5.27 (dt, J = 9.5, 2.5 Hz, 1 H), 4.64 (dd, J = 12.3, 2.21 Hz, 1 H), 4.56 (s, 2 H), 4.28–4.17 (m, 2 H), 2.35 (m, 1 H), 2.20 (t, J = 12.3 Hz, 1 H), 2.10 (s, 3 H), 2.00 (s, 3 H), 1.98 (s, 3 H), 1.91 (s, 3 H); MS, m/e (%) 451 (M – CO_2H, 2), 390 (12), 141 (24), 112 (12), 91 (100).

(±)-Methyl 4,5,7,8-Tetra-*O*-acetyl-2-*O*-benzyl-3-deoxy-D-*manno*-2-octulopyranosonate (23). A solution of the acid **22** (127 mg, 0.254 mmol) in ether (5 mL) was treated with an excess of etheral diazomethane. After 10 min, the solution was concentrated in vacuo. Flash chromatography (35% ethyl acetate/hexane, R_f 0.35) provided 124 mg (95%) of the title compound as a colorless glass: IR ($CHCl_3$) 1755, 1738, 1438, 1369, 1230 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.35 (m, 5 H), 5.42 (brs, 1 H), 5.40 (ddd, J = 12.3, 4.9, 2.5 Hz, 1 H), 5.27 (ddd, J = 9.8, 3.2, 2.3 Hz, 1 H), 4.63 (dd, J = 12.3, 2.3 Hz, 1 H), 4.58, 4.47 (AB, J = 12.2 Hz, 2 H), 4.23 (dd, J = 9.8, 1.2 Hz, 1 H), 4.21 (dd, J = 12.3, 3.2 Hz, 1 H), 3.79 (s, 3 H), 2.30 (ddd, J = 12.3, 4.9, 1.2 Hz, 1 H), 2.15 (t, J = 12.3 Hz, 1 H), 2.10 (s, 3 H), 2.00 (s, 3 H), 1.98 (s, 3 H), 1.92 (s, 3 H); MS, m/e (%) no M^+, 452 (2), 451 (7), 405 (9), 404 (45), 301 (18), 224 (10), 182 (18), 181 (21), 145 (12), 121 (12), 112 (12), 92 (10), 91 (100).

(±)-Methyl 2,4,5,7,8-Penta-*O*-acetyl-3-deoxy-D-*manno*-2-octulopyranosonate (24). A mixture of the benzyl ether **23** (111 mg, 0.217 mmol), 10% palladium on carbon (20 mg), and ethanol (3 mL) was stirred under a balloon of hydrogen for 20 h then filtered through Celite, washing with dichloromethane. The filtrate was concentrated in vacuo to give the crude alcohol, which was dissolved in dichloromethane (2 mL) and treated with acetic anhydride (44 mg, 0.43 mmol), pyridine (34 mg, 0.43 mmol) and 4-(dimethylamino)pyridine (2 mg). After 3 h, the solution was washed with 10% aqueous hydrochloric acid and saturated aqueous sodium bicarbonate, then dried ($MgSO_4$), and concentrated in vacuo to provide 93.1 mg (93%) of the title compound as a colorless solid, mp 129.0–129.5 °C (ethyl acetate/hexane) lit. mp[25] for (+)-**24** 155–158 °C, which was identical with material prepared from (+)-NH_4 KDO (Sigma) according to Unger[25] with regard to its TLC behavior (R_f 0.25, 40% ethyl acetate/hexane) and its IR, ^1H NMR (250 MHz), and mass spectra: IR ($CHCl_3$) 1748, 1429, 1363, 1220 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.38 (m, 1 H), 5.32 (ddd, J = 10.7, 6.5, 3.0 Hz, 1 H), 5.22 (ddd, J = 9.9, 3.9, 2.2 Hz, 1 H), 4.47 (dd, J = 12.3, 2.2 Hz, 1 H), 4.17 (dd, J = 9.9, 1.3 Hz, 1 H), 4.09 (dd, J = 12.3, 3.9 Hz, 1 H), 3.81 (s, 3 H), 2.23 (m, 2 H), 2.14 (s, 3 H), 2.08 (s, 3 H), 2.05 (s, 3 H), 2.002 (s, 3 H), 1.997 (s, 3 H); MS, m/e (%) no M^+, 431 (1), 405 (2), 404 (8), 403 (39), 361 (48), 301 (100), 300 (47), 282 (49), 259 (31), 241 (34), 240 (62), 227 (20), 217 (37), 199 (39), 198 (35), 185 (20), 181 (100), 180 (20), 168 (26), 167 (74), 157 (34), 155 (56), 145 (40), 143 (24), 139 (70), 128 (20), 127 (20), 126 (65), 115 (51), 103 (26).

(±)-Ammonium 3-Deoxy-D-*manno*-2-octulopyranosonate ((±)-NH_4 KDO) (1). A solution of the acid **22** (203 mg, 0.409 mmol) in methanol (4 mL) was stirred with sodium methoxide (111 mg, 2.05 mmol) for 6 h, then neutralized with methanol-washed Dowex 50-8x (20–50 mesh) ion-exchange resin. The mixture was filtered, washing the resin with small portions of methanol. Palladium (10% on charcoal, 50 mg) was added to the filtrate and the mixture was stirred under a balloon of hydrogen for 16 h then filtered through Celite, washing with methanol. The filtrate was treated with excess anhydrous methanolic ammonia, and the solution was concentrated in vacuo to provide 96.0 mg (92%) of the title compound as a colorless, amophous solid (mp 119–122 °C) whose 250-MHz ^1H NMR spectrum in D_2O was essentially identical with that of an authentic sample of (+)-NH_4 KDO (Sigma, mp 122–124 °C) with the exception of a few very minor impurities, which were absent after recrystallization. Mobility by TLC was identical with that of an authentic sample, R_f 0.58 (10:10:3 methanol/chloroform/water, p-anisaldehyde/sulfuric acid visualization). Slow crystallization from aqueous ethanol provided pure (±)-NH_4 KDO (**1**) as colorless plates, mp 122.5–124.0 °C (lit. mp[25a] of (+)-**1** 122–125 °C); ^1H NMR (250 MHz, D_2O, Me_4Si reference) δ 4.47–4.37 (m), 4.10 (m), 4.03–3.92 (m), 3.88–3.49 (m), 2.50 (dd, J = 14, 7 Hz), 2.25 (m), 2.03–1.76 (m).

Peracetylation and diazomethane esterification of 7.1 mg (0.028 mmol) of the crude product according to the literature procedure[25] afforded 10.4 mg (81%) of (±)-**24** as a colorless solid (mp 128–129 °C) after flash chromatography (40% ethyl acetate/hexane, R_f 0.31), which was identical in all respects with that prepared above from **23**.

Acknowledgment. This work was supported by PHS grant AI 50721. A PHS Postdoctoral Fellowship (Grant 1 F32 CA07251) to W.H.P. is gratefully acknowledged. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

Registry No. 1, 92693-58-8; **8**, 92641-45-7; *E*-**9**, 92622-29-2; *Z*-**9**, 92622-30-5; *E*-**10**, 92622-31-6; *Z*-**10**, 92622-32-7; **12**, 92622-33-8; **13**, 92641-46-8; **14**, 92622-34-9; **15**, 92641-47-9; **16**, 92622-35-0; **17**, 92622-36-1; **18**, 92622-37-2; **19**, 92622-38-3; **20**, 92622-39-4; **21**, 92622-40-7; **22**, 92622-41-8; **23**, 92622-42-9; **24**, 92693-59-9; 2-acetylfuran, 1192-62-7; (benzoyloxy)acetyl chloride, 54150-57-1; (benzoyloxy)acetic acid, 614-44-8; diphenyl diselenide, 1666-13-3; ethyl propenyl ether, 928-55-2.

Supplementary Material Available: Tables containing fractional coordinates, temperature factors, bond distances, and bond angles for compound **18** (5 pages). Ordering information is given on any current masthead page.

Total Synthesis of Vineomycinone B_2 Methyl Ester

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Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06511. *Received July 9, 1984*

Abstract: Two homo-Diels–Alder reactions and a hetero-Diels–Alder reaction, each using siloxydienes, were used in a total synthesis of the title compound.

Background

The anthracycline antibiotics such as adriamycin are among the most important of the natural products in antitumor chemotherapy.[1] These compounds characteristically contain an anthraquinone chromophore within a hydrotetracene ring system. The tetracene moiety is linked to a "carbohydrate region" through a glycosidic bond.

An interesting subgroup of anthracycline antibiotics are those in which an anthracene or a tetracene derivative is joined to a carbohydrate residue through a C-glycosidic bond.[2] In some instances there are two such C-glycosidic bonds. Combinations of C- and O-glycosidic attachments of sugars to an anthracycline system are also known. Finally, and most relevant to the inves-

(1) Cf. Inter. Alia: (a) "The Chemistry of Antitumor Antibiotics"; Remers, W. A., Ed.; Wiley: New York, 1978. (b) "Anticancer Agents Based on Natural Product Models"; Cassady, J. M.; Douros, J. D., Eds.; Academic Press: New York, 1980. (c) "Antineoplastic Agents"; Remers, W. A., Ed.; Wiley: New York, 1984.

(2) Cf. Inter. Alia. (a) nogalamycin: Hauser, F. M., Adams, T. C. *J. Org. Chem.* **1984**, *49*, 2296 and references therein. (b) Pluramycin A: Kondo, S.; Muyamoto, M.; Naganawa, H.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1977**, *12*, 1143. (c) Granaticin: Chang, C. J.; Floss, H. G.; Soong, P.; Chan, C. T. *Ibid.* **1975**, *28*, 156. (d) Griseusin: Kometani, T.; Takeuchi, Y.; Yoshi, E. *J. Org. Chem.* **1983**, *48*, 2311. (e) Aquayamycin: Sezaki, M.; Kondo, S.; Maeda, K.; Umezawa, H.; Ohno, M. *Tetrahedron* **1970**, *26*, 5171.

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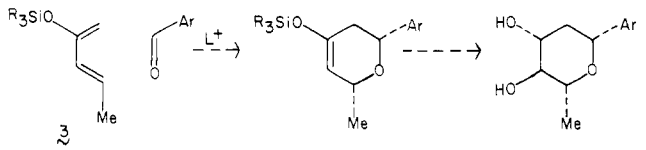
Scheme I

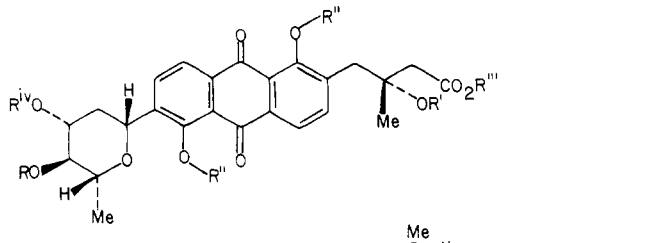


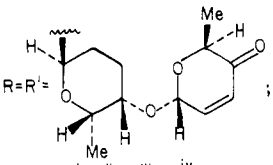
tigation described herein (vide infra), is the situation where a sugar residue, which is attached to the anthracycline through a C-glycosidic arrangement, is also joined to a carbohydrate section through a more conventional O-glycosidic linkage.[3]

The clinical efficacy of the C-glycosidic anthracyclines remains to be demonstrated. Also, the mechanisms of antitumor action of the C-glycosidic compounds, and particularly their similarity, if any, with those of the O-glycosidic drugs[4] await proper definition. Nonetheless, it seems, at least in principle, possible that the C-glycosidic compounds could eventually prove to be more efficacious than their O-glycosidic counterparts, in that their vulnerability toward deactivating deglycosylation might be less.

Moreover, the C-glycosides were also of considerable chemical interest to our laboratory. It seemed possible that the total synthesis of many of the C-glycosides could well be facilitated through the use of hetero-Diels–Alder reactions of aldehydes and siloxydienes.[5,6]

Vineomycins A_1, A_2, B_1, and B_2 were isolated from the culture broth of an actinomycete designated as *Streptomyces matensis vineus* from Takada in the Niigata Prefecture of Japan.[7] All of the vineomycins are active against gram-positive bacteria and against sarcoma 180 solid tumors in mice.[8] The structure of vineomycin B_2 was deduced to be that shown as **1** by its correlation



1 Vineomycin B_2; R=R'=  ; R''=R'''=R^{iv}=H

2a Vineomycinone B_2 R=R'=R''=R'''=R^{iv}=H

2b Vineomycinone B_2 methyl ester R=R'=R''=R^{iv}=H; R'''=Me

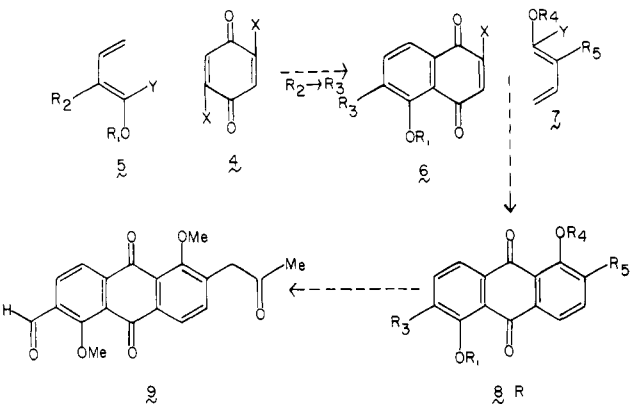
2c R=R''=R^{iv}=Ac; R'=H; R'''=Me

with vineomycin A_1 whose structure was ascertained by crystallographic methods.[9] Treatment of vineomycin B_2 with methanolic HCl affords the aglycone vineomycinone B_2 methyl ester (**2b**). Herein the total synthesis of this aglycon is described.

Synthetic Plan

Certainly the most provocative feature of structure **2** is the attachment of a 2,6-dideoxyglucose residue to an aromatic ring through a β-C-glycosidic bond.[10a] One might consider trying to establish such a bond by electrophilic attack of a suitably protected and activated hexose derivative, upon an appropriately activated aromatic system.[10b] However, an alternative and simpler formulation presented itself. The dideoxyglucose subunit could be fashioned *de-novo* by Lewis acid catalyzed cyclocondensation of a diene with an appropriate aromatic aldehyde.[5] A particularly concise version of this synthetic hypothesis was the permutation where the diene would be of the type **3**. If cycloaddition occurred in the pericyclic mode through an endo topology, the required stereochemistry of the C-glycoside would be established. Moreover, the resultant enoxysilane could well lend itself to orderly introduction of the required C_4 (glucose numbering) hydroxyl functionality in the necessary configurational sense (see Scheme I).

Scheme II



It seemed that an aromatic aldehyde such as **9** might serve well as a heterodienophile for cyclondensation with **3**. Another attractive feature of the plan could now be discerned. The required system could itself be assembled by sequential homo-Diels–Alder reactions of suitable quinones with well-chosen siloxydienes.[11] Indeed, closer examination of precursor type **8**, in the setting of Scheme II reveals an exploitable quasi-symmetry at the synthetic level. For the moment, issues of oxidation levels (i.e., the nature of functions X on the quinone and of functions Y on the dienes) are deferred. A homo-Diels–Alder reaction between quinone **4** and diene **5** could lead, after manipulation, to product **6**. A second Diels–Alder reaction between **6** and another 2-substituted diene (**7**) could lead to **8** and eventually to **9**.

From **9**, the dideoxyhexose segment is to be fashioned beginning with a hetero-Diels–Alder reaction on the aldehyde linkage. The 3-hydroxy-3-methylbutyric acid ester side chain would be reached via a Reformatsky-equivalent process on the ketone. This program offered no solution to the very significant problem of coordinating the two dissymmetric sectors of the molecule. Of course, the attainment of an effective stereochemical "liaison" between these remotely disposed pockets of stereogenicity would be no simple matter.

One could consider approaches based on essentially enantiotopic-type control in each region.[12] For instance, the construction of the hexose sector could involve joining a properly functionalized derivative of D-glucose to an aromatic residue.[10b] In a similar vein, either through the use of a resolved fragment or through methodology using enantiotopic reaction specificity,[13] the 3-methyl-3-hydroxybutyrate might be introduced in the required *R* configuration.

We would here register the opinion that chirality matching solutions of this type do not deal with the significant intellectual challenge of creating stereochemical interactivity. In the absence

(3) Cf. vineomycin A_1: Imamura, N.; Kakenuma, K.; Ikekawa, N.; Takana, H.; Omura, S. *Chem. Pharm. Bull.* **1981**, *29*, 1788.

(4) See: "Molecular Aspects of Anticancer Drug Action"; Neidle, S., Waring, M. J., Eds.; Verlag Chemie: Deerfield Beach, FL, 1983.

(5) For a full account of this work, see: Danishefsky, S.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.*, in press.

(6) For a preliminary account of this work, see: Danishefsky, S.; Uang, B.-J.; Quallich, G. *J. Am. Chem. Soc.* **1984**, *106*, 2453.

(7) Omura, S.; Tanaka, H.; Oieva, R.; Awaya, J.; Masura, R.; Tanaka, K. *J. Antibiot.* **1977**, *30*, 908.

(8) Imamura, N.; Kakinuma, K.; Ikekawa, N.; Takna, H.; Omura, S. *J. Antibiot.* **1981**, *34*, 1517.

(9) Ohta, K.; Kamiya, K. *J. Chem. Soc., Chem. Commun.* **1981**, 154.

(10) (a) The pyran is considered as a 1,2,6-dideoxy-*O*-glucose derivative with the anthraquinone residue replacing the anomeric hydroxyl at the 1 position. (b) Cf.: Eade, R. A.; Pham, H. P. *Aust. J. Chem.* **1979**, *32*, 2483.

(11) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400.

(12) The term enantiotopic control is meant to imply that configurations of the pyran (D or L sugar) and of the tertiary alcohol regions (*R* or *S* alcohol) are controlled independently of one another through a strategy which focuses on the absolute configuration in each sector rather than on interactivity of the two regions. Of course, the second element of enantiotopic control merges with "diastereotopic control" since the relative stereochemistry is also imposed.

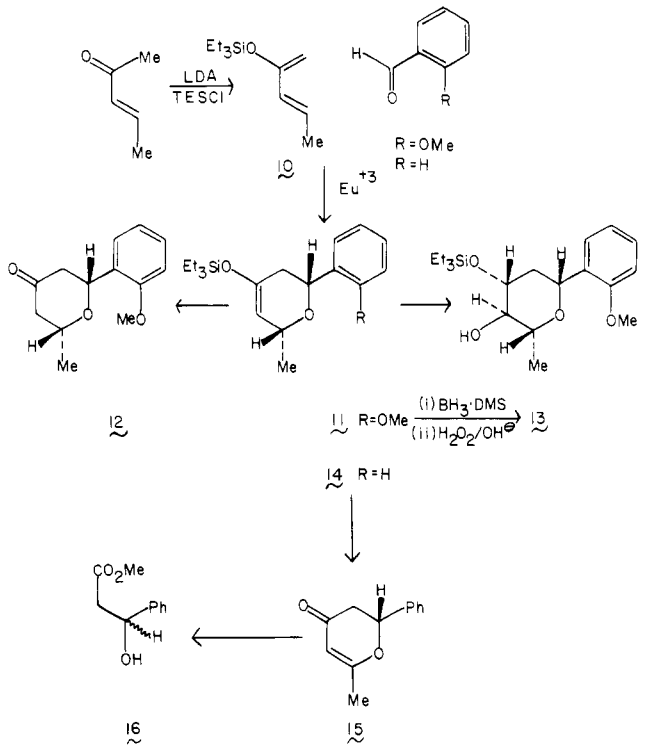
(13) Cf.: Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

of a pleasing intellectual solution to this most difficult problem, the quality of various synthetic approaches should be evaluated purely on the basis of efficiency and practicality.

Discussion of Results

(i) Model Studies: A Stereospecific Route to C-Glycosides. The feasibility of Lewis acid catalyzed cyclocondensation reactions of dienes of the type **3**, bearing an alkyl group at the terminal carbon instead of the usual 1-alkoxy function, had not yet been demonstrated.[14] Were a cycloaddition feasible, it would be of interest to address the question of endo vs. exo topology. Furthermore, the orderly introduction of functionality would be much simplified if the kinetic silyl enol ether (see Scheme I) could be isolated. The possibility of employing mild lanthanide catalysis toward this end was studied.[15a]

The commercially available methyl propenyl ketone was treated with lithium diisopropylamide (LDA) in tetrahydrofuran (THF). The resulting enolate was quenched to afford diene **10**. Reaction

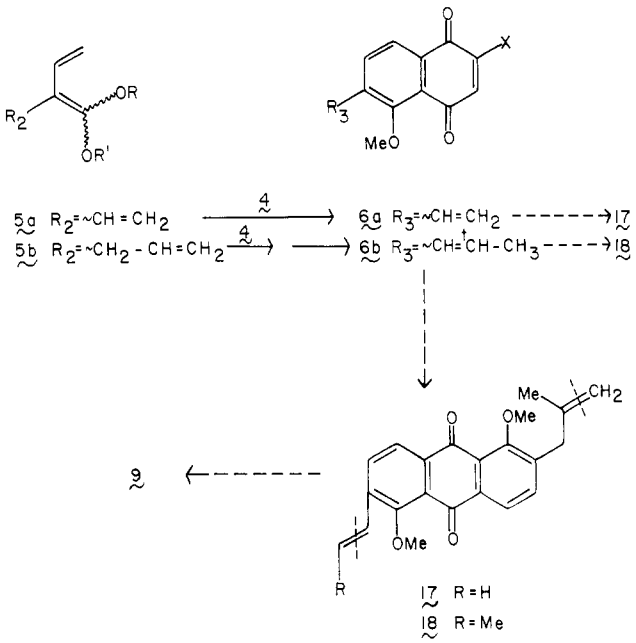


of **10** with *o*-methoxybenzaldehyde was carried out in chloroform at 65 °C in the presence of 5 mol % $Eu(fod)_3$[15b] over 12 h. A single cycloaddition product, **11**, was obtained in 86% yield. The stereochemistry of the dihydropyran was clarified by its acid-catalyzed hydrolysis to the tetrahydropyrone **12**. The high-field NMR spectrum (see Experimental Section) of this compound identifies its two tertiary protons to be axial. Thus, cycloaddition had indeed occurred with strict endo topology.

Reaction of the primary cycloaddition product **11** with 1 M equiv of borane–dimethylsulfide in methylene chloride followed by oxidation of the intermediate borane with alkaline hydrogen peroxide[16] afforded an overall hydration product, **13**, whose high-field NMR spectrum (see Experimental Section) reveals its four tertiary protons to be axial. A secure basis for proceeding on the vineomycinone project had been established. It is also to be noted that this chemistry provides a direct (two step) route to C-glycosides in the 2-deoxyglucose series.[10b]

It was of further interest to ascertain the extent of enantiotopic selectivity which could be realized by recourse to the chiral lanthanide catalyst $Eu(hfc)_3$.[17] Cycloaddition of diene **10** with benzaldehyde in the presence of $Eu(hfc)_3$ as above afforded silyl enol ether **14** in 91% yield. The latter was subjected to the action of palladium acetate in acetonitrile, thereby providing a 67% yield of the dihydropyrone **15**.[18] Ozonolysis of **15** followed by oxidative workup with hydrogen peroxide and esterification with diazomethane provided ester **16**. Analysis of the ^1H NMR spectrum of **16** by our usual protocols[17] showed there to be less than 5% of enantiotopic enrichment in the direction of the L sugar.

(ii) Synthesis of Ketoaldehyde 9. Attentions were now directed to the synthesis of ketoaldehyde **9**. The expectation was that cyclocondensation of this dicarbonyl compound with diene **10** would occur exclusively at the aldehyde center.[19] A logical precursor to **9** would be the diolefin **17**. Returning to Scheme II, in its simplest form, this could imply the use of diene **5a**. In that case, the resultant naphthoquinone would be **6a**.



We came to favor a somewhat less direct route wherein the diene would be that shown as **5b**. The naphthoquinone to be used for the second homo-Diels–Alder reaction (see Scheme II) would be **6b**. Compound **18**, which could be obtained from such a sequence, seemed to be an admirable precursor of the differentiated dicarbonyl system **9**. It would be necessary to change the nature of the R_2 function from allyl in **5b** to the propenyl group in **6b**. It was hoped that such a thermodynamically favorable tautomerization could be achieved at a stage between the two homo-Diels–Alder reactions (see Scheme II, $R_2 \rightarrow R_3$).

Deconjugative allylation of methyl crotonate according to Schlessinger[20] afforded the known **19**. Deprotonation of the β,γ-unsaturated ester followed by silylation with trimethylchlorosilane (TMSCl) afforded diene **20** in 81% yield. Diene **22**[21] was prepared in a similar way from methyl crotonate via its

(14) In the interim we have described the use of 1-alkyl and 1-alkyl-1-silyloxydienes in this chemistry. See: Danishefsky, S.; Harvey, D. F., Quallich, G.; Uang, B.-J. *J. Org. Chem.* **1984**, *49*, 392.

(15) (a) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716. (b) This is the trade name for tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium.

(16) For a related application which appeared after our communication,[6] see: Lepoittevin, J. P.; Benezra, C. *Tetrahedron Lett.* **1984**, 2505. See also: Larson, G. L.; Hernandez, D.; Hernandez, A. *J. Organomet. Chem.* **1974**, *76*, 9.

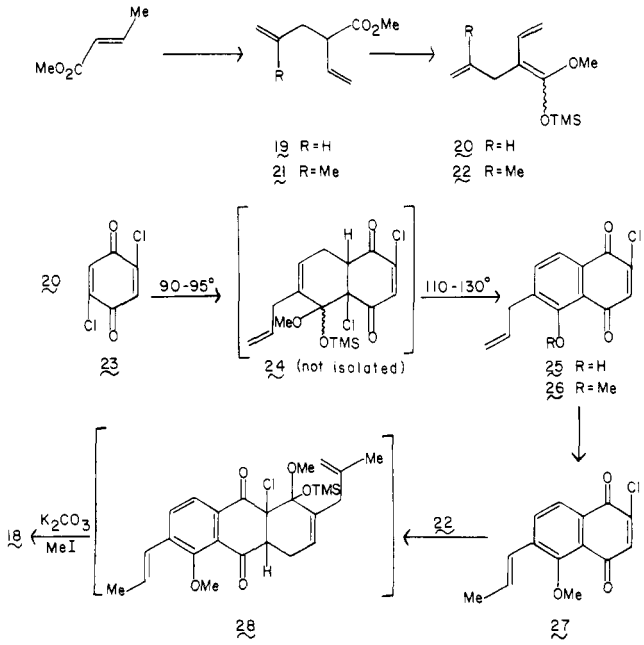
(17) Bednarski, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 3451.

(18) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *48*, 1011.

(19) We have thus far not encountered any cyclocondensation reactions with ketones. Professor Mark Midland of the University of California at Riverside has informed us that he has observed several cycloaddition reactions with ketones.

(20) Herman, T. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433.

(21) Diene **20** was originally prepared with a view toward the alternatie synthesis described later. See **29** → **18**. In the synthesis which starts with quinone **23**, it is likely that diene **22** could have been employed in both carboxycyclic Diels–Alder constructions; however, this possibility was not checked.



deconjugative methallylation product, **21**. The quinone selected as the starting material was the well-known and readily available 2,5-dichlorobenzoquinone (**23**).[22]

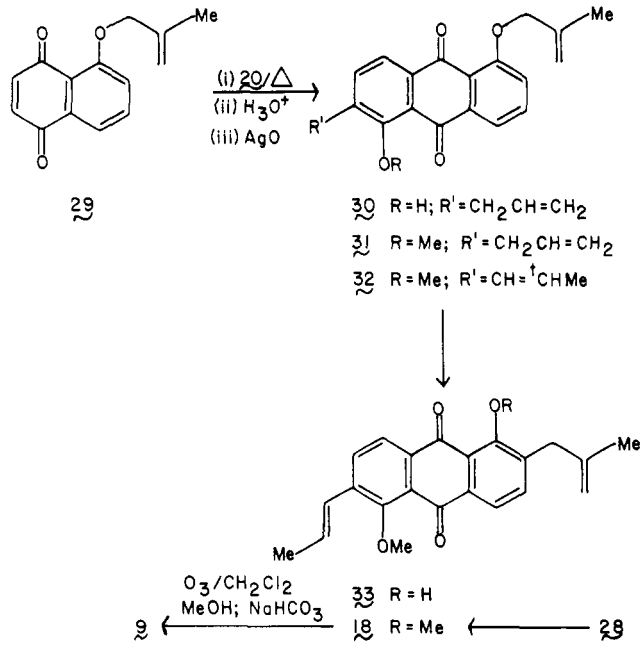
Diene **20** and quinone **23** were heated in benzene at 90 °C for 48 h. Thermolysis of the resultant material, presumed to be **24**, at 110–130 °C for 25 h, afforded a 70% yield of 2-allyl-6-chlorojuglone (**25**). Trace amounts of the O-methyl ether **26**, mp 96.5–97 °C, were also obtained. Compound **26** was in any case to be the next imtermediate in the synthesis. It was prepared in 95% yield by the O-methylation of **25** through the agency of silver oxide and methyl iodide. Predictably,[23] the Diels–Alder reaction was regiospecific. Both electronic and steric factors would converge to prompt "initial-bond" formation between C_3 of the quinone and C_4 of the diene. Another potential problem turned out not to pose any serious difficulties. In principle, diaddition of dienes to quinone **23** would be possible. In the event, however, a mono-Diels–Alder reaction of quinone **23** was readily achieved using a 1:1 mixture of diene **20** dienophile.

This result need occasion no surprise. Thus, **24**, which would be the expected product of cycloaddition of **20** and **23**, is no longer a quinone. The quinone linkage of **25** is only generated on thermolysis of **24**. Since quinones are more reactive dienophiles than enediones, diaddition would not have been expected to be a serious complicating factor.

The isomerization of the allyl function to the required propenyl group was accomplished through the reaction of **26** with $PdCl_2$·bisacetonitrile[24] in methylene chloride under reflux. Compound **27**, mp 149–150 °C, was obtained in 95% yield. The ability to carry out this conjugation in high yield at this strategic point was very valuable for the success of the enterprise. It provided the basis for the needed differentation of the 2 and 6 positions of the 1,5-dioxygenated anthraquinone. The timing for the second Diels–Alder reaction seemed to be propitious.

Reaction of **26** with diene **22** was carried out in benzene at 95 °C. The primary product of cycloaddition, presumed to be **28**, was not characterized. Attempts to convert it to the aromatic system by thermolysis were complicated by significant amounts of isomerization of the double bond of the methallyl group. Fortunately, this problem could be solved by reaction of the crude cycloaddition intermediate with potassium carbonate and methyl iodide in acetone. In this way, the desired anthraquinone **18**, mp 149–150 °C, was obtained in 79% yield. Thus, aromatization and methylation were achieved in one experimental operation.

The route described above to intermediate **18** was superior to another one which started with 2-methallyljuglone (**29**) prepared from juglone via reaction with silver oxide and methallyl iodide. Cycloaddition of **29** with diene **20** was carried out in benzene under reflux. The cycloadduct was treated with trifluoroacetic acid.



This crude product, which was in turn presumed to consist largely of 2-allyl-5-(methallyloxy)-1,9,10-anthracenetriol was oxidized with silver oxide to afford anthraquinone **30** which, upon methylation (73% overall), provided the methyl ether **31**.

It was interesting to find that treatment of **31** with $RhCl_3$[24] in ethanol led to faster isomerization of the allylic double bond than migration of the methallyl ether-like double bond. Compound **32** thus obtained in 58% yield was, upon thermolysis at 210 °C in *N,N*-diethylaniline, converted to **33** which, upon methylation (potassium carbonate–methyl iodide) was converted to the same compound **18** (56% from **32**). While this alternative was certainly very interesting and served to confirm the structures assigned in the double Diels–Alder route, it was not as practical. Most notably, the recourse to juglone as the starting material was far less attractive than reliance on quinone **23**. Also, the Diels–Alder reaction–oxidative aromatization sequence with **29** was less efficient in practice than the corresponding chemistry using haloquinones and silylketene acetals, wherein further oxidations are not required.

Ozonolysis of **18** in methylene chloride methanol in the presence of saturated sodium bicarbonate afforded an 84% yield of the desired ketoaldehyde **9**, 187.5–188.5 °C. The strategy for the construction of dideoxy-*C*-glycoside could now be launched.

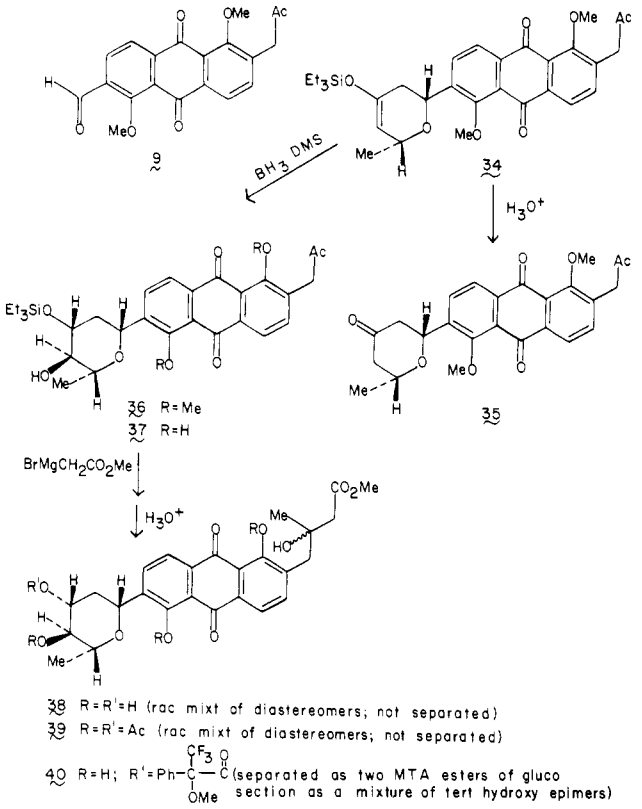
The information gained from the model studies (vide supra) proved relevant to substrate **9**. Reaction of ketoaldehyde **9** with diene **10** occurred in chloroform in the presence of 5 mol % $Eu(fod)_3$. There was thus obtained the silyl enol ether **34** in 90–95% yield. Hydrolysis of **34** gave tetrahydropyrone **35**. This cis relationship of the methyl and aromatic residues was seen most readily from the ^1H NMR spectrum of **35** wherein both methine protons were seen to be axial (see Experimental Section).

For maximum conciseness, hydroboration was to be carried on directly on silyl enol ether **34**. Since the substrate contained an unhindered ketone, mild conditions for hydroboration were sought. No reaction was seen upon treatment of **34** with 9-BBN. At-

(22) Ling, A. R. *J. Chem. Soc.* **1892**, *61*, 558.

(23) Cf. Inter alia: (a) Brassard, P.; Roberge, G. *J. Org. Chem.* **1981**, *46*, 4161 and earlier papers. (b) Bauman, J. G.; Barber, R. B.; Gless, R. D.; Rapaport, H. *Tetrahedron Lett.* **1980**, 4477. (c) Cameron, D. W.; Feutrill, G. I.; Perlmutter, P. *Aust. J. Chem.* **1982**, *35*, 1469. (d) Pearlman, B. A.; McNamara, J. M.; Hasan, I.; Hatakeyama, S.; Sekezaki, H.; Kishi, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4248. For the first example of annulation of a quinone with a siloxydiene, see: Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.

(24) (a) Hegedus, L. S.; Williams, R. E.; McGuire, M. A.; Hayashi, T. *J. Am. Chem. Soc.* **1980**, *102*, 4973. (b) Cf.: Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehrmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102.



tempted selective reaction with diborane itself was unsuccessful. However, differential reactivity was realized by treatment of **34** with 1 equiv of borane dimethylsulfide,[25] in methylene chloride at room temperature for 2 h. After oxidative workup with aqueous alkaline hydrogen peroxide, a 49% yield of **36** was obtained. These mild conditions resulted in a 30% recovery of starting compound **34**. However, avoidance of reduction of the ketone justified the inconvenience of chromotographic recovery and recycling of starting material. As in the case of model compound **11**, hydroboration occurred anti to the methyl and aryl groups. As before, the assignment of stereochemistry to **36** followed from its ^{1}H NMR spectrum (see Experimental Section) wherein each of the tertiary protons was revealed to be axial.

Attempts to achieve the two-carbon homologation of the ketone in compound **36** were unsuccessful. These included reactions with (carbomethoxy)methyllithium, (carbomethoxy)methylbromozinc, vinylmagnesium bromide, and potassium (dimethylphosphonyl)methylacetate. Such reactions afforded either unrecognizable materials or starting materials. It seemed that the required Reformatsky-like reactions were being undermined by proton transfer from the rather acidic benzylic methylene group and by competing reactions (alkylation or electron-transfer induced deterioration) of the quinone. In principle, both of these problems might be ameliorated if the two methyl ether functions would be cleaved at this stage. It was hoped that deprotonation of the resultant diphenol would considerably reduce the electrophilicity of the anthraquinone[26] and possible the acidity of the benzylic methylene group.

Demethylation was accomplished by treatment of **36** with boron tribromide in methylene chloride at −78 °C for 90 min. Remarkably, the triethylsilyl group survived this exposure. Compound **37** was obtained as an orange powder which was unstable to silica gel chromatography. Accordingly, it was used in less than fully homogeneous form.

The first indication that success was at hand arose from the reaction of **37** with the bromomagnesium salt, prepared from the reaction of (carbomethoxy)methyllithium with anhydrous magnesium bromide.[27] Chromatography of the crude reaction product and elution of a yellow band produced material with the same rf value as a sample of authentic aglycon methyl ester **2b**, which was prepared by known methods from aquayamycin.[2e] Interestingly, though by all chemical logic, it seemed certain that the synthetic product must be a diastereomeric mixture; its NMR spectrum in the mixed solvent system (CD_3OD–$CDCl_3$ 1:4) was suggestive of its being homogeneous and was identical with that of authentic **2b**. Indeed, even the 125-MHz ^{13}C NMR spectra of **38** and **2b** in the same mixed solvent system were identical, and there was no objective indication that the synthetic material was inhomogeneous. The same apparent homogeneity and identity with authentic material was manifested in the tetraacetate **39** obtained from the reaction of synthetic **38** with acetic anhydride and pyridine. Again, both the 500-MHz ^{1}H NMR and the 125-MHz ^{13}C NMR spectra of the synthetic **39** and **2c** derived from authentic **2b** material were identical.

The first indication that the synthetic **38** was in fact nonhomogeneous arose from its 500-MHz ^{1}H NMR spectrum in pure $CDCl_3$. In authentic **2b**, the spectrum of the benzylic methylene protons (adjacent to the tertiary alcohol) give rise to an AB quartet: H_1 3.12 (J = 13.5 Hz), H_2 3.04 (J = 13.5 Hz) ppm. In the synthetic material this quartet is seen, but there is discerned another quartet of roughly equal intensity ($H_{1'}$ 3.10 (J = 13.5 Hz), $H_{2'}$ 3.06 (J = 13.5 Hz) ppm) which is not seen in the authentic material. The remaining resonances of both spectra are identical. Accordingly, it was supposed that these latter resonances might correspond to the benzylic protons of the "epi" compound. Unfortunately, all attempts at HPLC separation were unsuccessful.

Another approach to the preparation of homogeneous synthetic **2** involved attempted bisacylation of the two chiral sectors of **3**, with L-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.[28] In principle, if each Mosher ester could "resolve" its end of the molecule, four compounds should be produced. This plan was foiled when only a two component mixture of *monoesters* was produced. The tertiary alcohol was not acylated. Separation of the two monoesters was achieved on a μ-Bondapak–CN column using 1:2:48 acetone/ethyl acetate/benzene. The ^{1}H NMR spectrum of each component showed that the "dideoxygluco" regions had been resolved via the Mosher ester **40**, but the ^{1}H NMR spectrum indicated that the tertiary alcohol center was still inhomogeneous.

The use of a chiral menthyl ester to "resolve" the β-hydroxyester region was examined. If this could be accomplished one could then turn to the Mosher ester to provide homogeneous material. *In this event, the menthyl esters themselves sufficed for separation of both ends of the molecule.*

Reaction of *l*-menthyl acetate with LDA–THF produced a lithio intermediate which, on treatment with anhydrous magnesium bromide, afforded the presumed **41** which reacted with **37** (10 equiv of **41**; 1 equiv of **37**). The product, obtained after standard workup, was separable by HPLC into two pure components. One was shown (vide infra) to be **42**, i.e., the *l*-menthyl ester of **2a**. Another pure component which could be obtained with the *l*-menthyl ester of one of the two antipodal forms of *epi*-vineomycinone. The configuration of the "anthracycline portion" of this substance is *arbitrarily assigned* as shown in **43**.[29] The other two components, i.e., *ent*-**43** *l*-menthyl ester (i.e., **44**) and *ent*-**2**

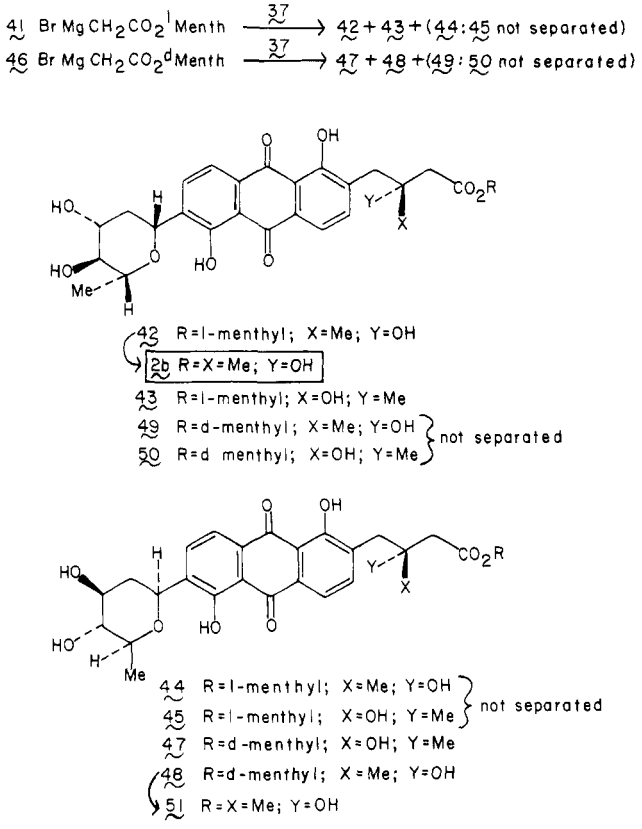
(25) For analogies for the susceptibility of both the quinonoid and the ketone functionalities see: (a) Minicione, E. *J. Org. Chem.* **1978**, *43*, 1829. (b) Pearson, D. E.; Weaver, D. J. *Org. Prep. Proced. Int.* **1978**, *10*, 29.

(26) Cf.: Kende, A. S.; Tsay, Y. G. *J. Chem. Soc., Chem. Commun.* **1977**, 140.

(27) Cf.: Mitsui, S.; Konno, K.; Onuma, I.; Shimizu, K. *J. Chem. Soc. Jpn.* **1964**, *85*, 437.

(28) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2453.

(29) At present we have no way to rigorously know whether the menthyl esters of vineomycinone and *epi*-vineomycinone which are obtained in homogeneous form are configurationally related in the pyran or the tertiary alcohol sectors. Therefore, the absolute configurations of the *epi*-methyl esters are also not known. For the sake of representation, we arbitrarily group the corresponding homogeneous compounds (**42** and **43** as well as **47** and **48**) on the basis of identical sugars which differ in the configuration of the tertiary alcohols.



l-menthyl ester (i.e., **45**) were not separable from one another.

Predictably, a similar result was obtained starting with *d*-menthyl acetate and proceeding via its bromomagnesium derivative **46**. From this theoretically four-component mixture, there could be obtained in homogeneous form the *d*-menthyl ester of ent-**2a** (i.e., **47**) and the *d*-menthyl ester of *epi*-vineomycinone whose absolute configuration in the "anthracycline protion" is *arbitrarily shown* as **48**.[29] The other two components, **49** and **50**, presumably present, were not separable.

Treatment of vineomycinone *l*-menthyl ester (**42**) with potassium carbonate in methanol accomplished trans esterification, affording a sample of the homogeneous, fully synthetic methyl ester **2b**. Similar processing of **48** afforded *epi*-vineomycinone methyl ester whose absolute configuration is arbitrarily expressed as **51**.[29] The fully synthetic **2b** had a melting point of 183–184 °C (authentic sample = 184–185 °C). Its optical rotation, $[\alpha]_D$ +109.1° (*c* 0.000 66, $CDCl_3$), is also in close accord with that of authentic **2**:, $[\alpha]_D$ +109.2° (*c* 0.000 65 $CDCl_3$). Comparison of the 500-MHz ^1H NMR spectra of **2b** and **51** shows them to be identical except for the resonances for the benzylic methylene groups (vide supra). Most decisively the spectra revealed the absence of contamination between fully synthetic **2b** and **51**. Accordingly, it can confidently be asserted that the total synthesis of homogeneous vineomycinone B_2 methyl ester has been accomplished.

In conclusion, the use of three cycloadditions with siloxydienes leads to a very concise route to ketone **37**. However, the penalty for the stereoandomness of the Reformatsky-like reaction (see **37** → **38** and the analogous reactions in the menthyl series) was quite severe in the practical preparative sense. Separation of the vineomycin and epi-vineomycin series was feasible only through recourse to HPLC and then only on small scales using "shaving and recycling" techniques. Needless to say, for any solution involving enantiotopic sepcificity to be of consequence at the preparative level, given the difficulties of chromatographic separation of the "vineo" and "*epi*-vineo" isomers, control would have to be exercised in *both* sectors of the molecule.

The ultimate solution, at the conceptual level, would involve retention of the simplicity of the scheme described herein, in a context in which effective stereochemical dialogue between the remote dissymmetric elements would be established. As the sophistication of organic synthesis continues to grow, such an idealized formulation could well fall within the scope of the feasible.

Experimental[30] Section

***trans*-2-((Triethylsilyl)oxy)-1,3-pentadiene (10).** To a stirred solution of LDA (130 mmol) in THF (55 mL) at −78 °C was added dropwise 3-penten-2-one (10.0 g, 65% pure from Aldrich) over a 50-min period. After the solution was stirred for 15 min, triethylsilyl chloride (19.7 g, 131 mmol) was added. The mixture was stirred at −78 °C for 30 min and then was slowly warmed to room temperature and stirred for an additional hour. After dilution with hexanes (250 mL), the mixture was washed with cold saturated $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Fractional distillation of the residue afforded diene **10**:[31] 11.2 g, 73%, 87–94 °C/10 mmHg; IR (neat) 2950, 2895, 2855, 1580, 1315, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.09 (dq, *J* = 15.1, 6.8 Hz, 1 H), 5.84 (dd, *J* = 15.1, 1.4 Hz, 1 H), 4.20 (s, 1 H), 4.17 (s, 1 H), 1.77 (dd, *J* = 6.8, 1.4 Hz, 3 H), 1.00 (t, *J* = 7.9 Hz, 9 H), 0.72 (q, *J* = 7.9 Hz, 6 H); MS (70 eV), *m/e* 198 (M^+).

***cis*-2-Methyl-6-(*o*-methoxyphenyl)-4-((triethylsilyl)oxy)-5,6-dihydro-2*H*-pyran (11).** A solution of *o*-methoxybenzaldehyde (217 mg, 1.59 mmol), diene **10** (850 mg, 4.29 mmol), and $Eu(fod)_3$[15b] (83 mg, 0.08 mmol) in chloroform (1.0 mL) was heated at 65 °C for 12 h. The volatiles were removed in vacuo. Compound **11** (459 mg, 86%) was obtained after flash column chromatography of the residue on silica gel: IR ($CDCl_3$) 2950, 2850, 1660, 1485, 1450, 1240, 1190 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8 Hz, 1 H), 7.27 (t, *J* = 8 Hz, 1 H), 7.02 (t, *J* = 8 Hz, 1 H), 6.88 (d, *J* = 8 Hz, 1 H), 5.01 (dd, *J* = 10.5, 3.3 Hz, 1 H), 4.87 (dd, *J* = 2.3, 2.0 Hz, 1 H), 4.45 (dddq, *J* = 3.2, 2.9, 2.0, 6.5 Hz, 1 H), 3.84 (s, 3 H), 2.35 (ddd, *J* = 16.4, 3.3, 2.9 Hz, 1 H), 2.18 (dddd, *J* = 16.4, 10.5, 3.2, 2.3 Hz, 1 H), 1.32 (d, *J* = 6.5 Hz, 3 H), 1.02 (t, *J* = 8.0 Hz, 9 H), 0.72 (q, *J* = 8.0 Hz, 6 H); MS (70 eV), *m/e* 334 (M^+).

***cis*-2-(*o*-Methoxyphenyl)-6-methyltetrahydro-4*H*-pyran-4-one (12).** A solution of enol ether **11** (17.0 mg, 0.051 mmol) in THF (1.0 mL) was treated with 1 N HCl μL, mL). After stirring for 40 min at room temperature, the mixture was neutralized with saturated $NaHCO_3$ solution and extracted with methylene chloride. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. Compound **12** (10.1 mg, 90%) was obtained after column chromatography (SiO_2, CH_2Cl_2) of the residue: IR ($CDCl_3$) 1715, 1485, 1245, 1045 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8, 1.6 Hz, 1 H), 7.27 (dt, *J* = 1.6, 8 Hz, 1 H), 7.02 (t, *J* = 8 Hz, 1 H), 6.87 (d, *J* = 8 Hz, 1 H), 5.03 (dd, *J* = 11.5, 2.5 Hz, 1 H), 3.93 (ddq, *J* = 11.0, 2.0, 6.1 Hz, 1 H), 3.81 (s, 3 H), 2.72 (ddd, *J* = 14.3, 2.5, 2.0 Hz, 1 H), 2.46 (ddd, *J* = 14.4, 2.0, 2.0 Hz, 1 H), 2.39–2.33 (m, 2 H), 1.41 (d, *J* = 6.1 Hz, 3 H); MS (70 eV), *m/e* 220.1 (M^+).

***rac*-β-(*o*-Methoxyphenyl)-3-(triethylsilyl)-2,6-dideoxyglucose (13).** To a methylene chloride (0.8 mL) solution containing enol ether **11** (22.8 mg, 0.068 mmol) was added borane–dimethyl sulfide (68.0 μL, 1 M in CH_2Cl_2) at 0 °C. The mixture was stirred at room temperature for 18 h. A solution of 1:1 3 N NaOH and 30% H_2O_2 (60 μL) and THF (0.9 mL) were added. The mixture was warmed in a 35 °C bath for 1.5 h with stirring. Powdered potassium carbonate and ether (5 mL) were added, leaving an organic layer and a solid residue. The organic layer was decanted after stirring. The solid residue was triturated with ether. The combined organic layers were concentrated in vacuo. The residue afforded 16 mg of compound **13** (68%) after column chromatography (SiO_2/EtOAC–hexane 1:2): IR ($CDCl_3$) 3580, 2945, 2855, 1490, 1460, 1245, 1070 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.24 (dt, *d* = 1.0, 8.0 Hz, 1 H), 7.00 (t, *J* = 8.0 Hz, 1 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 4.86 (dd, *J* = 11.1, 1.1 Hz, 1 H), 3.83 (s, 3 H), 3.81 (ddd, *J* = 9.0, 8.9, 4.9 Hz, 1 H), 3.48 (dq, *J* = 9, 5.9 Hz, 1 H), 3.20 (dd, *J* = 9.9, 8.9 Hz, 1 H), 2.33 (ddd, *J* = 11.7, 4.9, 1.1 Hz, 1 H), 1.55

(30) ^1H NMR spectra were recorded on a Varian EM 390 and Brucker 250-MHz or 500-MHz spectrometers. Data are reported as (megahertz, solvent) chemical shift in parts per million with chloroform (δ 7.27) as the internal standard. Infrared spectra were recorded on a Perkin-Elmer 710B spectrometer using sodium chloride solution cells and are referenced to polystyrene (1601 cm^{-1}). Mass spectra were obtained with an HP-5985 GC-MS spectrometer by direct insertion. High-performance liquid chromatography was performed with a Waters 6000A HPLC system. Combustion analyses were performed by Dr. Rittner of Olin Corp., New Haven, and Galbraith Laboratories, Inc., Knoxville, TN.

(31) This diene was obtained in >90% purity. The contaminant was 2-((triethylsilyl)oxy)-4-methyl-1,3-pentadiene, which did not interfere with the cycloaddition of diene **10** with aldehyde **9**.

(ddd, J = 11.7, 11.1, 9.0 Hz, 1 H), 1.32 (d, J = 5.9 Hz, 3 H), 1.02 (t, J = 7.9 Hz, 9 H), 0.72 (q, J = 7.9 Hz, 6 H); MS (20 eV), m/e 352 (M^+).

***cis*-2-Methyl-6-phenyl-4-((triethylsilyl)oxy)-5,6-dihydro-2*H*-pyran (14).** A solution of benzaldehyde, (1.04 g, 9.80 mmol), diene **10** (0.800 g, 4.03 mmol), and Eu(hfc)$_3$ (32.0 mg, 0.035 mmol) in $CHCl_3$ (1 mL) was heated at 65 °C for 9 h. The volatiles were then removed in vacuo. Column chromatography of the residue on silica gel and elution with EtOAC–hexane (1:15) afforded 276 mg (91%) of 2-methyl-6-phenyl-4-((triethylsilyl)oxy)-5,6-dihydro-2*H*-pyran (**14**): IR ($CDCl_3$) 2950, 2850, 1665, 1345, 1200, 1175 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.15–7.33 (m, 4 H), 4.77 (dd, J = 1.6, 1.6 Hz, 1 H), 4.55 (dd, J = 10.6, 3.6 Hz, 1 H), 4.34 (dddq, J = 3.3, 2.5, 1.6, 6.8 Hz, 1 H), 2.26 (dddd, J = 16, 10.6, 3.3, 1.6 Hz, 1 H), 2.11 (ddd, J = 16, 3.6, 2.5 Hz, 1 H), 1.22 (d, J = 6.8 Hz, 3 H), 0.93 (t, J = 7 Hz, 9 H), 0.63 (q, J = 7 Hz, 6 H); MS (70 eV), m/e 304 (M^+).

6-Methyl-2-phenyl-2,3-dihydro-4*H*-pyran-4-one (15). To a stirred solution of CH_3CN (0.5 mL) containing $Pd(OAc)_2$ (0.13 g, 0.58 mmol) was added enol ether **14** (0.17 g, 0.58 mmol) at room temperature. The mixture was stirred for 24 h, diluted with methylene chloride, and filtered. The filtrate was concentrated in vacuo. After chromatography (EtOAc–hexane 1:6), the residue gave 73 mg (67%) of compound **15**: IR ($CDCl_3$) 1655, 1605, 1390, 1350, 1325, 1245 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.45–7.39 (m, 5 H), 5.45 (s, 1 H), 5.40 (dd, J = 13.0, 4.5 Hz, 1 H), 2.82 (dd, J = 15.0, 13.0 Hz, 1 H), 2.60 (dd, J = 15.0, 4.5 Hz, 1 H), 2.10 (s, 3 H); MS, m/e 188 (M^+).

Methyl 2-Ethenyl-4-pentenoate (19). To a stirred soltuion of LDA (165 mmol) in THF (65.0 mL) was added HMPA (30.0 mL) at −78 °C. The mixture was stirred for 30 min at −78 °C. Methyl crotonate (15.9 mL, 150 mmol) was added dropwise at −78 °C over a 20-min period. After stirring was continued for 40 min, allyl bromide (15.0 mL, 173 mmol) was added. The mixture was stirred for 70 min at −78 °C. The reaction was quenched with 20 mL of saturated NH_4Cl. The mixture was allowed to warm up to 0 °C and was diluted with hexanes (300 mL). The organic layer was washed with water (100 mL × 7). The combined aqueous layers were extracted with hexanes (200 mL), and the extract was washed with water (100 mL × 2). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Fractional distillation of the residue afforded 10.7 g (76.4 mmol, 51%) of compound *19* (*57–61 °C/10 mmHg*) and *2.75 g (10%) of the diallylated* product methyl 2-ethenyl-2-(2-propenyl)-4-pentenoate, 2-(*n*-propenyl)-4-pentenoate, **19a** (bp 80–83 °C/10 mmHg). For compound **19**: IR (neat) 3050, 2950, 2930, 2880, 1740, 1635, 1430, 1340, 1261, 1190, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.52–6.02 (m, 2 H), 4.9–5.2 (m, 4 H), 3.67 (s, 3 H), 3.1 (dt, J = 7, 7 Hz, 1 H), 2.2–2.7 (m, 2 H); MS (20 eV), m/e 140.1 (M^+). For compound **19a**: IR (neat) 3050, 2960, 2930, 2900, 1735, 1640, 1435, 1270, 1210, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.47–6.1 (m, 3 H), 4.9–5.25 (m, 6 H), 3.65 (s, 3 H), 2.47 (d, J = 7 Hz, 4 H); MS (20 eV), m/e 180.1 (M^+).

Formation of 2-Ethenyl-1-methoxy-1-((trimethylsilyl)oxy)-1,4-pentadiene (20) as a 3:2 Ratio of Isomers. To a stirred solution of LDA (80 mmol) in THF (32 mL) was added dropwise compound **19** (10.5 g, 75 mmol) over 15 min at −78 °C. After the solution was stirred for 20 min, trimethylsilyl chloride (8.56 g, 92.5 mmol) was added. The mixture was warmed from −78 to 0 °C over 30 min with stirring. After dilution with hexanes (350 mL), the mixture was poured into a saturated $NaHCO_3$ solution (50 mL) containing ice (50 g). After the solution was shaken, the aqueous layer was removed and the organic layer was washed with water (50 mL × 2). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Reduced pressure distillation of the residue from 72 to 75 °C (0.8 mmHg) afforded 12.8 g (60.5 mmol, 81%) of ketene acetal **20** as a ca. 3:2 mixture of geometric isomers. For the mixture: IR (neat) 3050, 2950, 2810, 1640, 1435 cm^{-1}. ^{1}H NMR ($CDCl_3$) (major isomer) δ 6.5 (dd, J = 13, 11.5 Hz, 1 H), 5.5–6.1 (m, 1 H), 4.7–5.15 (m, 4 H), 3.56 (s, 3 H), 2.9 (d, J = 6 Hz, 2 H), 0.25 (s, 9 H), (minor isomer) 6.7 (dd, J = 13, 11.5 Hz, 1 H), 5.5–6.1 (m, 1 H), 4.7–5.15 (m, 4 H), 3.6 (s, 3 H), 2.85 (d, J = 6 Hz, 2 H), 0.23 (s, 9 H); MS (20 eV), m/e 212.1 (M^+).

2-Chloro-5-hydroxy-6-(2-propenyl)naphthoquinone (25). A solution of the mixed ketene acetals **20** (6.29 g, 29.6 mmol) and quinone **23** (5.20 g, 29.3 mmol) in benzene (60 mL) was heated (85 °C bath) for 58 h. The volatiles were removed in vacuo. The residue was heated in a 110 °C bath for 2 h. After the solution was cooled, the residue was dissolved in CH_2Cl_2 and passed through SiO_2. The filtrate was concentrated in vacuo, and the residue was recrystallized from EtOH to give 4.73 g (65%) of compound **25** as orange needles: mp 126–126.5 °C; IR ($CDCl_3$) 1675, 1635, 1590, 1425, 1305, 1250, 845 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.64 (d, J = 8 Hz, 1 H), 7.49 (d, J = 8 Hz, 1 H), 7.14 (s, 1 H), 5.7–6.2 (m, 1 H), 4.95–5.25 (m, 2 H), 3.48 (d, J = 6 Hz); MS (20 eV), m/e 248.1 (M^+, 100%), 250.1 (M + 2, 31.0%). Anal. Calcd: C, 62.79%; H, 3.64%; Cl, 14.26%. Found: C, 62.51%; H, 3.75%; Cl, 14.55%.

2-Chloro-5-methoxy-6-(2-propenyl)naphthoquinone (26). A CH_2Cl_2 solution (100 mL) containing quinone **25** (7.88 g, 31.7 mmol), methyl iodide (8.72 g, 63.4 mmol), and Ag_2O (11.0 g, 47.5 mmol) was heated under reflux. Additional methyl iodide (8.72 g, 63.4 mmol) was introduced twice during the reflux period. After 21 h, the mixture was cooled, filtered, and concentrated in vacuo. The residue was redissolved in 1:1 hexanes–CH_2Cl_2, passed through SiO_2 (30 g), and eluted with 1:1 hexanes–CH_2Cl_2. The eluate was concentrated and recrystallized from hexanes. Quinone **26** (8.30 g, 99%) was obtained as yellow needles: mp 96.5–97 °C; IR ($CDCl_3$) 1675, 1655, 1601, 1575, 1240, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 8 Hz, 1 H), 7.55 (d, J = 8 Hz, 1 H), 7.06 (s, 1 H), 5.7–6.15 (m, 1 H), 4.9–5.2 (m, 2 H), 3.83 (s, 3 H), 3.5 (d, J = 7 Hz, 2 H); MS (20 eV), m/e 262.0 (M^+, 87.8%), 264.0 (M + 2, 32.5%). Anal. Calcd: C, 64.01%; H, 4.22%. Found: C, 63.91%; H, 4.23%.

2-Chloro-5-methoxy-6-(*trans*-1-propenyl)naphthoquinone (27). A solution of CH_2Cl_2 (5 mL) containing $PdCl_2(CH_3CN)_2$ (4.2 mg, 0.018 mmol) and quinone **26** (202 mg, 0.771 mmol) was heated under reflux for 12 h. After the solution cooled, a deep orange–red solid was obtained. The solid was dissolved in CH_2Cl_2. The solution was passed through SiO_2 (1 g). Elution with 1:1 hexanes–CH_2Cl_2 and recrystallization from ethyl acetate afforded quinone **27** (192.4 mg, 95%) as orange needles: mp 139–140 °C; IR ($CDCl_3$) 2910, 1675, 1605, 1570, 1240, 1150, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 8 Hz, 1 H), 7.78 (d, J = 8 Hz, 1 H), 7.09 (s, 1 H), 6.78 (d, J = 16 Hz, 1 H), 6.46 (dq, J = 16, 6 Hz, 1 H), 3.84 (s, 3 H), 1.99 (d, J = 6 Hz, 3 H); MS (20 eV), m/e 262.0 (M^+, 100%), 264.0 ((M + 2)$^+$, 34.8%). Anal. Calcd: C, 64.01%; H, 4.22;. Found: C, 63.83%; H, 4.20%.

Methyl 2-Ethenyl-4-methyl-4-pentenoate (21). To a solution of LDA (162.5 mmol) in THF (65 mL) was added HMPA (29 mL) at −75 °C. After the solution was stirred for 40 min, methyl crotonate (15.1 g, 151 mmol) was introduced dropwise over 30 min. The mixture was stirred at −70 °C for a further 30 min and then 2-methyl-3-iodopropene (32.0 g, 176 mmol) was added. After 1 h, the reaction was quenched with a saturated NH_4Cl solution (30 mL) and allowed to warm to 0 °C. The mixture was diluted with hexanes (250 mL) and washed with water (100 mL × 6). The combined aqueous layers were extracted with hexanes (200 mL), and the organic layer was washed with water (100 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Reduced pressure distillation of the residue afforded 17.45 g (75%) of compound **21**: bp 58–60 °C/10 mmHg; IR ($CDCl_3$) 3070, 2945, 1735, 1640, 1440, 1270, 1200, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.6–6.0 (m, 1 H), 4.95–5.2 (m, 2 H), 4.71 (br s 1 H), 4.67 (br s, 1 H), 3.63 (s, 3 H), 3.22 (ddd, J = 7, 7, 7 Hz, 1 H), 2.47 (dd, J = 14, 7 Hz, 1 H), 2.20 (dd, J = 14, 7 Hz, 1 H), 1.70 (s, 3 H); MS (20 eV), m/e 154 (M^+).

Formation of 2-Ethenyl-1-methoxy-4-methyl-1-((trimethylsilyl)oxy)-1,4-pentadiene (22) as a 2:1 Mixture of Isomers. To a solution of LDA (39 mmol) in THF (16 mL) was added dropwise ester **21** (5.37 g, 34.9 mmol) over 30 min at −78 °C. After 20 min, trimethylsilyl chloride (5.0 g, 46.3 mmol) was introduced. The reaction temperature was allowed to warm to 0 °C. After 40 min the mixture was diluted with hexanes (350 mL) and washed with cold $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Reduced pressure distillation of the residue afforded diene **22** (6.27 g, 79.5%) boiling from 48 to *52 °C/0.8 mmHg* as a 2:1 mixture of isomers: IR (neat) 3070, 2955, 1645, 1440, 1250, 1220, 1095, 845 cm^{-1}; ^{1}H NMR ($CDCl_3$) (major isomer) δ 6.52 (dd, J = 16, 11 Hz, 1 H), 4.85 (dd, J = 16, 2 Hz, 1 H), 4.74 (dd, J = 11, 2 Hz, 1 H), 4.59 (m, 2 H), 3.55 (s, 3 H), 2.89 (br s, 2 H), 1.72 (br s, 3 H), (minor isomer) 6.67 (dd, J = 16, 11 Hz, 1 H), 4.85 (dd, J = 16, 2 Hz, 1 H), 4.74 (dd, J = 11, 2 Hz, 1 H), 4.59 (m, 2 H), 3.59 (s, 3 H), 2.81 (br s, 2 H), 1.72 (br s, 3 H); MS (20 eV), m/e 226 (M^+).

1,5-Dimethoxy-2-(*trans*-1-propenyl)-6-(2-methyl-2-propenyl)-9,10-anthraquinone (18). A benzene (30 mL) solution containing quinone **27** (0.99 g, 3.77 mmol) and triene **22** (1.50 g, 6.64 mmol) was heated in a 90 °C bath for 15 h. *The volume of the solution was reduced to about* 5–10 mL by blowing N_2 over the surface of the solution. Acetone (30 mL) and K_2CO_3 (1.90 g, 13.8 mmol) were added to the residue. The mixture was stirred at room temperature for 2 h, treated with methyl iodide (2.18 g, 15.3 mmol), and heated on a 50 °C bath. Additional methyl iodide (2.18 g, 15.3 mmol) was added 3 times at 8-h intervals during heating. After 44 h the reaction mixture was cooled and concentrated in vacuo. Ether–CH_2Cl_2 (1:1, 200 mL) was added to the residue. The organic solution was washed with cold 0.2 N HCl (50 mL × 2) and brine (50 mL × 3), dried over $MgSO_4$, and concentrated in vacuo. Compound **18** (1.08 g, 79%) was obtained as a yellow solid which, after recrystallization from benzene, afforded yellow needles: mp 149–150 °C; IR ($CDCl_3$) 2910, 1670, 1570, 1555, 1255, 1070, 1000

cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00 (d, J = 8 Hz, 1 H), 7.99 (d, J = 8 Hz, 1 H), 7.80 (d, J = 8 Hz, 1 H), 7.56 (d, J = 8 Hz, 1 H), 6.80 (br d, J = 16.5 Hz, 1 H) 4.64 (br s, 1 H), 3.89 (s, 3 H), 3.46 (br s, 2 H), 1.96 (d, J = 6 Hz, 3 H), 1.73 (br s, 3 H); MS (20 eV), m/e 362.1 (M^+). Anal. Calcd: C, 76.22%; H, 6.12%. Found: C, 76.03%; H, 6.11%.

1,5-Dimethoxy-2-formyl-6-(2-oxopropyl)-9,10-anthraquinone (9). To a solution of CH_2Cl_2 (105 mL) containing compound **18** (1.85 g, 5.10 mmol), MeOH (0.8 g, 19.7 mmol), and $NaHCO_3$ (150 mg, 178 mmol) was bubbled O_3 at −78 °C until the color of the solution started to change to green. The greenish solution was treated with dimethyl sulfide (10 mL) and stirred at room temperature for 8 h. The mixture was concentrated in vacuo. After the residue was passed through a short column (8 g of SiO_2–CH_2Cl_2), compound **9** (1.51 g, 4.28 mmol, 84%) was obtained as yellow crystals: mp 187.5–188.5 °C; IR ($CDCl_3$) 2920, 1720, 1695, 1675, 1580, 1565, 1270, 1230, 1070, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.58 (br s, 1 H), 8.24 (d, J = 8.1 Hz, 1 H), 8.18 (d, J = 8.1 Hz, 1 H), 8.33 (d, J = 8 Hz, 1 H), 7.38 (d, J = 8 Hz, 1 H), 4.12 (s, 3 H), 3.19 (s, 2 H), 3.89 (s, 3 H), 2.31 (s, 3 H); MS (20 eV), m/e 352.1 (M^+).

1,5-Dimethoxy-2-(5,6-dihydro-2-methyl-4-((triethylsilyl)oxy)-2*H*-pyran-6-yl)-6-(2-oxopropyl)-9,10-anthraquinone (34). To a $CHCl_3$ (25 mL) solution containing aldehyde **9** (1.5 g, 4.25 mmol) and Eu(fod)$_3$ (0.14 g, 0.135 mmol) was added diene **10** (3.4 mL, 16.8 mmol). The resulting solution was heated on a 65 °C bath for 17 h. Triethylamine (1 mL) was added, and the mixture was concentrated in vacuo. Flash column chromatography of the residue on silica gel (35 g) and elution with EtOAc–hexane (1:2) afforded enol ether **34** (2.15 g, 92%): IR ($CDCl_3$) 2950, 2850, 1710, 1665, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.13 (d, J = 1 Hz, 1 H), 8.07 (d, J = 8 Hz, 1 H), 8.01 (d, J = 8 Hz, 1 H), 7.57 (d, J = 8 Hz, 1 H), 5.06 (dd, J = 10, 4 Hz, 1 H), 4.89 (br s, 1 H), 4.55–4.35 (m, 1 H), 3.96 (s, 3 H), 3.9 (5.5 H), 2.3 (s, 3 H), 2.4–2.0 (m, 2 H), 1.36 (d, J = 6 Hz, 3 H), 1.15–0.9 (m, 9 H), 0.85–0.6 (m, 6 H); MS (20 eV), m/e 550.4 (M^+). Anal. Calcd: C, 67.61%; H, 6.95%; Si, 5.10%. Found: C, 67.42%; H, 6.85%; Si, 5.31%.

1,5-Dimethoxy-6-(2-oxopropyl)-2-(*cis*-6-methyl-2,3,5,6-tetrahydro-4*H*-pyran-4-on-2-yl)-9,10-anthraquinone (35). A solution containing THF (0.40 mL), H_2O (0.40 mL), acetic acid (1.20 mL), and enol ether **34** (16.9 mg, 0.030 mmol) was stirred at room temperature for 3 h and then concentrated in vacuo. The residue afforded compound **35** (11 mg, 0.025 mmol, 82%) after column chromatography (SiO_2/EtOAc–$CHCl_3$ 1:9): IR ($CDCl_3$) 1720, 1670, 1565, 1265 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.14 (d, J = 8.1 Hz, 1 H), 8.06 (d, J = 7.9 Hz, 1 H), 8.03 (d, J = 8.1 Hz, 1 H), 7.57 (d, J = 7.9 Hz, 1 H), 5.10 (dd, J = 11.6, 2.5 Hz, 1 H), 3.96 (ddq, J = 11.0, 2.0, 6.1 Hz, 1 H), 3.94 (s, 3 H), 3.89 (s, 2 H), 3.88 (s, 3 H), 2.80–2.73 (m, 1 H), 2.55–2.34 (m, 3 H), 2.29 (s, 3 H), 1.44 (d, J = 6.1 Hz, 3 H); MS (20 eV), m/e 436.1 (M^+), 421.1 (65%), 404.1 (75%), 337.1 (75%), 293.1 (87.5%).

1,5-Dimethoxy-2-(tetrahydro-5-hydroxy-6-methyl-4-((triethylsilyl)-oxy)-2*H*-pyran-2-yl)-6-(2-oxopropyl)-9,10-anthraquinone (36). To a solution of enol ether **34** (208 mg, 0.378 mmol) in CH_2Cl_2 (6 mL) was added borane–dimethyl sulfide (0.38 mL, 1 M CH_2Cl_2) solution at room temperature. The mixture was stirred for 2 h, and then THF (4 mL), MeOH (1 mL), and a 30% H_2O_2–3 N NaOH (1:1) solution (6 mL) were added. Effervescence was observed. After the bubbling of gases ceased, the mixture was warmed on a 40 °C water bath for 2.5 h. Powdered K_2CO_3 was added, and stirring was continued for 10 min. The aqueous layer was extracted with ether (200 mL × 3). The combined ethereal layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography of the residue afforded recovered enol ether **34** (64 mg) and product **36** (103 mg, 69%): IR ($CDCl_3$) 3575, 2945, 2925, 2855, 1715, 1670, 1565, 1270, 1255, 1075, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.12 (d, J = 8.3 Hz, 1 H), 8.08 d, J = 8.3 Hz, 1 H), 7.96 (d, J = 8.3 Hz, 1 H), 7.58 (d, J = 8.3 Hz, 1 H), 4.92 (dd, J = 11, 1.7 Hz, 1 H), 3.96 (s, 3 H), 3.88 (s, 5 H), 3.81 (ddd, J = 11, 8.7, 3.9 Hz, 1 H), 3.5 (dq, J = 9.2, 6 Hz, 1 H), 3.20 (dd, J = 9.2, 8.7 Hz, 1 H), 2.29 (s, 3 H), 2.23 (ddd, J = 11.8, 3.9, 1.7 Hz, 1 H), 1.59 (ddd, J = 11.8, 11, 11 Hz, 1 H), 1.24 (d, J = 6 Hz, 3 H), 1.00–0.94 (m, 9 H), 0.65–0.60 (m, 6 H); MS (20 eV), m/e 568.3 (M^+), 455.1 (42.9%), 423 (26.0%), 171.2 (88%), 145.1 (71.7%), 103.2 (100%). Anal. Calcd: C, 65.47%; H, 7.09%; Si, 4.94%. Found: C, 65.47%; H, 7.26%; Si, 4.92%.

Demethylation of Anthraquinone 36. Formation of 37. To a solution of **36** (22.5 mg, 0.0395 mmol) in CH_2Cl_2 (1 mL) was added BBr_3 (45 μL, neat) at −78 °C. The mixture was stirred at −78 °C for 75 min, diluted with CH_2Cl_2 (30 mL), and poured into ice-cold aqueous NH_4Cl. The color of the organic layer changed from purple to orange. The organic layer was separated from the aqueous layer and washed twice with brine and ice. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford **37** (21.2 mg, 0.0392 mmol; 99%) as an orange solid. Compound **37** was used directly without any purification because it tends to decompose on silica gel: ^1H NMR (90 MHz, $CDCl_3$ partial spectrum) δ 7.90–7.50 (m, 4 H), 3.85 (s, 2 H), 2.30 (s, 3 H), 1.10–0.90 (m, 9 H), 0.70–0.50 (m, 6 H).

Formation of Diastereomer Mixture (38). To a solution of $(Me_3Si)_2NH$ (0.138 g, 0.855 mmol) in THF (0.4 mL) was added *n*-BuLi (2.6 M in hexane, 0.33 mL, 0.86 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. Methyl acetate (57.8 mg, 0.78 mmol) was added dropwise to the $LiN(SiMe_3)_2$ solution at −78 °C over a period of 20 min. After the solution was stirred for 35 min at −78 °C, anhydrous $MgBr_2$ (0.78 mmol) in THF (4 mL) was added. The mixture was stirred for another 25 min at −78 °C and then was added to a solution of **37** (121 mg, 0.22 mmol) in THF (15 mL) at −20 °C. The reaction mixture was stirred at room temperature for 1 day. After dilution with CH_2Cl_2 (150 mL), the mixture was poured into ice–water. The mixture was carefully acidified with the addition of 1 N H_2SO_4 until the pH of the aqueous layer was ca. 1.5. The organic layer was washed with water (50 mL × 3), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2/$CHCl_3$–MeOH 50:1 then $CHCl_3$–MeOH 10:1) to afford a 19-mg (49%) mixture of two diastereomers corresponding to **38**: IR ($CDCl_3$) 1715, 1620, 1600, 1255 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 7.9 Hz, 2 H), 7.87 (d, J = 8.1 Hz, 2 H), 7.82 (d, J = 7.9 Hz, 2 H), 7.71 (d, J = 8.1 Hz, 2 H), 4.96 (dd, J = 10.5, 1.2 Hz, 2 H), 3.88 (ddd, J = 11.8, 9.0, 4.2 Hz, 2 H), 3.72 (s, 6 H), 3.55 (dq, J = 8.9, 6.1 Hz, 2 H), 3.23 (dd, J = 9.0, 8.9 Hz, 2 H), 3.04 (d, J = 13.5 Hz, 1 H), 2.58 (d, J = 14 Hz, 2 H), 2.57 (d, J = 14 Hz, 2 H), 2.55 (ddd, J = 12.0, 4.2, 1.2 Hz, 2 H), 1.50 (ddd, J = 12.0, 11.8, 10.5 Hz, 2 H), 1.43 (d, J = 6.1 Hz, 6 H), 1.32 (s, 6 H).

Formation of the Mixture of Fully Synthetic Tetraacetyl Derivative (39). The tetraacetyl derivative of the synthetic mixture **38** was prepared according to the literature procedure[2e] for the converison of pure aglycon **2b** to **2c**. A mixture of **38** (21.7 mg, 43.3 mmol), pyridine (0.5 mL), and acetic anhydride (0.5 mL) was allowed to stand at room temperature for 3 h and then ice–water (10 mL) was added. After standing at room temperature for 1 h, the mixture was extracted with ether. The organic layer was washed with water, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified on silica gel column to afford 22.5 mg of **39** as a yellow powder: ^1H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 8.0 Hz, 1 H), 8.13 (d, J = 8.0 Hz, 1 H), 7.99 (d, J = 8.0 Hz, 1 H), 7.83 (br d, J = 8.0 Hz, 1 H), 5.15 (m, 1 H), 4.86 (dd, J = 9.0, 9.0 Hz, 1 H), 4.76 (br s, 1 H), 3.74 (s, 3 H) 3.70 (dq, J = 9.0, 6.1 Hz, 1 H), 2.99 (br d, J = 13.5 Hz, 1 H), 2.89 (br d, J = 13.5 Hz, 1 H), 2.55–2.52 (m, 3 H), 2.54 (s, 3 H), 2.52 (s, 3 H), 2.09 (s, 3 H), 2.02 (s, 3 H), 1.68 (m, 1 H), 1.31 (d, J = 6.1 Hz, 3 H), 1.27 (s, 3 H). Though compound **39** is in fact a mixture of diastereomers, its NMR spectrum is identical with that from **2c**.

***d*-Menthyl 6-(2,6-dideoxy-β-arabinohexopyranosyl)-9,10-dihydro-1,5-dihydroxy-β-methyl-9,10-dioxo-2-anthracenebutanoate 47 and 48.** To a solution of diisopropylamine (1.67 g, 16.5 mmol) in THF (6.5 mL) was added *n*-BuLi (16.1 mmol) at 0 °C. After stirring for 50 min, the LDA solution was cooled to −78 °C, and *d*-menthyl acetate (2.90 g, 14.6 mmol) was added dropwise over a period of 50 min. After the solution was stirred for another 40 min at −78 °C, $MgBr_2$–THF solution (14.6 mmol in 40 mL of THF) was added to the enolate solution. The Grignard reagent was stirred at −78 °C for 30 min and then was added to compound **37** (755 mg, 1.40 mmol) in THF (30 mL) at 0 °C. A reddish solution was formed. The reaction mixture was stirred at room temperature for 45 h and then was diluted with CH_2Cl_2 (300 mL) and was carefully acidified with 0.5 N H_2SO_4 (100 mL). The organic layer was washed with ice–water (100 mL × 2), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 35 g/$CHCl_3$–MeOH 50:1 and then $CHCl_3$–MeOH 10:1). A yellow solid was obtained (534.7 mg, 0.857 mmol, 61.2%) as a mixture of four isomers. The mixture was further purified by HPLC (μ-Bondapak–CN/acetone–ethyl acetate hexanes 1:1:20/flow rate 2 mL/min). Fraction 3, *ent*-vineomycinone B_2 *d*-menthyl ester **47**: IR ($CDCl_3$) 1700, 1620, 1420, 1255 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 8.0 Hz, 1 H), 7.88 (d, J = 8.0 Hz, 1 H), 7.83 (d, J = 8.0 Hz, 1 H), 7.73 (d, J = 8.0 Hz, 1 H), 4.97 (dd, J = 11.1, 1.5 Hz, 1 H), 4.78 (ddd, J = 10.9, 10.9, 4.6 Hz, 1 H), 3.87 (m, 1 H), 3.55 (dq, J = 9.2, 6.0 Hz, 1 H), 3.24 (dd, J = 9.0, 8.9 Hz, 1 H), 3.11 (d, J = 13.3 Hz, 1 H), 3.05 (d, J = 13.3 Hz, 1 H), 2.60–2.50 (m, 3 H), 2.33–0.90 (m, 10 H), 1.43 (d, J = 6.0 Hz, 3 H), 1.30 (s, 3 H), 0.92 (d, J = 7 Hz, 3 H), 0.91 (d, J = 7 Hz, 3 H), 0.75 (d, J = 7 Hz, 3 H). Fraction 1, *epi*-vineomycinone B_2 *d*-menthyl ester **48**: IR ($CDCl_3$) 2940, 2900, 1700, 1620, 1425, 1260 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 8.0 Hz, 1 H). 7.88 (d, J = 8.0 Hz, 1 H), 7.83 (d, J = 8.0 Hz, 1 H), 7.73 (d, J = 8.0 Hz, 1 H), 4.97 (dd, J = 11.1, 1.5 Hz, 1 H), 4.75 (ddd, J = 10.9, 10.9, 4.2 Hz, 1 H), 3.87 (m, 1 H), 3.55 (dq, J = 9.2, 6.0 Hz, 1 H), 3.24 (dd, J = 9.0, 8.9 Hz, 1 H), 3.09 (d, J = 13.3 Hz, 1 H), 3.06 (d, J = 13.3 Hz, 1 H), 2.57–2.54 (m, 1 H), 2.54 (s, 2 H), 2.33–0.90 (m, 10 H), 1.43 (d, J = 6 Hz, 3 H), 1.31 (s, 3 H), 0.90 (d, J = 7 Hz, 3 H), 0.88 (d, J = 7 Hz, 3 H), 0.78 (d, J = 7 Hz, 3 H); MS (20 eV), m/e 384.0 (52.9%),

280.0 (33.1%), 139.1 (42.9%), 83.2 (92.5%).

***l*-Menthyl 6-(2,6-dideoxy-β-arabinohexapyranosyl)-9,10-dihydro-1,5-dihydroxy-β-methyl-9,10-dioxo-2-anthracenebutanonate 42 and 43.** Reaction of *l*-menthyl ester bromomagnesium salt **41** with ketone **37** under the above reaction conditions afforded *epi*-vineomycinone B_2 *l*-menthyl ester **43** in fraction 1, vineomycinone B_2 *l*-menthyl ester **42** in fraction 3, and two other isomers in fraction 2. The IR, ^1H NMR, and mass spectra of *l*-menthyl ester **42** were identical with those of *d*-menthyl ester **47**, and the corresponding spectrum of *l*-menthyl ester **43** was identical with that of *d*-menthyl ester **48**.

Vineomycinone B_2 Methyl Ester 2b. A mixture of *l*-menthyl ester **42** (8.0 mg, 0.013 mmol), anhydrous K_2CO_3 (100 mg), and MeOH (0.5 mL) in a stoppered flask was heated in a 70 °C bath for 22 h. Ice–water (5 mL) was added to the mixture, and the solution was carefully acidified with 1 N H_2SO_4 until the pH of the solution was 3. The acidified solution was extracted with CH_2Cl_2 (40 mL × 2). The combined organic layers were dried over Na_2SO_4 and then CH_2N_2/Et_2O (1.4 mg, 0.5 mmol) solution was added at 0 °C. After stirring for 1 h the solution was concentrated in vacuo. The residue (6.0 mg) was purified by HPLC (μ-Bondapak–CN/ethyl acetate–hexane 1:3/2 mL/min) to afford vineomycinone B_2 methyl ester **2b** (0.8 mg, 0.0016 mmol) and recovered *l*-menthyl ester **42** (1.0 mg, 0.0016 mmol): IR ($CDCl_3$) 1715, 1620, 1600, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 13.23 (s, 1 H), 13.11 (s, 1 H), 7.93 (d, J = 7.9 Hz, 1 H), 7.87 (d, J = 8.1 Hz, 1 H), 7.82 (d, J = 7.9 Hz, 1 H), 7.71 (d, J = 8.1 Hz, 1 H), 4.96 (dd, J = 10.5, 1.2 Hz, 1 H), 3.88 (ddd, J = 11.8, 9.0, 4.2 Hz, 1 H), 3.72 (s, 3 H), 3.55 (dq, J = 8.9, 6.1 Hz, 1 H), 3.23 (dd, J = 9.0, 8.9 Hz, 1 H), 3.12 (d, J = 13.5 Hz, 1 H), 3.04 (d, J = 13.5 Hz, 1 H), 2.58 (d, J = 14 Hz, 1 H), 2.57 (d, J = 14 Hz, 1 H), 2.55 (ddd, J = 12.0, 4.2, 1.2 Hz, 1 H), 1.50 (ddd, J = 12.0, 11.8, 10.5 Hz, 1 H), 1.43 (d, J = 6.1 Hz, 3 H), 1.32 (s, 3 H); MS (20 eV), m/e 485.1 ($M^+ - 15$), 384.1 (35%), 281.1 (18.9%), 280.0 (50.9%), 117.1 (100%); $[\alpha]_D$ +109.1° (c 0.000 66, $CDCl_3$), mp 183–184 °C.

***epi*-Vineomycinone B_2 Methyl Ester 51.** Treatment of *d*-menthyl ester **48** with potassium carbonate in methanol under the above reaction conditions afforded *epi*-vineomycinone B_2 methyl ester **51**: IR ($CDCl_3$) 1713, 1640, 1450, 1250 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 13.23 (s, 1 H), 13.11 (s, 1 H), 7.93 (d, J = 7.9 Hz, 1 H), 7.87 (d, J = 8.1 Hz, 1 H), 7.82 (d, J = 7.9 Hz, 1 H), 7.71 (d, J = 8.1 Hz, 1 H), 4.96 (dd, J = 10.5, 1.2 Hz, 1 H), 3.88 (ddd, J = 11.8, 9.0, 4.2 Hz, 1 H), 3.72 (s, 3 H), 3.55 (dq, J = 8.0, 6.1 Hz, 1 H), 3.23 (dd, J = 9.0, 8.9 Hz, 1 H), 3.10 (d, J = 13.5 Hz, 1 H), 3.06 (d, J = 13.5 Hz, 1 H), 2.58 (d, J = 14 Hz, 1 H), 2.57 (d, J = 14 Hz, 1 H), 2.55 (ddd, J = 12.0, 4.2, 1.2 Hz, 1 H), 1.50 (ddd, J = 12.0, 11.8, 10.5 Hz, 1 H), 1.43 (d, J = 6.1 Hz, 3 H), 1.32 (s, 3 H).

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Registry No. 2b, 89495-27-2; **9**, 89414-68-6; **10**, 88083-96-9; **11**, 94110-19-7; **12**, 94110-20-0; **13**, 94110-21-1; **14**, 94110-22-2; **15**, 94110-23-3; **18**, 94110-24-4; **19**, 922-00-9; **19a**, 94110-25-5; **20** (isomer 1), 94110-26-6; **20** (isomer 2), 94110-27-7; **21**, 94110-28-8; **22** (isomer 1), 94110-29-9; **22** (isomer 2), 94110-30-2; **23**, 615-93-0; **25**, 94110-31-3; **26**, 89414-71-1; **27**, 94110-32-4; **29**, 94110-33-5; **30**, 94110-34-6; **31**, 94110-35-7; **32**, 94110-36-8; **33**, 94110-37-9; **34**, 94110-38-0; **35**, 94110-39-1; **36**, 94160-45-9; **37**, 94160-46-0; **38** (diastereomer 1), 94160-47-1; **38** (diastereomer 2), 94160-48-2; **39** (diastereomer 1), 94160-49-3; **39** (diastereomer 2), 94160-50-6; **41**, 55284-67-8; **42**, 89414-79-9; **43**, 89495-29-4; **44**, 94160-51-7; **45**, 94160-52-8; **47**, 94160-53-9; **48**, 94160-54-0; **49**, 89495-31-8; **50**, 89495-30-7; **51**, 94233-39-3; 3-penten-2-one, 625-33-2; triethylsilyl chloride, 994-30-9; *o*-methoxybenzaldehyde, 135-02-4; benzaldehyde, 100-52-7; methyl crotonate, 18707-60-3; 2-methyl-3-iodopropene, 3756-30-7; methyl acetate, 79-20-9; *d*-menthyl acetate, 5157-89-1; juglone, 481-39-0.

Supplementary Material Available: Full experimental procedures for the alternate route to compound **18** via juglone (3 pages). Ordering information given on any current masthead page.

Palladium-Mediated Cycloaddition Approach to Loganin Aglucon

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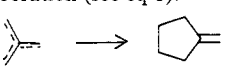
Abstract: The concept of a cycloaddition approach to the most illustrious member of the iridoid family, loganin aglucon, is outlined. Palladium-catalyzed cycloaddition of a substituted 2-[(trimethylsilyl)methyl]allyl carboxylate to cyclopentenone creates the proper substitution pattern of loganin. Conversion of the [(2,4,6-triisopropylphenyl)sulfonyl]hydrazone of the adduct to its corresponding vinyllithium and carboxylation are followed by deconjugation of the enoate. The crucial resultant bicyclo[3.3.0]octene suffers double cleavage in a single step to create the keto form of loganin alucon in five steps from cyclopentenone. The efficiency of this approach demonstrates the utility of a cycloaddition strategy. The questions associated with the use of substituted TMM units in complex synthesis are probed.

The explosive growth in the number of natural products containing five-membered rings provided great stimulation to develop cyclopentannulation methods.[1] In considering the types of strategy that would be particularly useful, a cycloaddition approach seemed most appealing. Among the types of cycloadditions that could be considered, the addition of trimethylenemethane offers the opportunity of forming a five-membered ring and simultaneously introducing the exocyclic methylene group as a useful functionality for further structural elaboration (see eq 1).[1c,2-10] Metal-catalyzed



(1)

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