lyxo*-pyranosyl]-ε-pyrromycinone. (C$_1$· Epiclclamycin 0). A solution of trans-diequatorial-substituted compound (120 mg, 0.112 mmol) in a 3:3:2 mixture of acetic acid, tetrahydrofuran, and methanol (20 mL) was stirred at room temperature for 36 h. Saturated sodium bicarbonate solution (200 mL) was then added, and the mixture was extracted (3 × 100 mL) with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford crude diol. The residue was chromatographed on 2% KH_2PO_4–silica gel (99.5:0.5 dichloromethane–methanol) to furnish diol (86 mg, 83%) as a red solid. Recrystallization from methanol gives 2′-epi **20** as red needles: mp 148.5–149.0 °C dec; $[\alpha]^{22}_D$ = +263.5° (*c* 0.40, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 9.72 (s, 1 H), 9.08 (s, 1 H), 9.00 (s, 1 H), 7.71 (s, 1 H), 7.32 (d, *J* = 9.5 Hz, 1 H), 7.27 (d, *J* = 9.5 Hz, 1 H), 5.52 (d, *J* = 2.7 Hz, 1 H), 5.04 (t, *J* = 7.2 Hz, 1 H), 4.99 (d, *J* = 8.9 Hz, 1 H), 4.92 (d, *J* = 2.2 Hz, 1 H), 4.42 (q, *J* = 6.7 Hz, 1 H), 4.25 (s, 1 H), 4.18 (s, 1 H), 4.09 (q, *J* = 6.5 Hz, 1 H), 4.05 (m, 1 H), 3.80–3.66 (m, 4 H), 3.66 (s, 3 H), 3.54 (d, *J* = 1.8 Hz, 1 H), 2.63 (d, *J* = 14.6 Hz, 1 H), 2.54–2.46 (m, 5 H), 2.18–1.45 (m, 6 H), 1.27 (d, *J* = 6.7 Hz, 3 H), 1.22 (d, *J* = 6.5 Hz, 3 H), 1.12 (d, *J* = 6.3 Hz, 3 H), 1.10 (t, *J* = 7.2 Hz, 3 H); IR ($CHCl_3$) 3480, 3400, 2920, 1720, 1590, 1443, 1288, 1152, 1100, 1030, 1003 cm^{-1}; HRMS (FAB) *m/e* 949.1799 ((M + Na)$^+$) calcd for $C_{40}H_{47}O_{17}INa$ 949.1756.

A solution of diol (50 mg, 0.054 mmol) in benzene (50 mL) was treated with triphenyltin hydride (455 mg, 1.30 mmol) and azobis(isobutyronitrile) (5.5 mg, 0.034 mmol). This mixture was then heated at reflux for 40 min. Evaporation of the solvent gave crude product which was purified by flash chromatography on 2% KH_2PO_4–silica gel (99.6:0.4 dichloromethane–methanol) to afford 1′-epiciclamycin 0 (34 mg, 79%) as a red solid: mp 143–144 °C dec; $[\alpha]^{22}_D$ = +213.2° (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 9.71 (s, 1 H), 9.14 (s, 1 H), 9.01 (s, 1 H), 7.70 (s, 1 H), 7.32 (d, *J* = 9.5 Hz, 1 H), 7.27 (d, *J* = 9.5 Hz, 1 H), 5.51 (t, *J* = 1.9 Hz, 1 H), 5.05 (t, *J* = 5.6 Hz, 1 H), 4.92 (d, *J* = 2.5 Hz, 1 H), 4.86 (dd, *J* = 1.9, 8.41 Hz, 1 H), 4.64 (s, 1 H), 4.44 (q, *J* = 6.7 Hz, 1 H), 4.21–4.03 (m, 3 H), 4.17 (s, 1 H), 3.75–3.60 (m, 1 H), 3.67 (s, 3 H), 3.53 (q, *J* = 6.2 Hz, 1 H), 3.45 (d, *J* = 0.9 Hz, 1 H), 2.52–2.36 (m, 5 H), 2.20–1.96 (m, 3 H), 1.86 (dt, *J* = 1.4, 12.5 Hz, 1 H), 1.75–1.45 (m, 5 H), 1.28 (d, *J* = 6.7 Hz, 3 H), 1.21 (d, *J* = 6.8 Hz, 3 H), 1.18 (d, *J* = 6.2 Hz, 3 H), 1.08 (t, *J* = 7.2 Hz, 3 H); IR ($CHCl_3$) 3410, 2920, 1721, 1591, 1444, 1310, 1290, 1156, 1095, 1035, 1010, 905 cm^{-1}; HRMS (FAB) *m/e* 823.2852 ((M + Na)$^+$) calcd for $C_{40}H_{48}O_{17}Na$ 823.2789.

7-*O*-[4-*O*-[4-*O*-(2,3,6-Trideoxy-α-L-*glycero*-hexopyranosid-4-ulosyl)-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl]-2,6-dideoxy-2-iodo-α-L-galactopyranosyl]-ε-pyrromycinone (20). A solution of iodide **17** (121 mg, 0.113 mmol) in a 3:2:2 mixture of acetic acid, tetrahydrofuran, and methanol (20 mL) was stirred at room temperature for 42 h. Saturated sodium bicarbonate solution (200 mL) was then added and the mixture was extracted (3 × 100 mL) with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford crude diol. The residue was chromatographed on 2% KH_2PO_4–silica gel (99.7:0.3 dichloromethane–methanol) to furnish diol **20** (83 mg, 79%) as a red solid. Recrystallization from isopropyl alcohol gives red needles: mp 155 °C dec; $[\alpha]^{22}_D$ = +170.6° (*c* 0.33, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 9.74 (s, 1 H), 9.07 (s, 1 H), 9.01 (s, 1 H), 7.73 (s, 1 H), 7.31 (d, *J* = 9.5 Hz, 1 H), 7.27 (d, *J* = 9.5 Hz, 1 H), 5.60 (d, *J* = 3.4 Hz, 1 H), 5.36 (br s, 1 H), 5.07 (t, 6.5 Hz, 1 H), 4.96 (d, *J* = 2.7 Hz, 1 H), 4.45 (q, *J* = 6.7 Hz, 1 H), 4.27 (q, *J* = 6.2 Hz, 1 H), 4.22–4.05 (m, 4 H), 4.16 (s, 1 H), 3.84–3.72 (m, 3 H), 3.68 (s, 3 H), 2.57 (dd, *J* = 4.3, 15.5 Hz, 1 H), 2.46–2.03 (m, 6 H), 1.92 (dt, *J* = 3.7, 12.4 Hz, 1 H), 1.71 (m, 1 H), 1.55 (s, 2 H), 1.52 (m, 1 H), 1.31 (d, *J* = 6.7 Hz, 3 H), 1.29 (d, *J* = 6.2 Hz, 3 H), 1.23 (d, *J* = 6.4 Hz, 3 H), 1.06 (t, *J* = 7.3 Hz, 3 H); IR ($CHCl_3$) 3490, 3390, 2960, 2920, 1721, 1590, 1445, 1310, 1290, 1155, 1110, 10190, 1020, 1000, 975, 904 cm^{-1}. Anal. Calcd for $C_{40}H_{47}O_{17}I$: C, 51.84; H, 5.11. Found: C, 51.76; H, 5.25.

7-*O*-[4-*O*-[4-*O*-(2,3,6-Trideoxy-α-L-*glycero*-hexopyranosid-4-ulosyl)-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl]-2,6-dideoxy-2-iodo-3-*O*-(trimethylsilyl)-α-L-talopyranosyl]-ε-pyrromycinone (18). A solution of iodide **16** (514 mg, 0.480 mmol) in a 3:2:2 mixture of acetic acid, tetrahydrofuran, and methanol (80 mL) was stirred at room temperature for 1 h. Saturated sodium bicarbonate solution (400 mL) was then added, and the mixture was extracted (3 × 200 mL) with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford crude alcohol. This was chromatographed on 2% KH_2PO_4–silica gel (2:1 hexane–ethyl acetate) to furnish alcohol **18** (464 mg, 97%). Recrystallization from isopropyl alcohol gives red needles: mp 164–165.5 °C; $[\alpha]^{22}_D$ = +10.7° (*c* 0.46, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 9.78 (s, 1 H), 9.15 (s, 1 H), 9.05 (s, 1 H), 7.74 (s, 1 H), 7.35 (d, *J* = 9.5 Hz, 1 H), 7.31 (d, *J* = 9.5 Hz, 1 H), 5.90 (br s, 1 H), 5.29–5.23 (br s, 2 H), 5.09 (br t, *J* = 6.2 Hz, 1 H), 4.93 (br s, 1 H), 4.50 (q, *J* = 6.7 Hz, 1 H), 4.14 (s, 1 H), 3.71 (s, 3 H), 4.60–3.66 (m, 5 H), 3.80 (br s, 1 H), 2.58–1.98 (m, 8 H), 1.82 (dt, *J* = 3.5, 12.5 Hz, 1 H), 1.80–1.40 (m, 3 H), 1.34 (br s, 3 H), 1.33 (d, *J* = 6.7 Hz, 3 H), 1.21 (d, *J* = 6.4 Hz, 3 H), 1.07 (t, *J* = 7.1 Hz, 3 H), 0.13 (br s, 9 H); IR ($CHCl_3$) 3480, 2920, 1722, 1593, 1446, 1310, 1290, 1160, 1118, 1032, 1010, 968 cm^{-1}; HRMS (FAB) *m/e* 1021.2190 ((M + Na)$^+$), calcd for $C_{43}H_{55}O_{17}INaSi$ 1021.2151.

7-*O*-[4-*O*-[4-*O*-(2,3,6-Trideoxy-α-L-*glycero*-hexopyranosid-4-ulosyl)-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl]-2,6-dideoxy-2-iodo-α-L-talopyranosyl]-ε-pyrromycinone (19). A solution of alcohol **18** (58 mg, 0.058 mmol) in tetrahydrofuran (20 mL) was treated with tetrabutylammonium fluoride (0.02 M solution in tetrahydrofuran, 3.7 mL, 0.074 mmol). The resulting mixture was stirred at room temperature for 40 min. Water (50 mL) was then added, and the mixture was extracted (3 × 100 mL) with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give crude diol. Flash chromatography on 2% KH_2PO_4–silica gel (99:1 dichloromethane–methanol) afford 21 mg (36.2%) of alcohol **18** and 22 mg (41%) of diol **19**. Recrystallization from methanol gives red needles: mp 149 °C dec; $[\alpha]^{22}_D$ = −25.8° (*c* 0.36, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 9.80 (s, 1 H), 9.14 (s, 1 H), 9.06 (s, 1 H), 7.73 (s, 1 H), 7.35 (d, *J* = 9.6 Hz, 1 H), 7.30 (d, *J* = 9.6 Hz, 1 H), 5.92 (s, 1 H), 5.29 (d, *J* = 3.5 Hz, 1 H), 5.10 (t, *J* = 5.9 Hz, 1 H), 4.86 (d, *J* = 2.9 Hz, 1 H), 4.61 (q, *J* = 7.1 Hz, 1 H), 4.49 (q, *J* = 6.9 Hz, 1 H), 4.36 (d, *J* = 3.0 Hz, 1 H), 4.29–4.11 (m, 2 H), 4.13 (s, 1 H), 3.83 (s, 1 H), 3.76 (s, 1 H), 3.71 (s, 3 H), 3.48–3.38 (m, 2 H), 3.14 (d, *J* = 7.6 Hz, 1 H), 2.60–2.34 (m, 4 H), 2.31 (d, *J* = 15.7 Hz, 1 H), 2.22–1.98 (m, 2 H), 1.91 (dt, *J* = 4.3, 12.6 Hz, 1 H), 1.80–1.40 (m, 3 H), 1.36 (d, *J* = 7.1 Hz, 3 H), 1.34 (d, *J* = 6.9 Hz, 3 H), 1.25 (d, *J* = 6.4 Hz, 3 H), 1.09 (t, *J* = 7.3 Hz, 3 H); IR ($CHCl_3$) 3500, 3418, 2960, 2920, 1721, 1592, 1447, 1428, 1397, 1310, 1290, 1158, 1111, 1030, 1010, 972 cm^{-1}. Anal. Calcd for $C_{40}H_{47}O_{17}I$: C, 51.84; H, 5.11. Found: C, 51.58; H, 5.07.

Ciclamycin 0 (1). Method A. A solution of iodide **20** (18.5 mg, 0.02 mmol) in benzene (18 mL) was treated with triphenyltin hydride (210 mg, 0.598 mmol) and azobis(isobutyronitrile) (2.5 mg, 0.015 mmol). The resulting mixture was then heated at reflux for 30 min. Evaporation of the solvent afforded crude product which was chromatographed on 2% KH_2PO_4–silica gel (99.5:0.5 dichloromethane–methanol) to afford 4.1 mg (22%) of iodide **20** and 8.8 mg (55%) of ciclamycin 0 (**1**) as a red solid.

Method B. A solution of iodide **19** (55 mg, 0.059 mmol) in benzene (55 mL) was added triphenyltin hydride (412 mg, 1.17 mmol) and azobis(isobutyronitrile) (7 mg, 0.043 mmol). The mixture was then heated at reflux for 2.5 h. Removal of the solvent gave crude product which was chromatographed on 2% KH_2PO_4–silica gel (99.5:0.5 dichloromethane–

methanol) to furnish 14 mg (25.5%) of iodide **19** and 32 mg (72%) of ciclamycin 0 (**1**) as a red solid. Recrystallization from methanol gives ciclamycin 0 as red needles: mp 165.5–166.0 °C; $[\alpha]^{22}_D$ = +64.8° (*c* 0.29, $CHCl_3$); ^1H NMR ($CDCl_3$ 500 MHz) δ 12.99 (s, 1 H), 12.84 (s, 1 H), 12.26 (s, 1 H), 7.74 (s, 1 H), 7.34 (d, *J* = 9.4 Hz, 1 H), 7.31 (d, *J* = 9.4 Hz, 1 H), 5.50 (d, *J* = 3.6 Hz, 1 H), 5.26 (d, *J* = 4.2 Hz, 1 H), 5.16 (t, *J* = 6.1 Hz, 1 H), 4.99 (d, *J* = 3.1 Hz, 1 H), 4.49 (q, *J* = 6.7 Hz, 1 H), 4.23 (q, *J* = 6.5 Hz, 1 H), 4.15 (q, *J* = 6.4 Hz, 1 H), 4.14 (m, 1 H), 4.11 (s, 1 H), 3.77 (m, 1 H), 3.75 (s, 1 H), 3.71 (s, 3 H), 3.60 (s, 1 H), 2.53 (dd, *J* = 4.2, 15.2 Hz, 1 H), 2.50–2.44 (m, 3 H), 2.31 (d, *J* = 15.2 Hz, 1 H), 2.17 (m, 1 H), 2.09 (dd, *J* = 4.0, 12.2, Hz, 1 H), 1.93 (dd, *J* = 3.6, 12.7 Hz, 1 H), 1.92 (dt, *J* = 4.0, 12.2 Hz, 1 H), 1.79 (dt, *J* = 4, 12.7 Hz, 1 H), 1.75 (m, 1 H), 1.57 (s, 3 H), 1.52 (m, 1 H), 1.34 (d, *J* = 6.7 Hz, 3 H), 1.31 (d, *J* = 6.4 Hz, 3 H), 1.25 (d, *J* = 6.5 Hz, 3 H), 1.09 (t, *J* = 7.3 Hz, 3 H); IR ($CHCl_3$) 3450, 3410, 2940, 2910, 2850, 1720, 1590, 1442, 1310, 1286, 1151, 1110, 1095, 1030, 1000 cm^{-1}; HRMS (FAB) *m/e* 823.2811 ((M + Na)$^+$), calcd for $C_{40}H_{48}O_{17}Na$ 823.2789.

Reaction of Daunomycinone (21) and Trisaccharide 14. To a solution of daunomycinone **21** (53 mg, 0.132 mmol) and ketone **14** (60 mg, 0.120 mmol) in dichloromethane (7 mL) was added 4-Å sieves (60 mg). The resulting mixture was stirred at room temperature for 30 min, cooled to 0 °C in an ice bath, and stirred for an additional 1 h. The mixture was then treated with I(*sym*-collidine)$_2ClO_4$ (**4**) (90%, 70 mg, 0.156 mmol). After stirring at 0 °C for 1 h, the mixture was diluted with dichloromethane (30 mL) and filtered through Celite. The filtrate was washed with 10% sodium thiosulfate (10 mL), 10% copper sulfate (10 mL), water (10 mL), and brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated. Flash chromatography on 2% KH_2PO_4–silica gel (2:1 hexane–ethyl acetate) furnished 54 mg (44%) of a 7:1 mixture of **22** and the diequatorial isomer, **20** mg (16%) of **23**.

7-*O*-[4-*O*-[4-*O*-(2,3,6-Trideoxy-α-L-*glycero*-hexopyranosid-4-ulosyl)-2,6-dideoxy-3-*O*-(trimethylsilyl)-α-L-*lyxo*-hexopyranosyl]-2,6-dideoxy-2-iodo-3-*O*-(trimethylsilyl)-α-L-talopyranosyl]daunomycinone (22): $[\alpha]^{22}_D$ = −5.0° (*c* 0.04, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 13.95 (s, 1 H), 13.24 (s, 1 H), 8.00 (d, *J* = 7.8 Hz, 1 H), 7.76 (t, *J* = 8.2 Hz, 1 H), 7.38 (d, *J* = 8.3 Hz, 1 H), 5.88 (br s, 1 H), 5.30 (br s, 1 H), 5.07 (at, *J* = 5.8 Hz, 1 H), 4.92 (m, 2 H), 4.48–4.12 (m, 5 H), 4.08 (s, 3 H), 3.87–3.60(m, 2 H), 3.20 (d, *J* = 19.0 Hz, 1 H), 2.93 (d, *J* = 19.0 Hz, 1 H), 2.65 (m, 1 H), 2.56–2.40 (m, 2 H), 2.40 (s, 3 H), 2.28–2.00 (m, 6 H), 1.35–1.20 (m, 9 H), 0.13 (s, 18 H); IR ($CHCl_3$) 3500, 3000, 2930, 2850, 1715, 1620, 1580, 1415, 1385, 1305, 1125, 1100 cm^{-1}; HRMS (FAB) *m/e* 1063.2401 ((M + Na)$^+$), calcd for $C_{45}H_{61}O_{16}INaSi_2$ 1063.2441.

7-*O*-[4-*O*-[4-*O*-(2,3,6-Trideoxy-α-L-*glycero*-hexopyranosid-4-ulosyl)-2,6-dideoxy-3-*O*-(trimethylsilyl)-α-L-*lyxo*-hexopyranosyl]-2,6-dideoxy-2-iodo-3-*O*-(trimethylsilyl)-α-L-galactopyranosyl]daunomycinone (23): $[\alpha]^{22}_D$ = +36.9° (*c* 0.13, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 14.08 (s, 1 H), 13.30 (s, 1 H), 8.04 (d, *J* = 7.0 Hz, 1 H), 7.78 (t, *J* = 8.3 Hz, 1 H), 7.40 (d, *J* = 8.4 Hz, 1 H), 5.59 (d, *J* = 3.1 Hz, 1 H), 5.48 (br s, 1 H), 5.09 (at, *J* = 3.7 Hz, 1 H), 5.00 (d, *J* = 2.3 Hz, 1 H), 4.87 (q, *J* = 6.7 Hz, 1 H), 4.56, (s, 1 H, OH), 4.30–4.10 (m, 4 H), 4.09 (s, 3 H), 3.88 (dd, *J* = 2.6, 10.8 Hz, 1 H), 3.80–3.68 (m, 2 H), 3.31 (d, *J* = 19.3 Hz, 1 H), 3.02 (d, *J* = 19.2 Hz, 1 H), 2.77–2.58 (m, 1 H), 2.42 (s, 3 H), 2.50–2.00 (m, 6 H), 1.81 (dd, *J* = 4.2, 12.0 Hz, 1 H), 1.30 (d, *J* = 6.5 Hz, 3 H), 1.26 (d, *J* = 6.5 Hz, 3 H), 1.22 (d, *J* = 6.8 Hz, 3 H), 0.20 (s, 9 H), 0.16 (s, 9 H); IR ($CHCl_3$) 3480, 2940, 1715, 1610, 1565, 1400, 1270, 1250, 1090, 1000, 850, 820 cm^{-1}; HRMS (FAB) *m/e* 1063.2434 ((M + Na)$^+$), calcd for $C_{45}H_{61}O_{16}INaSi_2$ 1063.2441.

7-*O*-[4-*O*-[4-*O*-(2,3,6-Trideoxy-α-L-*glycero*-hexopyranosid-4-ulosyl)-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl]-2,6-dideoxy-2-iodo-α-L-talopyranosyl]daunomycinone (24). To a stirred solution of **22** (30 mg, 0.029 mmol) in THF (4.0 mL) at 0 °C was added HF–pyridine complex (0.2 mL). The mixture was stirred at room temperature for 3 h, neutralized with saturated sodium bicarbonate, and extracted with dichloromethane. The combined extracts were washed with 10% copper sulfate (15 mL), water (10 mL), and brine (10 mL). The organic layer was then dried ($MgSO_4$) and concentrated. Flash chromatography on 2% KH_2PO_4–silica gel (20:1 chloroform–methanol) furnished diol **24** (18 mg, 69%) as a red solid: mp 163.0–165.0 °C; $[\alpha]^{22}_D$ = −87.5° (*c* 0.16, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 14.01 (s, 1 H), 13.28 (s, 1 H), 8.03 (d, *J* = 7.9 Hz, 1 H), 7.79 (t, *J* = 8.3 Hz, 1 H), 7.40 (d, *J* = 8.4 Hz, 1 H), 5.91 (s, 1 H), 5.26 (br s, 1 H), 5.09 (t, *J* = 5.8 Hz, 1 H), 4.86 (d, *J* = 3.1 Hz, 1 H), 4.57 (q, *J* = 6.4 Hz, 1 H), 4.48 (q, *J* = 6.7 Hz, 1 H), 4.36–4.12 (m, 2 H), 4.17 (s, 1 H, OH), 4.10 (s, 3 H), 3.80–3.67 (m, 4 H), 3.48 (m, 1 H), 3.23 (d, *J* = 19.0 Hz, 1 H), 3.05 (d, *J* = 7.41 Hz, 1 H), 2.95 (d, *J* = 19.0 Hz, 1 H), 2.57–2.40 (m, 2 H), 2.40 (s, 3 H), 2.33 (d, *J* = 15.2 Hz, 1 H), 2.22–2.05 (m, 4 H), 1.89 (dt, *J* = 3.6, 12.4 Hz, 1 H), 1.35 (d, *J* = 6.0 Hz, 3 H), 1.32 (*J* = 6.5 Hz, 3 H), 1.24 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 211.2, 209.6, 186.9, 186.7, 161.2, 156.2, 155.6, 135.6, 135.5, 134.3, 133.5, 121.0, 119.8, 118.5, 111.6, 111.5, 105.1, 101.9, 100.0, 82.0, 79.7, 77.2, 71.9, 70.3, 68.7, 67.4, 65.5, 65.1, 56.7, 35.0, 33.9, 33.4, 33.3, 29.9, 27.7, 24.5, 16.9, 16.5, 14.8; IR ($CHCl_3$) 3600–3300, 3100, 3020, 1730, 1715, 1620, 1580, 1450, 1415, 1190, 1015, 1000 cm^{-1}; UV-vis λ_{max} (MeOH) 533 (ε 5500), 497 (10000), 480 (10000), 293 (6700), 254 (21000), 235 (29000); HRMS (FAB) *m/e* 1063.2434 ((M + Na)$^+$), calcd for $C_{39}H_{45}O_{16}INa$ 919.1651.

7-*O*-[4-*O*-[4-*O*-(2,3,6-Trideoxy-α-L-*glycero*-hexopyranosid-4-ulosyl)-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl]-2,6-dideoxy-2-iodo-α-L-galactopyranosyl]daunomycinone (25). To a stirred solution of **23** (42 mg, 0.040 mmol) in THF (10.0 mL) at 0 °C was added HF–pyridine complex (0.3 mL). The mixture was stirred at room temperature for 3 h, neutralized with saturated sodium bicarbonate, and extracted with dichloromethane. The combined extracts were washed with 10% copper sulfate (15 mL), water (10 mL), and brine (10 mL). The organic layer was then dried ($MgSO_4$) and concentrated. Flash chromatography on 2% KH_2PO_4–silica gel (20:1 chloroform–methanol) furnished diol **25** (22 mg, 60%) as a red solid: mp 164.5–165.5 °C; $[\alpha]^{22}_D$ = +62.2° (*c* 0.06, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 14.07 (s, 1 H), 13.30 (s, 1 H), 8.05 (d, *J* = 7.8 Hz, 1 H), 7.78 (t, *J* = 8.1 Hz, 1 H), 7.39 (d, *J* = 8.2 Hz, 1 H), 5.63 (d, *J* = 3.5 Hz, 1 H), 5.45 (br s, 1 H), 5.09 (at, *J* = 6.0 Hz, 1 H), 4.98 (d, *J* = 2.7 Hz, 1 H), 4.47 (q, *J* = 6.8 Hz, 1 H), 4.44 (s, 1 H, OH), 4.32–4.04 (m, 4 H), 4.09 (s, 3 H), 3.29 (d, *J* = 19.0 Hz, 1 H), 3.92–3.63 (m, 5 H), 3.03 (d, *J* = 19.1 Hz, 1 H), 2.53–2.42 (m, 2 H), 2.40 (s, 3 H), 2.28–2.05 (m, 5 H), 1.91 (dt, *J* = 3.8, 12.3 Hz, 1 H), 1.32 (d, *J* = 6.6 Hz, 3 H), 1.30 (d, *J* = 5.1 Hz, 3 H), 1.25 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 211.4, 209.4, 187.0, 187.0, 161.2, 156.1, 155.7, 135.7, 135.6, 134.8, 133.5, 121.0, 119.8, 118.5, 111.6, 110.1, 100.9, 100.6, 100.1, 82.6, 81.8, 76.8, 72.0, 70.2, 68.1, 67.9, 65.0, 56.7, 35.3, 34.2, 34.0, 33.4, 32.1, 27.7, 24.6, 16.9, 16.6, 14.8; IR ($CHCl_3$) 3580–3230, 2995, 2920, 1720, 1615, 1580, 1280, 1265, 1250, 1115, 1100, 1015 cm^{-1}; UV-vis λ_{max} (MeOH) 533 (ε 3600), 497 (6400), 480 (6400), 288 (4200), 251 (13200), 232 (15000); HRMS (FAB) *m/e* 919.1596 ((M + Na)$^+$), calcd for $C_{39}H_{45}O_{16}I$ 919.1651.

7-*O*-[4-*O*-[4-*O*-(2,3,6-Trideoxy-α-L-*glycero*-hexopyranosid-4-ulosyl)-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl]-2,6-dideoxy-α-L-galactopyranosyl]daunomycinone (26), Method A. Through a solution of iodide **24** (14 mg, 0.016 mmol) and triphenyltin hydride (82 mg, 0.234 mmol) in benzene (3 mL) was passed nitrogen for 10 min. To the reaction mixture was then added azobis(isobutyronitrile) (2.5 mg, 0.015 mmol). The resulting mixture was then heated to 55 °C for 12 h. Additional azobis(isobutyronitrile) (2 mg) was added every 1 h. The reaction mixture was diluted with acetonitrile (20 mL) and washed with hexanes (3 × 10 mL). The acetonitrile layer was concentrated and the crude product chromatographed on 2% KH_2PO_4–silica gel (30:1 chloroform–methanol) to afford 8 mg (65%) of **26** as a red solid and 2 mg (16%) of the leuco isomer **27** as a yellow residue.

Method B. Through a solution of iodide **25** (12 mg, 0.013 mmol) and triphenyltin hydride (45 mg, 0.130 mmol) in benzene (2 mL) was passed nitrogen for 10 min. To the reaction mixture was then added azobis(isobutyronitrile) (2.5 mg, 0.015 mmol). The resulting mixture was then heated to 55 °C for 10 h. Additional azobis(isobutyronitrile) (2 mg) was added every 1 h. The reaction mixture was diluted with acetonitrile (20 mL) and washed with hexanes (3 × 10 mL). The acetonitrile layer was concentrated and the crude product chromatographed on 2% KH_2PO_4–silica gel (30:1 chloroform–methanol) to afford 4 mg (40%) of **26** as a red solid and 2 mg (15%) of the leuco isomer **27** as a yellow residue.

26: mp 234.0–235.0 °C; $[\alpha]^{22}_D$ = −24.1° (*c* 0.06, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 13.98 (s, 1 H), 13.29 (s, 1 H), 8.03 (d, *J* = 6.9 Hz, 1 H), 7.78 (t, *J* = 8.0 Hz, 1 H), 7.39 (d, *J* = 7.8 Hz, 1 H), 5.54 (d, *J* = 3.2 Hz, 1 H), 5.28 (br s, 1 H), 5.09 (t, *J* = 6.2 Hz, 1 H), 4.98 (d, *J* = 2.7 Hz, 1 H), 4.60 (s, 1 H, OH), 4.48 (q, *J* = 6.7 Hz, 1 H), 4.19–4.11 (m, 3 H), 4.09 (s, 3 H), 3.90–3.58 (m, 5 H), 3.24 (d, *J* = 18.9 Hz, 1 H), 2.96 (d, *J* = 18.9 Hz, 1 H), 2.60–2.40 (m, 3 H), 2.40 (s, 3 H), 2.30 (d, *J* = 14.1 Hz, 1 H), 2.21–2.05 (m, 4 H), 1.92 (dt, *J* = 3.7, 12.2 Hz, 1 H), 1.75 (dt, *J* = 3.8, 12.4 Hz, 1 H), 1.32 (d, *J* = 6.7 Hz, 3 H), 1.29 (d, *J* = 6.4 Hz, 3 H), 1.24 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 211.4, 209.2, 187.0, 186.8, 163.2, 156.0, 135.8, 135.6, 134.6, 134.3, 123.0, 119.9, 118.7, 111.7, 111.5, 106.0, 101.5, 100.1, 82.7, 81.9, 76.9, 72.0, 69.6, 68.0, 67.7, 65.6, 65.1, 56.8, 35.2, 34.4, 34.1, 33.6, 33.4, 27.9, 25.0, 17.1, 17.0, 14.8; IR ($CHCl_3$) 3580–3230, 3000, 2940, 1730, 1715, 1620, 1580, 1450, 1435, 1415, 1290 cm^{-1}; UV-vis λ_{max} (MeOH) 540 (ε 4212) 500 (9500), 480 (9300), 293 (7000), 254 (22000) 235 (32000); HRMS (FAB) *m/e* 793.2654 ((M + Na)$^+$), calcd for $C_{39}H_{46}O_{16}Na$ 793.2684.

27: ^1H NMR ($CDCl_3$, 250 MHz) δ 14.29 (s, 1 H), 13.39 (s, 1 H), 8.06 (d, *J* = 7.9 Hz, 1 H), (t, *J* = 8.0 Hz, 1 H), 7.19 (d, *J* = 7.8 Hz, 1 H), 5.29 (d superimposed on a br s, *J* = 4.5 Hz, 2 H), 4.84 (t, *J* = 6.4 Hz, 1 H), 4.79 (d, *J* = 2.7 Hz, 1 H), 4.41–4.36 (m, 2 H), 4.12–4.00 (m,

3 H), 4.08 (s, 3 H), 3.67 (s, 1 H, OH), 3.50 (m, 3 H), 3.34 (br s, 1 H), 3.24 (m, 1 H), 2.73 (dd, J = 15.7, 5.6 Hz, 1 H), 2.51-2.25 (m, 6 H), 2.32 (s, 3 H), 2.18-1.88 (m, 5 H), 1.77 (dt, J = 2.8, 8.5 Hz, 1 H), 1.23 (at, 6.5 Hz, 6 H), 0.54 (d, J = 6.4 Hz, 3 H); IR ($CHCl_3$) 3600-31—, 3000, 2920, 1725, 1705, 1575, 1450, 1390, 1110, 1100 cm^{-1}; UV-vis λ_{max} (MeOH) 448 (ϵ 17 220), 421 (15 773), 397 (9760), 266 (24 283), 241 (25 533).

Acknowledgment. We thank the National Institutes of Health (PHS Grant Al 16943) for financial support of this work. Support from the Kyowa Hakko Kogyo Co., Ltd., Tokyo, Japan to K.S., Killiam and NSERC Postdoctoral Fellowships to R.W.F., and an American Cancer Society Postdoctoral Fellowship (Grant No. PF-3296) to G.A.S. are gratefully acknowledged. We thank Dr. D. Vyas of the Bristol Myers Company for a sample of the bohemic acid complex and Professor L. W. Bieber of the Universidade Federal de Pernambuco, Brazil for a sample of ciclamycin 0. NMR spectra were obtained through the auspicies of the Northeast Regional NSF/NMR facility at Yale University, which was supported by NSF Chemistry Division Grant No. CHE 7916210.

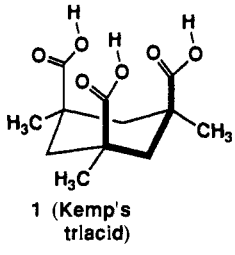
Convergent Functional Groups. 9. Complexation in New Molecular Clefts

James S. Nowick, Pablo Ballester, Frank Ebmeyer, and Julius Rebek, Jr.*

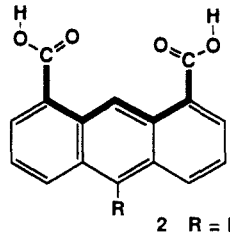
Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139. *Received April 23, 1990*

Abstract: Two new 2,7-di-*tert*-alkyl-9,9-dimethylxanthene-4,5-dicarboxylic acids are prepared as organic soluble, U-shaped modules for the construction of molecular hosts. Condensation of two diacid units with spacers (e.g., hydroquinone, 4,4'-biphenol, and 2,6-diaminonaphthalene) gives large structures capable of assuming cleftlike shapes that complex sizable guests such as DABCO, quinine, quinidine, and quinoxaline-2,3-dione. The xanthene diacids and their derivatives are shown to contain intramolecular hydrogen bonds that organize the binding sites and modify their chemical properties.

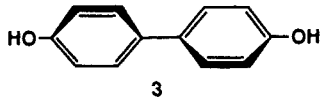
Molecules featuring convergent functional groups in cleftlike shapes have emerged as useful receptors for small molecules.[1] In our own laboratory, structures derived from Kemp's[2] triacid **1** have



1 (Kemp's triacid)



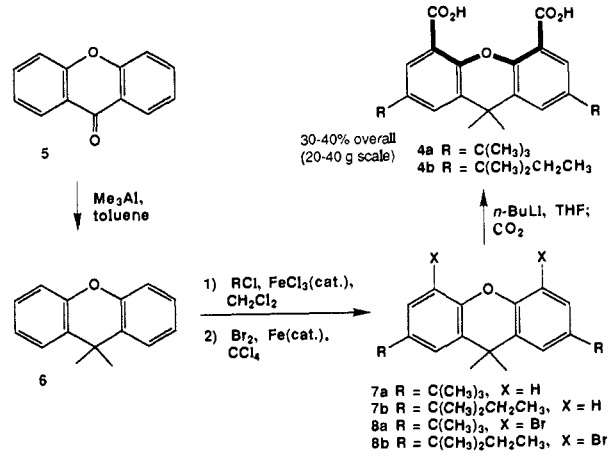
2 R = H or *n*-octyl



3

proven effective probes for studies of molecular recognition. The U-shaped relationship that exists between any two carboxyl functions in **1** in conjunction with spacer elements permits the construction of molecules that fold back upon themselves. We have now explored new modular units based upon xanthene-4,5-dicarboxylic acid derivatives and report here on their advantages for complexation of larger target structures.

Anthracene-4,5-dicarboxylic acids[3] **2** provide U-shaped relationships between functions, but the low solubilities of these compounds and the clefts derived from them with diol or diamine spacers (e.g., biphenol **3**) in most organic solvents thwarted studies of their intermolecular complexes. Systems derived from xanthenes proved tractable. When methyl groups were appended to the 9-position and *tert*-alkyl groups to the 2- and 7-positions of xanthene-4,5-dicarboxylic acid derivatives **4**, highly soluble and readily accessible molecules were at hand. These *tert*-alkylated diacids are prepared from commercially available xanthone (**5**) in four steps (eq 1). Treatment of **5** with Me_3Al in toluene,[4]



(1)

followed by Friedel-Crafts alkylation[5] and bromination, generates compounds **8**. These dibromo compounds were converted to diacids **4** by means of their lithium derivatives. The di-*tert*-amylated compounds (**7b**, **8b**, and **4b**) were each found to contain

(1) For a recent review, see: Rebek, J., Jr. *Angew. Chem.* **1990**, *102*, 261; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245.
(2) Kemp, D. S.; Petrakis, K. S. *J. Org. Chem.* **1981**, *46*, 5140. Commercially available from the Aldrich Chemical Co.
(3) For recent uses and leading references, see: Fillers, J. P.; Ravichandran, K. G.; Abdalmuhdi, I.; Tulinsky, A.; Chang, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 417.
(4) Meisters, A.; Mole, T. *Aust. J. Chem.* **1974**, *27*, 1655.
(5) Roberts, R. M.; Khalaf, A. A. *Friedel-Crafts Alkylation Chemistry*; Marcel Dekker: New York, 1984.

0002-7863/90/1512-8902$02.50/0