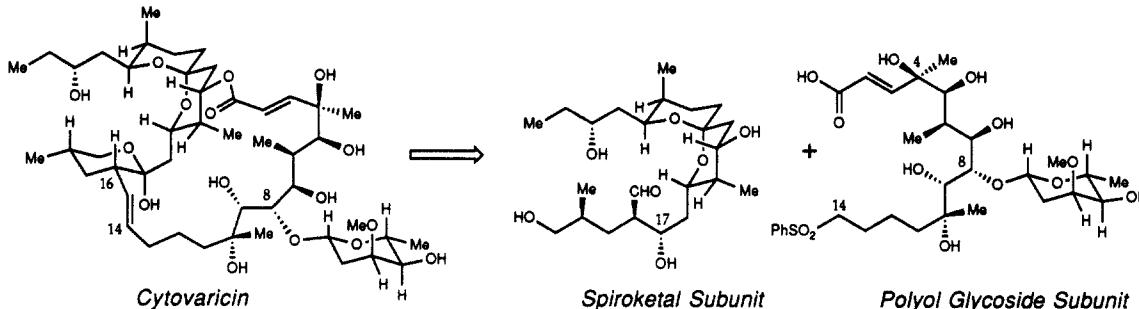


Total Synthesis of the Macrolide Antibiotic Cytovaricin

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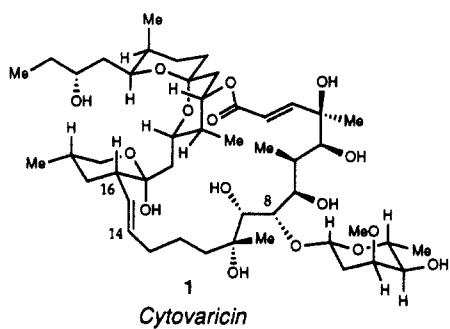
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Abstract: A convergent asymmetric synthesis of the antineoplastic macrolide antibiotic cytovaricin has been achieved through the synthesis and coupling of the illustrated spiroketal and polyol glycoside subunits. All absolute stereochemical relationships within the target structure were ultimately controlled by the use of asymmetric aldol, alkylation, or epoxidation methodology. Union of the two subunits was accomplished by Julia-Lythgoe trans olefination, providing direct access to a suitable macrocyclization substrate. A high-yielding ring closure (92%) and subsequent three-step refunctionalization of the macrocyclic



product afforded cytovaricin. In supporting studies, the solution conformation and chemical reactivity of the natural product were also examined. Three-dimensional overlay of cytovaricin with rutamycin A indicates an unexpected homology between the two structures, in turn suggesting a potential mode of action for cytovaricin.

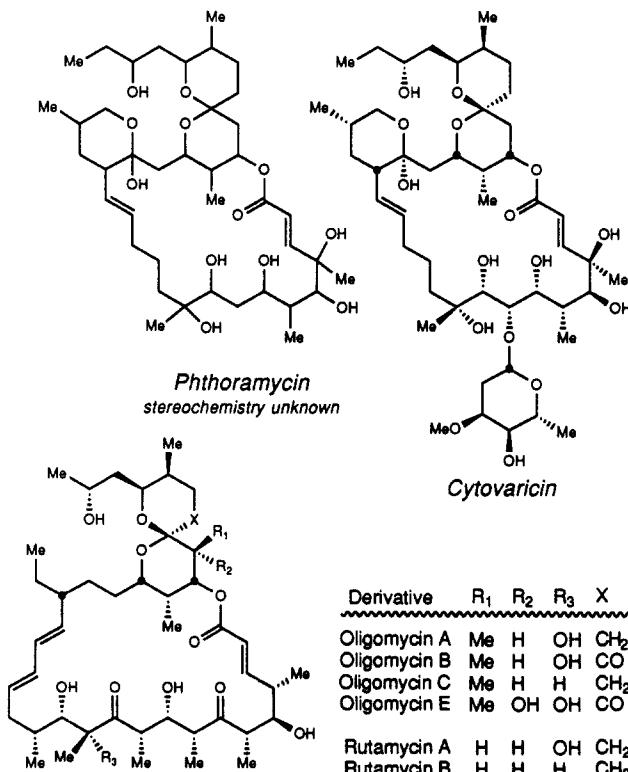
Cytovaricin (**1**) was isolated by Isono and co-workers in 1981 from cultures of *Streptomyces diastatochromogenes*.² Its "potent inhibitory activity" against Yoshida sarcoma cells in tissue culture prompted structure elucidation efforts, leading to the successful X-ray analysis of the antibiotic in 1983.³ Subsequent degradation of cytovaricin by treatment with methanolic acid afforded the known glycoside methyl- β -D-cymaroside, thereby securing the absolute configuration of the macrolide.⁴



As an outgrowth of our involvement with the development of new stereoselective methods for the synthesis of polypropionate-derived natural products, we describe our successful efforts to develop the first synthesis of this antineoplastic macrolide.

Studies detailing the biosynthesis of cytovaricin reveal that the glycon is assembled from one isobutyrate, six propionate, and nine acetate building blocks.⁵ Cytovaricin appears to be related biogenetically to the oligomycin/rutamycin family of antibiotics,⁶ and it is reasonable that it be included as a member of this class of spiroketal macrolides (Scheme I). By inspection, the spiroketal subunits of the two classes of compounds are quite similar. With the exception of the acetate starter unit,⁷ rutamycin A and B both possess spiroketals with a substitution pattern and relative stereochemistry identical with that of cytovaricin. One of the noteworthy differences between cytovaricin and these related ma-

Scheme I



crolides is the incorporation of two additional propionate fragments into the rutamycin/oligomycin 26-membered macrocycle. Re-

(1) Taken from the Ph.D. thesis of S. W. Kaldor, Harvard University, 1989.

(2) Kihara, T.; Kusakabe, H.; Nakamura, G.; Sakurai, T.; Isono, K. *J. Antibiot.* 1981, 34, 1073–1074.

(3) Sakurai, T.; Kihara, T.; Isono, K. *Acta Cryst.* 1983, C39, 295–297.

^{*}Harvard University.
[†]Cornell University.

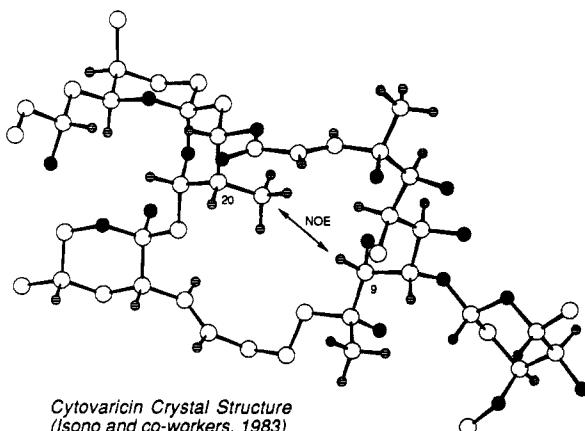


Figure 1. Transannular nuclear Overhauser effect.

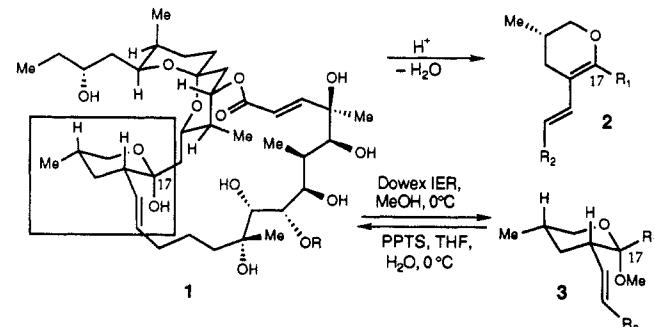
cently, two new macrolides closely related to cytovaricin have been reported.⁸ Phthoramycin, a new antifungal antibiotic reported by Omura and co-workers, appears to be the decymarosyl-8-deoxy cytovaricin analogue (Scheme I).^{8a,b} The gross structure of the closely related macrolide kaimonolide A, which exhibits potent plant growth inhibition superior to that exhibited by abscisic acid, has also been disclosed.^{8c} The complete structure elucidation of both of these compounds await further studies.

The structural similarities between cytovaricin and the oligomycins/rutamycins, whose absolute configurations have yet to be determined, provide circumstantial evidence for a common absolute configurational assignment consistent with that found for cytovaricin. This prediction has recently been confirmed in our laboratory by correlation of a rutamycin B degradation fragment with material produced by asymmetric synthesis.⁹ In conclusion, the rutamycins, and most probably the oligomycins, share a common absolute configuration with cytovaricin.

Preliminary Studies

NMR Spectroscopic Analysis of Cytovaricin. At the outset of the project, no NMR spectroscopic or chemical stability data was available for the natural product. Since such information is invaluable in the design stages of any complex synthesis plan,¹⁰ both spectroscopic and chemical studies were undertaken. With a sample of natural cytovaricin provided by Isono, NMR spectroscopy was utilized to analyze the solution conformation of the macrolide. Although cytovaricin crystallizes in its lactol form, the macrolide possesses the potential for ring-chain tautomerism. The "closed" lactol form of cytovaricin depicted in the crystal structure masks a tautomeric "open" form in which a β,γ -unsaturated keto alcohol is revealed. The 500-MHz ^1H , COSY-90,¹¹ and ^{13}C NMR spectra of cytovaricin in a variety of solvents indicated that only one discernible tautomer exists in solution, with the macrolide exhibiting a large equilibrium preference for

Scheme II



the lactol structure. NOE measurements established that the solution conformation closely resembles the crystal structure. For example, the observation of a transannular NOE between the axial C_{20} methyl group of the spiroketal and the C_9 methine proton of the polyol portion of the molecule provides perhaps the most dramatic piece of evidence in support of this assertion (Figure 1). Interestingly, despite being flanked by two antiperiplanar $\text{C}-\text{O}$ bonds, the C_9 proton also appears significantly further *upfield* in the ^1H NMR spectrum of cytovaricin than all other protons on oxygen-bearing carbons in the macrolide.¹² The reasons for this anomalous chemical shift remain unclear.¹³

Reactivity Studies. The stability of cytovaricin was evaluated under a variety of reaction conditions. The overriding constraint was the sensitivity of the molecule to acid. For example, if care was not taken to use base-washed glassware, rapid transformation of the natural product to a UV-active substance ensued. This compound proved to be the dienol ether **2** formed by elimination of water from the lactol portion of the molecule (Scheme II). In fact, this acid-catalyzed process proved facile under more controlled conditions.¹⁴ In the presence of a variety of acids, rapid and irreversible dehydration was again observed. All attempts to effect rehydration of this dienol ether were uniformly unsuccessful,¹⁵ indicating that its production at any point during the synthesis would constitute a serious setback. This same predisposition towards dehydration has also been recently reported for the related macrolide kaimonolide A.^{8c}

Through a systematic study of the media in which acid-catalyzed reactions were conducted, conditions were eventually identified for functionalizing the cytovaricin lactol moiety without concomitant elimination (Scheme II). Treatment of the macrolide with methanol in the presence of Dowex-50 sulfonic acid resin¹⁶ resulted in quantitative formation of the lactol methyl ether **3** (0°C , 1.5 h). This result stands in contrast to the use of "homogeneous" acids such as camphorsulfonic acid (methanol,

(12) In CD_3CN , the C_9 methine proton appears at 2.98 ppm, whereas the remaining protons α to oxygen in cytovaricin occur in the range of 3.30–5.18 ppm. Normally, antiperiplanar $\text{C}-\text{O}$ bonds afford a relatively large *de-shielding* effect. In fact, in a fully deprotected synthetic polyol glycoside fragment consisting of the C_3-C_{14} portion of cytovaricin, the C_9 -methine proton appears at 4.20 ppm in CD_3CN .

(13) Transannular steric shielding is a possibility, but the relatively large interatomic distance between the C_9 methine proton and its nearest transannular partner, the C_{20} methyl group (ca. 2.5–2.6 Å on the basis of crystal structure measurements) suggests that such shielding should have only a minor effect on the chemical shift of this proton. For leading references on steric influences on NMR chemical shifts in rigid bicyclic systems, see: Marchand, A. P. *Methods Stereochem. Anal.* 1982, 1, 15–19.

(14) Acidic conditions which were surveyed and which induced dienol ether formation include: camphorsulfonic acid (methanol, 0°C , 1 min), aqueous hydrochloric acid (THF, 0°C , 10 min), aqueous oxalic acid (CH_2Cl_2 , 25°C , 10 min), aqueous acetic acid (THF, 25°C , 10 min), and pyridinium *p*-toluenesulfonate (methanol, 0°C , 15 min). As a cautionary note, in all NMR studies on cytovaricin, strictly anhydrous chlorinated solvents such as chloroform or dichloromethane should be avoided to preclude acid-catalyzed decomposition of the natural product.

(15) A related problem was encountered in the synthesis of the antibiotic X-206: Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* 1988, 110, 2506–2526.

(16) (a) Patwardhan, S. A.; Dev, S. *Synthesis* 1974, 348–349. (b) See also ref 15.

(4) Kihara, T.; Isono, K. *J. Antibiot.* 1983, 36, 1263.

(5) Kihara, T.; Ubukata, M.; Uzawa, J.; Isono, K. *J. Antibiot.* 1989, 42, 919–925. The full ^{13}C NMR assignment of cytovaricin may be found in this paper.

(6) For leading references see: (a) *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: Orlando, FL, 1984. (b) Kobayashi, K.; Nishino, C.; Ohya, J.; Sato, S.; Shiobara, Y.; Kodama, M.; Nishimoto, N. *J. Antibiot.* 1987, 40, 1053–1057.

(7) Assumed here by analogy with biosynthetic work performed on oligomycin A: Bu'lock, J. D.; Morris, G. A.; Richards, M. K. *Tetrahedron Lett.* 1986, 27, 2917–2920.

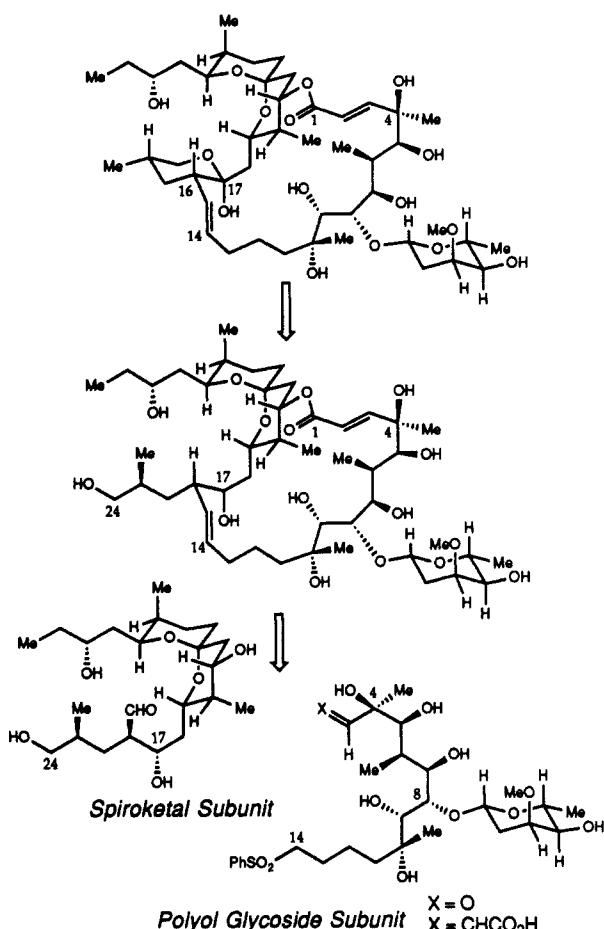
(8) (a) Nakagawa, A.; Miura, S.; Imai, H.; Imamura, N.; Omura, S. *J. Antibiot.* 1989, 42, 1324–1327. (b) Omura, S.; Tanaka, Y.; Hisatome, K.; Miura, S.; Takahashi, Y.; Nakagawa, A.; Imai, H.; Woodruff, H. B. *J. Antibiot.* 1988, 41, 1910–1912. (c) Hirota, A.; Okada, H.; Kanza, T.; Nakayama, M.; Hirota, H.; Isogai, A. *Agric. Biol. Chem.* 1989, 53, 2831–2833.

(9) Dr. Dale Rieger, Department of Chemistry, Harvard University.

(10) Two landmark syntheses may be used to illustrate the point: Kishi, Y. *J. Nat. Prod.* 1979, 42, 549–568 (mitomycins). (b) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopalan, B.; Larsen, S. D.; Siret, P.; Gras, J.-L. *J. Am. Chem. Soc.* 1978, 100, 8034–8036 (gibberellic acid).

(11) (a) Aue, W. P.; Bartholdi, E.; Ernst, R. R. *J. Chem. Phys.* 1976, 64, 2229–2235. (b) Nagayama, K.; et al. *J. Magn. Res.* 1980, 40, 321–328.

Scheme III



0 °C, 1 min) or pyridinium *p*-toluenesulfonate (methanol, 0 °C, 15 min), which resulted in rapid dienol ether formation. The success of the resin-mediated ketalization is perhaps best ascribed to the heterogeneity of the reaction conditions. Reconversion of this mixed ketal to cytovaricin was then achieved in 80% yield with pyridinium *p*-toluenesulfonate in aqueous tetrahydrofuran (-3 °C, 24 h).^{17,18} It thus appears that only aqueous media provide sufficient buffering to prevent dienol ether formation in the presence of a soluble acid catalyst.

We next assayed cytovaricin's stability under basic conditions. Submission of the macrolide to powdered potassium carbonate in methanol (23 °C, 10 min) resulted in rapid decomposition of the natural product, while short exposure to tetrabutylammonium fluoride (THF, 0 °C, 5 min) afforded a similar result. In exploring alternative conditions which might be suitable for the removal of silicon protecting groups, it was found that cytovaricin was moderately stable to pyridinium hydrofluoride buffered with excess pyridine.¹⁹ Under optimized reaction conditions, less than 10% dienol formation was noted after 60 h at 23 °C.²⁰

The preceding studies on the natural product led us to the following conclusions: First, any viable approach to cytovaricin would surely hinge on the development of a successful plan for dealing with the acid lability of the cytovaricin lactol. This in turn implied that the unmasking of the intact lactol–olefin moiety

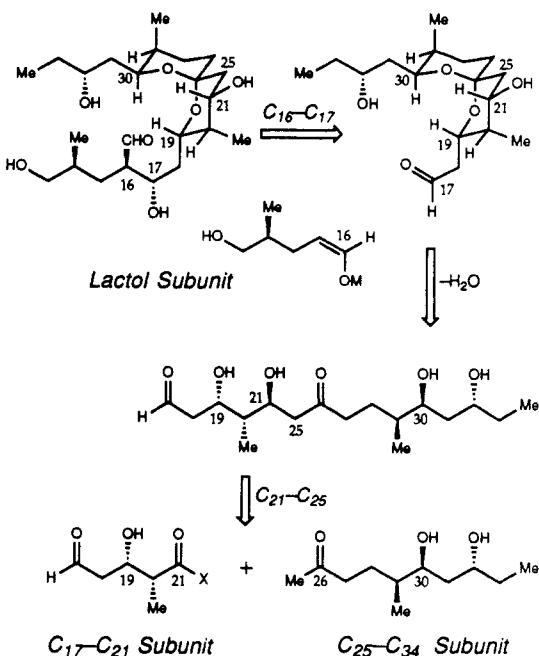
(17) Sterzycki, R. *Synthesis* 1979, 724–725. (b) Miyashita, M.; Yoshi-koshi, A.; Grieco, P. A. *J. Org. Chem.* 1977, 42, 3772–3774.

(18) Dienol formation could not be entirely suppressed under these reaction conditions, accounting for the remainder (18%) of the material.

(19) Trost, B. M.; Caldwell, C. G.; Murayama, E.; Heissler. *J. Org. Chem.* 1983, 48, 3252–3265. Commercially available HF-pyridine (Aldrich Chemical Co.) without added base rapidly destroyed the natural product (THF, 0 °C, 1 min).

(20) For optimal reaction conditions, see the Experimental Section. It should be noted that HF-pyridine obtained from Fluka and Aldrich, despite similar specifications, behaved quite differently, implying that the commercial grade reagents were of different composition.

Scheme IV



should be postponed until late in the synthesis, preferably being deferred until the final step. Second, the reaction conditions to which the natural product is stable afforded little latitude with regard to a final deprotection step. Therefore, only a silicon-based protection scheme with masking groups removable at room temperature with buffered HF-pyridine was considered acceptable.

Retrosynthetic Analysis. Not surprisingly, our first disconnection involved the cytovaricin lactol. We elected to carry this portion of the molecule in reduced oxidation state until late in the synthesis, hoping to effect oxidation to the C₁₇ ketone only in the penultimate step (Scheme III). Deprotection of the primary alcohol at C₂₄ to reveal the lactol would then constitute the final synthetic operation, thus diminishing the duration of exposure of this heterocycle to the acidic medium required for the reaction. In the interest of convergency, the reduced lactol intermediate was then dissected into two subunits of comparable complexity, termed the spiroketal and polyol glycoside subunits (Scheme III). In the synthetic direction, Julia olefination to provide the *trans* C₁₄–C₁₅ olefin was considered a viable coupling option.²¹ Two macrocyclization strategies could then be pursued: carbon–carbon ring closure at C₂–C₃ by an intramolecular Horner–Emmons–Wittig reaction, or carbon–oxygen closure by macrolactonization of the seco acid precursor. In the following sections, the design and construction of synthetic equivalents to the polyol glycoside and spiroketal subunits depicted in Scheme III will be described.

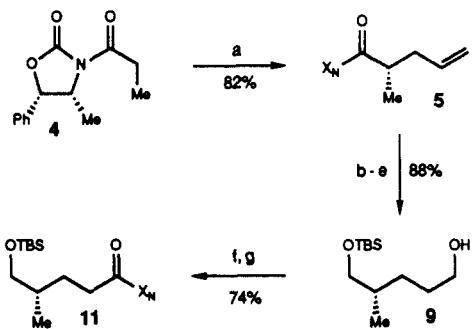
Synthesis of the Spiroketal Subunit

Retrosynthetic Analysis. Our analysis of the spiroketal synthon hinged on the identification of four potential aldol relationships, three of which (C₁₆–C₁₇, C₁₉–C₂₀, and C₂₉–C₃₀) required syn bond constructions, thought to be accessible with chiral imide enolate methodology (Scheme IV).²² Initial aldol disconnection of the reduced lactol at C₁₆–C₁₇ would provide the parent spiroketal ring system. Further simplification of this structure through a methyl ketone aldol or acylation transform at C₂₁–C₂₅ (cytovaricin numbering) would complete a convergent disconnection of this portion of the structure into three segments envisioned to be amenable to asymmetric synthesis. Key issues to be addressed involved the development of an efficient coupling/spiroketalization strategy, along with the definition of an effective method for obtaining the equatorial alcohol stereocenter at C₂₁.

(21) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* 1973, 4833–4836. For a recent review see: Kocienski, P. *Phosphorus Sulfur* 1985, 24, 97–127.

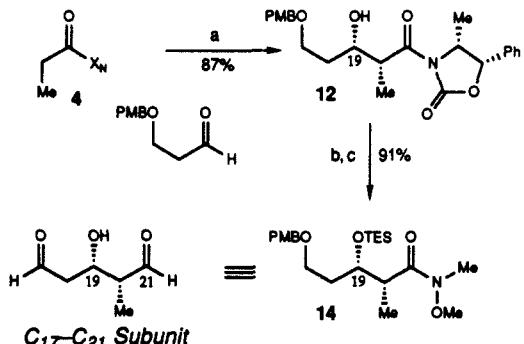
(22) Evans, D. A.; Bartroli, J. A.; Shih, T. L. *J. Am. Chem. Soc.* 1981, 103, 2127–2129.

Scheme V



(a) NaHMDS, THF, allyl iodide, -78 °C; (b) LiOH, THF, H₂O, 0 °C; (c) LiAlH₄, THF-Et₂O, 0 to 25 °C; (d) TBSCl, Et₃N, DMAP, CH₂Cl₂, 25 °C; (e) 9-BBN, THF, 0 °C; H₂O₂; (f) cat. RuCl₃-3H₂O, K₂S₂O₈, H₂O, t-BuOH, 25 °C; (g) Et₃N, (CH₂)₃COCl, Et₂O, -78 to 0 °C; XyLi, THF, -78 to 0 °C

Scheme VI



(a) 4-n-Bu₂BOTf, Et₃N, CH₂Cl₂, 0 °C; RCHO, -78 °C; H₂O₂, 0 °C; (b) AlMe₃, MeONHMe-HCl, THF, 0 °C; (c) TESCl, imidazole, DMF.

In examining potential routes to the three spiroketal subunits (Scheme IV), we concluded that the bulk of the required stereochemical relationships in this portion of the macrolide could be efficiently obtained by the use of chiral carboximide enolates. In fact, with the exception of the glycoside, all of the chirality in cytovaricin is ultimately obtained from the (1*S*,2*R*)-norephedrine-derived oxazolidone auxiliary (X_N) (vide infra).

Asymmetric Synthesis of the Masked Lactol Subunit 11. Alkylation of the sodium enolate of carboximide 4 with allyl iodide, according to the established procedure, provided the crystalline alkylation product 5 (82%) in >99% diastereomeric purity after recrystallization (Scheme V).²³ Removal of the auxiliary with lithium hydroperoxide provided the corresponding acid,²⁴ which was in turn reduced to the corresponding alcohol with LiAlH₄. Subsequent protection of this alcohol as its *tert*-butyldimethylsilyl ether followed by hydroboration of the terminal olefin with 9-borabicyclo[3.3.1]nonane (9-BBN) provided 9 in 88% yield for the four-step process.²⁵ Oxidation of the primary alcohol 9 to the corresponding acid proved more difficult than anticipated because of the propensity of the product to cyclize to the corresponding δ -lactone under both acidic and basic conditions. However, the lactonization-prone acid could be obtained in 79% yield with potassium ruthenate in dilute potassium hydroxide.²⁶ Immediate activation of the acid through the intermediacy of its mixed pivaloyl anhydride and subsequent treatment with the lithiated norephedrine oxazolidone afforded the desired masked lactol fragment 11 in good yield (94%).

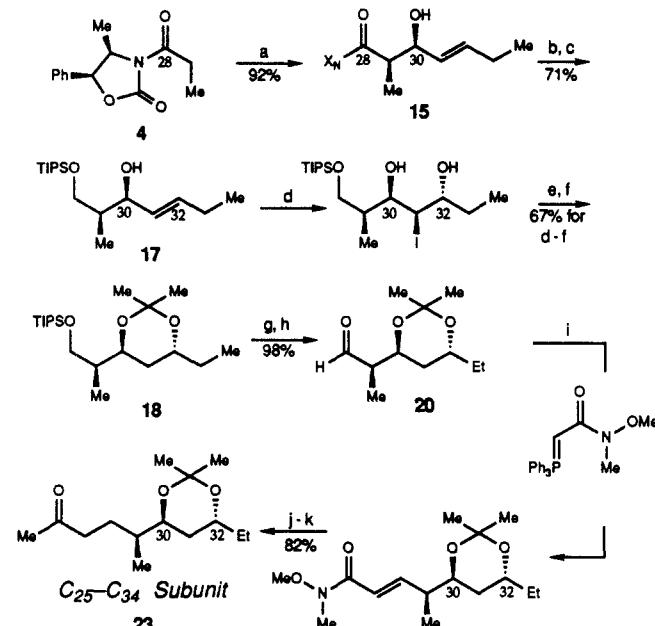
(23) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* 1982, 104, 1737–1739. (b) Mathre, D. J. Ph.D. Dissertation, California Institute of Technology, 1985.

(24) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* 1987, 28, 6141–6144.

(25) TBS ether 8 has also been prepared via direct LiAlH₄ reduction of 5 in lower overall yield (ref 15).

(26) (a) Schroder, M.; Griffith, W. P. *J. Chem. Soc., Chem. Commun.* 1979, 58–59. (b) Corey, E. J.; Meyers, A. G. *J. Am. Chem. Soc.* 1985, 107, 5574–5576.

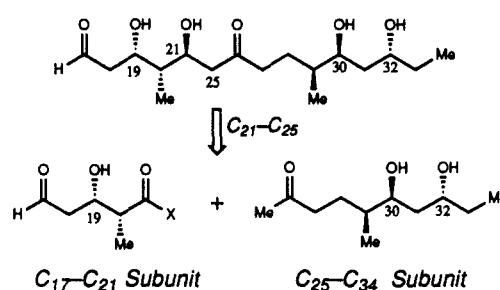
Scheme VII



(a) 4, n-Bu₂BOTf, Et₃N, CH₂Cl₂, 0 °C; 2-pentenal, -78 °C; H₂O₂, THF, 25 °C; LiBH₄, 0 °C; H₂O₂; (b) 15, HOAc, Bu₃B, I₂, THF, 4 °C; (c) TiPSCl, DMAP, CH₂Cl₂, 25 °C; (d) 0.25 M KH₂PO₄, I₂, THF, 4 °C; (e) n-Bu₃SnH, toluene, 25 °C; (f) TsOH, (CH₃)₂C(OCH₃)₂, 25 °C; (g) n-Bu₄NF-3H₂O, THF, 0 °C; (h) (CCl₃)₂, DMSO, CH₂Cl₂, -78 °C; Et₃N, -78 to -30 °C; (i) (Ph₃P)₃PCHCON(OCH₃)CH₃, CH₂Cl₂, 25 °C; (j) H₂, 5% Pd/C, EtOAc; (k) MeLi, Et₂O.

Synthesis of the C₁₇–C₂₁ Spiroketal Subunit. The C₁₇–C₂₁ portion of the spiroketal was synthesized by applying our asymmetric aldol methodology to establish the necessary stereochemical relationships at C₁₉ and C₂₀ (Scheme VI). Addition of the boron enolate derived from 4 to 3-[*p*-methoxybenzyl]oxy]propanal²⁷ provided crystalline imide 12 in 87% yield as a single diastereoisomer. Transamination to the N-methoxy-N-methylamide²⁸ followed by triethylsilyl protection of the alcohol functionality cleanly provided 14 (91%), a versatile laboratory equivalent of the dialdehyde synthon revealed in the retrosynthetic analysis.

Synthesis of the C₂₅–C₃₄ Spiroketal Subunit. Whereas the construction of the C₁₇–C₂₁ fragment proceeded uneventfully, its partner, the C₂₅–C₃₄ synthon, provided a somewhat greater challenge.

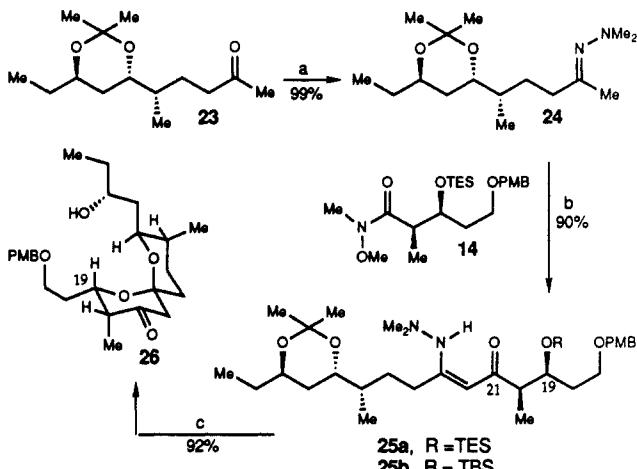


Two of the three stereochemical relationships required for this segment were secured through reaction of the boron enolate derived from imide 4 with *trans*-2-pentenal in 92% yield (Scheme VII). Although the resulting aldol adduct 15 seemed poised for introduction of the final stereogenic center required for the fragment, attempts at oxymercuration or iodohydration of olefin 15 met with only modest success, primarily due to competing lactonization of the corresponding iodonium and mercuronium intermediates.²⁹ After considerable experimentation, it was

(27) Synthesized by mono-*p*-methoxybenzylolation of propanediol followed by Swern oxidation: Mancuso, A. J.; Swern, D. *Synthesis* 1981, 165–185.

(28) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* 1977, 4171–4174. (b) Avrin, J. L.; Turos, E.; Weinreb, S. M. *Synth. Commun.* 1982, 12, 989–993. (c) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* 1988, 110, 2506–2526.

Scheme VIII



(a) TMSCl, NH₂NMe₂, CH₂Cl₂, 0 to 25 °C; (b) 24, LDA, Et₂O-THF, 0 °C; 14, -45 °C; (c) 9/1 [95/5 CH₃CN : 47% aq. HF]:H₂O, 25 °C.

discovered that the triisopropylsilyl ether 17 derived from reduction and monosilylation of the aldol adduct 15 (71%) possessed sufficient steric bulk to suppress oxygen participation during the subsequent iodohydration reaction.³⁰ A three-step procedure was developed for providing anti acetonide 18 in which rapid processing of intermediates was necessary to insure a 67% overall yield of the desired product. It is noteworthy that the diastereoselectivity associated with this addition reaction was exceptional (96:4) and superior in both selectivity and yield to a related transformation which was initially explored with mercuric trifluoroacetate.³¹ Subsequent homologation of 18 through a five-step sequence³² provided access to the methyl ketone 23, the appropriately protected C₂₅-C₃₄ synthon.

Coupling and Spiroketal Formation. With syntheses of the C₁₇-C₂₁ and C₂₅-C₃₄ spiroketal fragments 14 and 23 in hand, their coupling was undertaken. Among a number of bond construction options examined, unquestionably the most successful method for achieving the union of these fragments involved acylation of the metallated hydrazone derived from 23 with the N-methoxy-N-methylamide 14. As illustrated in Scheme VIII, formation of the 1,1-dimethylhydrazone of ketone 23 was effected in essentially quantitative yield (99%) by the use of trimethylsilyl chloride as a dehydrating agent. The deprotonation of 24 and its subsequent acylation with amide 14 was accomplished in the following manner. Treatment of a tetrahydrofuran solution of hydrazone 24 with lithium diisopropylamide (LDA) prepared from halide-free methylolithium in ether resulted in quantitative conversion to the corresponding metalloenamine, as determined by control experiments involving a methyl iodide quench. The solvent and concentration effects observed in this deprotonation step were pronounced. The use of LDA prepared from n-butyllithium in hexane (1.6 M) or attempted metalloenamine formation at concentrations of less than 0.35 M resulted in incomplete metalation.³³ Subsequent addition of a concentrated solution of the N-meth-

(29) Halolactonization of analogous carboximide substrates has recently been documented: Bradbury, R. H.; Revill, J. M.; Rivett, J. E.; Waterson, D. *Tetrahedron Lett.* 1989, 30, 3845-3848.

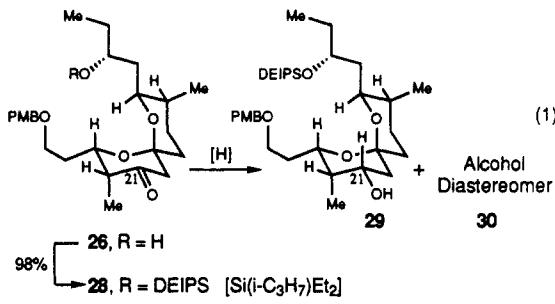
(30) Chamberlain, A. R.; Mulholland, R. L., Jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* 1987, 109, 672-677 and references cited therein.

(31) Giese, B.; Bartmann, D. *Tetrahedron Lett.* 1985, 26, 1197-1200.

(32) On large-scale (>7 mmol) direct homologation of aldehyde 20 to the α,β -unsaturated enone using acetyl methylphosphonate in the presence of LiCl and DBU resulted in complete epimerization of the allylic methyl stereocenter: Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* 1984, 25, 2183-2186.

(33) The use of HMPA facilitated deprotection, but adversely affected the subsequent acylation step. Although a "salt effect" (LiBr or LiCl) is conceivable because of the relative solubilities of lithium halides in hexane versus ether, it must be pointed out that "halide-free" methyl- and butyllithium were employed in all experiments. Denmark has observed a similar solvent effect in the 1,2-addition of nucleophiles to SAMP and RAMP hydrazones (personal communication). See also: Denmark, S. E.; Weber, T.; Piotrowski, D. W. *J. Am. Chem. Soc.* 1987, 109, 2224-2225.

Table I. Stereoselective Reduction of Ketone 28

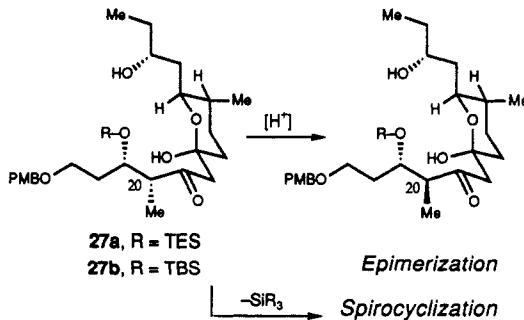


^a Ratios based on isolated yields. ^b Values refer to isolated yields of product with a diastereomeric purity >200:1. ^c Cleavage of the PMB ether was observed.

oxy-N-methylcarboxamide 14 to the bright yellow metallo enamine solution (final concentration >0.40 M) followed by stirring at -45 °C for 19 h afforded the desired vinylous amide 25a in 90% yield.³⁴ We surmise that the specific requirements for methyl-lithium/ether in the preparation of the LDA for the hydrazone deprotonation may be ultimately associated with a salt effect rather than a solvent effect.

Deprotection and spiroketal formation from the coupled product 25a was achieved in one synthetic operation. Treatment of the vinylous amide 25a with hydrofluoric acid in acetonitrile buffered with sufficient water to attenuate the acidity of the medium provided spiroketal alcohol 26 as the only discernible reaction product (92%).³⁵ The overall yield for this coupling/spirocyclization sequence was reproducibly greater than 80%.

The selection of a triethylsilyl protecting group for the C₁₉ alcohol in this spirocyclization reaction was not arbitrary. In earlier experiments, attempted spiroketal formation from the corresponding TBS derivative 25b resulted in significant (ca. 8%) epimerization of the C₂₀ methyl-bearing stereocenter adjacent to the ketone. A subsequent control experiment indicated that the product spiroketal 26 was stable to the reaction conditions, implying that epimerization must be occurring on an intermediate formed prior to 26. We were able to isolate the intermediate lactol TBS ether 27b produced in the spiroketalization of 25b when the reaction was quenched prior to completion. Resubmission of this lactol to the reaction conditions confirmed that epimerization was occurring from 27. Thus, by turning to the more labile triethylsilyl protecting group, epimerization was minimized by diminishing the lifetime of this vulnerable lactol intermediate.

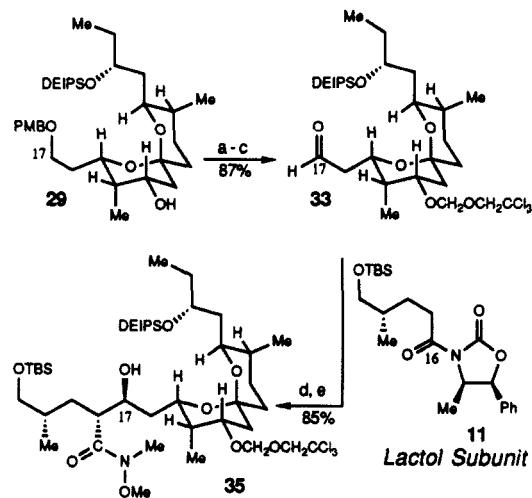


Spiroketal Ketone Reduction. The reduction of the spiroketal C₂₁ ketone to the requisite equatorial alcohol was not seen a priori

(34) A recent paper has appeared independent of our work documenting the acylation of ester enolates with N-methoxy-N-methyl amides. The authors also report one example involving the acylation of the lithium enolate of acetone dimethylhydrazone with N-methoxy-N-methylbenzamide: Turner, J. A.; Jacks, W. S. *J. Org. Chem.* 1989, 54, 4229-4231.

(35) Without sufficient water, cleavage of the p-methoxybenzyl ether, along with other modes of decomposition, was observed.

Scheme IX



(a) $\text{BrCH}_2\text{OCH}_2\text{CCl}_3$, proton sponge, CH_3CN , 0 to 25 °C; (b) DDQ, H_2O , CH_2Cl_2 , 5–25 °C; (c) $(\text{COCl})_2$, DMSO, CH_2Cl_2 , -78 °C; Et_3N , -78 to -30 °C; (d) 11, $n\text{-Bu}_2\text{BOTf}$, Et_3N , CH_2Cl_2 , -78 to 0 °C; 33, -78 to 0 °C; H_2O_2 ; (e) AlMe_3 , MeCONHMe-HCl , THF , 0 °C

as a particular problem, given the diversity of reducing agents currently available. It was thus with some surprise that we noted that reductions of this type remain largely an unsolved problem in the syntheses of the milbemycins and avermectins.³⁶

In order to avoid potential diol differentiation problems, keto alcohol 26 was protected as its diethylisopropylsilyl (DEIPS) ether 28 prior to ketone reduction.³⁷ In contrast to the corresponding triethylsilyl and *tert*-butyldimethylsilyl ethers, control experiments indicated that this silyl ether possessed sufficient stability to remain affixed to the relatively unhindered C₃₂ alcohol under a variety of reaction conditions, while still offering reasonable lability in the presence of buffered pyridinium hydrofluoride. With a suitably masked ketone in hand, we then turned to a systematic survey of reducing agents.

In light of the poor selectivities observed in the kinetic reductions of milbemycin–avermectin ketospiroketals, we elected to examine reducing agents that were likely to afford some measure of thermodynamic control. After a number of disappointing results, we evaluated a mild variant of the Meerwein–Ponndorf–Verley reduction developed by Kagan involving the use of samarium diiodide as catalyst (Table I).³⁸ Treatment of a solution of the spiroketal ketone 28 and 10 equiv of 2-propanol in tetrahydrofuran with 0.10 equiv of freshly prepared samarium diiodide (25 °C) resulted in a rapid, stereoselective reduction, providing a 65:1 ratio of alcohols, from which the required equatorial product 29 could be isolated in 98% yield. By comparison, all other reduction methods surveyed were markedly inferior. For example, reduction with LiAlH_4 afforded exclusively the unwanted axial alcohol 30, while dissolving metal conditions afforded nearly a 1:1 mixture of alcohols. The back-up reagent proved to be the radical reducing agent diphenyltin dihydride,³⁹ which afforded a 4.9:1 ratio of products favoring the desired equatorial alcohol 29.⁴⁰ The impressive selectivity of the samarium diiodide/2-propanol reducing agent is not generally appreciated, and the present example

(36) For leading references, see: (a) Crimmins, M. T., Bankaitis-Davis, D. M.; Hollis, W. G., Jr. *J. Org. Chem.* 1988, 53, 652–657. (b) Crimmins, M. T.; Hollis, W. G.; Bankaitis-Davis, D. M. *Tetrahedron Lett.* 1987, 28, 3651–3654. (c) Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. C. *J. Am. Chem. Soc.* 1982, 104, 4708–4710. (d) Alibzati, K. F.; Perron, F. *Chem. Rev.* 1989, 89, 1617–1661.

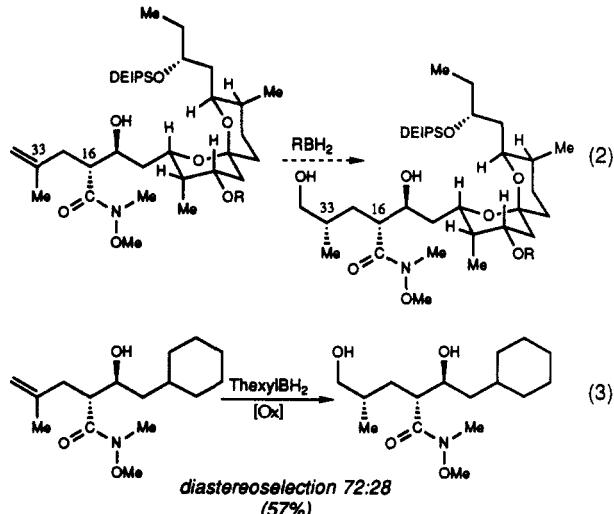
(37) Toshima, K.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* 1988, 61, 2369–2381.

(38) Collin, J.; Namy, J.-L.; Kagan, H. B. *Nouv. J. Chim.* 1986, 10, 229–232.

(39) Kuivila, H. G. *Synthesis* 1970, 499–509. (b) Kuivila, H. G.; Beumel, O. F., Jr. *J. Am. Chem. Soc.* 1958, 80, 3798.

(40) A number of other reducing agents were examined with poor results. Notably, samarium diiodide in $\text{H}_2\text{O}/\text{THF}$ provided only 3.9:1 selectivity in favor of 29: Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* 1987, 109, 6187–6189.

Scheme X



provides a good advertisement for its potential utility in other applications. We have begun to investigate the origin of this unexpected stereoselectivity and have established that reaction stereoselectivity appears to be a consequence of kinetic rather than thermodynamic control with the possible involvement of the transannular axial spiroketal ether oxygen in reagent delivery.⁹

Completion of the Spiroketal Subunit. The remaining operations necessary for the synthesis of the spiroketal moiety involved refunctionalization of alcohol 29 to the C₁₇ aldehyde followed by introduction of the masked lactol synthon by means of an aldol bond construction. Equatorial alcohol 29 was first protected as its (2,2,2-trichloroethoxy)methoxy ether (97%) by treatment with bromomethyl 2,2,2-trichloroethyl ether⁴¹ in acetonitrile in the presence of proton sponge (Scheme IX).⁴² This rather unusual protecting group was selected with the anticipated C₁₄–C₁₅ olefination sequence in mind. It was hoped that sodium amalgam would also effect reductive cleavage of this protecting group during the reductive elimination step in the Julia–Lythgoe coupling (vide infra).

The C₁₇ spiroketal aldehyde was obtained by oxidative deprotection (DDQ)⁴³ followed by Swern oxidation to provide aldehyde 33 in 87% overall yield. Treatment of 33 with the boron enolate derived from imide 11 effected aldol coupling of the two components and provided the desired aldol adduct as a single diastereomer (87%). Transamination was then achieved with excess aluminum amide reagent (7 equiv) to give the amide 35 in 98% yield.

During the early stages of the synthesis of this portion of cytovaricin, we also explored an alternate strategy for the incorporation of the C₃₃ (cytovaricin numbering) methyl-bearing stereocenter (Scheme X). On the basis of observations that we had made several years ago,⁴⁴ we projected that the illustrated hydroboration would proceed with the desired sense of asymmetric induction (eq 2). Indeed, a model study (eq 3) supported this prediction and the desired diastereomer was obtained in an isolated yield of 57% with modest diastereoselectivity (72:28). Nonetheless, this approach to the integration of the lactol synthon into the spiroketal subunit was ultimately rejected in favor of the high-

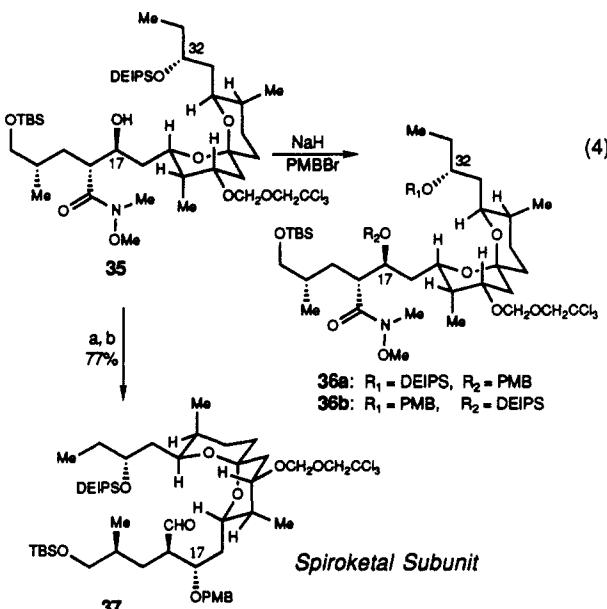
(41) Observed bp for bromomethyl 2,2,2-trichloroethyl ether: 32–35 °C (0.015 mm). Prepared in analogy with benzyl bromomethyl ether (BOM bromide): Connor, D. S.; Klein, G. W.; Taylor, G. N.; Boeckman, R. K., Jr.; Medwid, J. B. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. 6 pp 101–103. See also: Hindsgaul, O.; Norberg, T.; Le Pendu, J.; Lemieux, R. U. *Carbohydr. Res.* 1982, 109, 109–142.

(42) (a) Jacobson, R. M.; Clader, J. W. *Syn. Commun.* 1979, 9, 57–62. (b) Use of other bases resulted in a markedly more sluggish reaction. For an analogous case involving a BOM protection see: Evans, D. A.; Bender, S. L. *Tetrahedron Lett.* 1986, 27, 799–802.

(43) For a review see: Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* 1986, 42, 3021–3028.

(44) Evans, D. A.; Bartroli, J.; Godel, T. *Tetrahedron Lett.* 1982, 23, 4577–4580.

Scheme XI



er-yielding solution illustrated above (Scheme IX) on the basis of the overall efficiency of the two sets of bond constructions.

With amide **35** in hand, only two synthetic operations remained to arrive at an intermediate suitable for coupling with the polyol glycoside: alcohol protection at C_{17} and reductive conversion of the amide to an aldehyde. The choice of a suitable protecting group was of considerable importance since deprotection of the C_{17} alcohol, one of nine masked hydroxyl groups, was required at a late stage in the synthesis as a prelude to ketone formation. A *p*-methoxybenzyl group was considered the best candidate on the basis of our previous success with the deprotection of PMB ether **31**. Under basic conditions (NaH , PMBBr , DMF/THF , 0°C , 24 h) *p*-methoxybenylation of **35** could indeed be achieved. However, two alkylation products were observed in an approximate ratio of 2:1. After cleavage of the isomeric benzylic ethers, it was found that the desired C_{17} ether **36a** was the minor reaction product, whereas the major benzylation product proved to be the isomeric compound **36b**, resulting from intramolecular exchange of the C_{32} diethylsopropylsilyl and C_{17} PMB ethers (eq 4, Scheme XI). While the reasons for this transformation are not known with certainty, examination of molecular models suggests that the substrate **35** is well disposed for intramolecular silyl transfer. Subsequent alkylation of the less hindered C_{32} alkoxide thus formed would then offer a reasonable explanation for this unanticipated result.⁴⁵ It is noteworthy that the orientation of the C_{31} - C_{34} side chain required for such a silyl transfer is quite similar to the preferred conformation of cytovaricin adopted by this side chain in both the crystalline state and in solution (Figures 1 and 2).

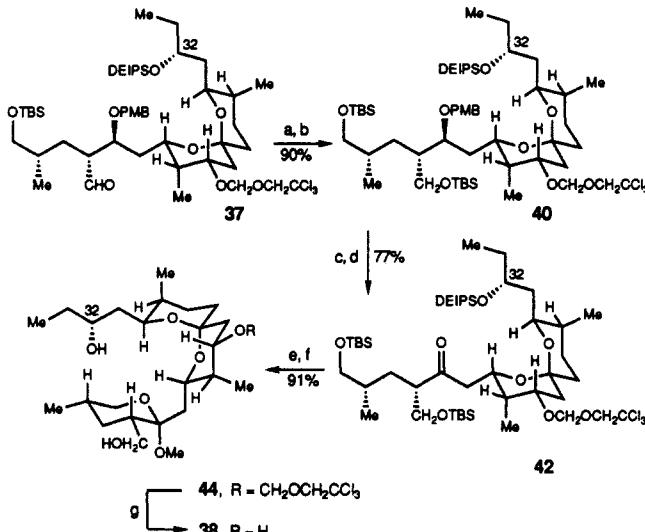
Although alcohol **35** could not be converted cleanly to the desired *p*-methoxybenzyl ether **36** under basic conditions, this transformation was eventually achieved under mildly acidic reaction conditions.⁴⁶ Treatment of **35** with *p*-methoxybenzyl trichloroacetimidate in the presence of a catalytic amount of triflic acid provided ether **36b** in 77% yield after one recycle of recovered starting material (Scheme XI).⁴⁷ Reduction of this amide was

(45) This migration was not observed when the C_{32} alcohol was protected as its triisopropylsilyl ether.

(46) A number of bases (KH, NaH , proton sponge, potassium dimyristate, Hunig's base) and alkylating agents [PMBBr , PMBCl , "PMBOT" (polymerization on attempted formation), PMBBr with (*n*-Bu)₄NI] were examined.

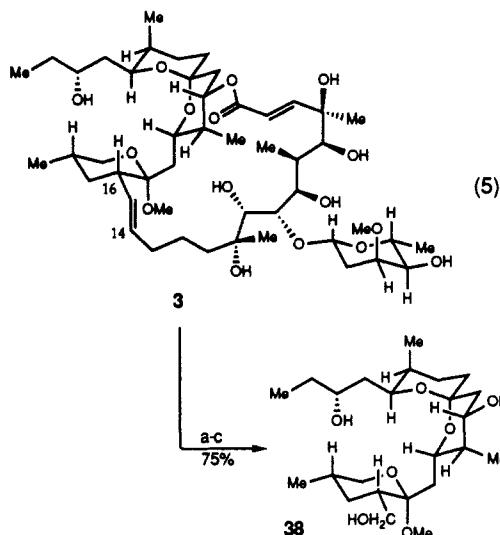
(47) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* 1988, 29, 4139-4142. To drive the reaction further toward completion, it was found advantageous to employ a CCl_4 /cyclohexane solvent system to retard rearrangement of the imidate to the corresponding amide. See: Wessel, H. P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc. Perkin Trans. I* 1985, 2247-2250.

Scheme XII



achieved without incident by treatment of **36b** with diisobutyl-aluminum hydride to afford the spiroketal aldehyde **37** in 92% yield. The 10-step sequence from the two spiroketal subunits **14** and **24** can be performed on multigram scale in 43% yield (92% average per step).

Correlation of Spiroketal Aldehyde 37 to a Cytovaricin Degradation Product. As delineated in eq 5, a "one-pot" procedure was devised for obtaining triol lactol methyl ether **38**, a degradation product of cytovaricin suitable for comparison to synthetic material. Treatment of the lactol methyl ether of cytovaricin (**3**) with 2 equiv of ozone⁴⁸ in methanolic dichloromethane followed by reductive cleavage of the resulting bis-ozonide with sodium borohydride and subsequent ester cleavage with potassium carbonate, provided **38** in 75% yield for the three-step process.⁴⁹ This



same intermediate was then constructed from the advanced spiroketal intermediate **37** (Scheme XII). Reduction of **37** was achieved with sodium borohydride (95%), and the resulting primary alcohol was protected as its *tert*-butyldimethyl silyl (TBS) ether **40** (95%). Removal of the PMB ether with DDQ (78%)

(48) Quantitative measurement of ozone: Rubin, M. B. *J. Chem. Ed.* 1964, 388.

(49) The mixed methyl ketal **38** exhibited acid sensitivity comparable to the natural product and was best handled in the presence of added triethylamine.

was followed by oxidation with the Dess–Martin periodinane reagent⁵⁰ (98%) to provide ketone **42**. Subsequent treatment of **42** with buffered pyridinium hydrofluoride effected unmasking of the three silyl ethers to give lactol **43** as a 1:1 tautomeric mixture of open and closed forms (benzene-*d*₆). This mixture was next submitted without hesitation to Dowex-50 ion exchange resin in methanol at 0 °C, affording the lactol methyl ether **44** in 91% overall yield from ketone **42**. Finally, deprotection to provide the triol lactol methyl ether, suitable for comparison to the degradation fragment, was achieved with samarium diiodide in THF at 25 °C (71%).⁵¹ Synthetic lactol methyl ether **38** proved identical in all respects (¹H, ¹³C, and COSY-90 NMR; IR; TLC; GC; combustion analysis; MS) with its natural counterpart, allowing us to proceed with the synthesis with confidence.

It is of some interest that the ease of lactol methyl ether formation strongly depended upon the nature of the C₃₂ oxygen substituent. Although the transformation of **42** to **44** proceeded without difficulty, the *prior loss of the C₃₂ silicon protecting group was shown to be a precondition for lactol methyl ether formation*. It was for this reason that the lactol ring construction was postponed until the latter stages of the synthesis.

Construction of the Polyol Glycoside Subunit

One of our primary concerns in evaluating potential routes to cytovaricin was the design of a suitable macrocyclization substrate. In particular, we hoped to facilitate ring closure by constraining the ring torsion angles of the macrocycle to those found in the X-ray structure of cytovaricin. Such conformational ordering might be accomplished by the selective use of bridging-oxygen protecting groups in the C₃–C₁₀ polypropionate region of the macrolide. This diol protection scheme presents seven bridging opportunities for the connection of the six annular oxygens in either 1,2- or 1,3-relationships. This number is reduced to four opportunities if cymarose is incorporated into the structure at C₈ prior to cyclization. During the evaluation of the various bridging options, care was taken to avoid the introduction of serious transannular interactions that might otherwise defeat attempts at macrocyclization. Accordingly, the decision was made to bridge only those pairs of hydroxyl groups that both pointed away from the ring interior and were as close to syn planarity as possible (Figure 2). In light of these requirements, the C₅–C₇ and C₈–C₁₀ 1,3-diol relationships appeared to be attractive candidates for bridging based on the X-ray structure, whereas the remainder of the 1,2- and 1,3-diol dihedral relationships were too far out of alignment to consider constraining them in a similar fashion. When the decision was made to incorporate cymarose into the cyclization precursor, the attractive C₈–C₁₀ 1,3-diol bridging opportunity was sacrificed. When this strategy was combined with the decision to employ silicon-based protecting groups, the selection of a di-*tert*-butylsilylene protecting group bridging the C₅–C₇ 1,3-diol relationship followed.^{52,53} We then opted for triethylsilyl ethers for the three remaining annular hydroxyl functions.

With two noteworthy exceptions, the majority of the bond constructions and stereochemical issues contained within potential routes to the polyol glycoside subunit seemed tractable. An efficient means for effecting stereoselective glycosidation to yield the nonanomerically stabilized equatorial glycosidic linkage remained to be defined. In addition, there was the strategic problem of defining an efficient protocol for the stereoselective construction of the C₄ and C₁₀ carbinol stereocenters, while incorporating those oxygen protecting groups required for further elaboration of the subunit.

(50) Dess, D. B.; Martin, J. C. *J. Org. Chem.* 1983, 48, 4155–4156.

(51) For the use of SmI₂ in the cleavage of a 2-chloroethyl carbamate, see: Ananthanarayanan, T. P.; Gallagher, T.; Magnus, P. *J. Chem. Commun.* 1982, 709–710.

(52) (a) Trost, B. M.; Caldwell, C. G. *Tetrahedron Lett.* 1981, 22, 4999–5002. (b) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* 1982, 47, 4871–4874. (c) Trost, B. M.; Caldwell, C. G.; Murayama, E.; Heissler, D. *J. Org. Chem.* 1983, 48, 3252–3265.

(53) For a recent use of this diol protecting group in the total synthesis of podophyllotoxin, see: Van der Eycken, J.; De Clercq, P.; Vandewalle, M. *Tetrahedron* 1986, 42, 4297–4308.

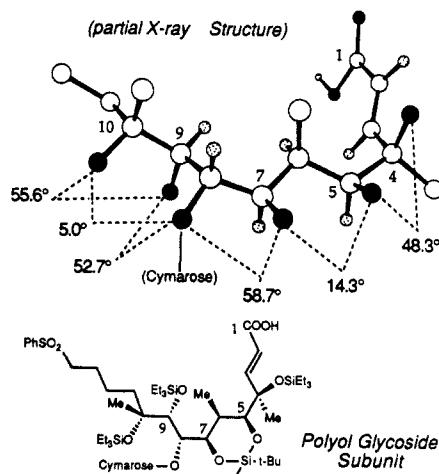
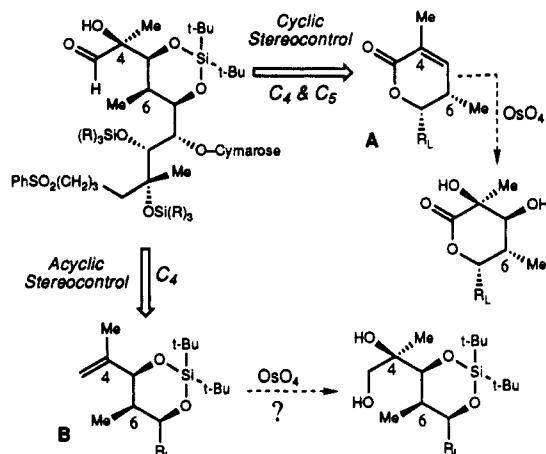


Figure 2. O–O torsion angle relationships in the C₁–C₁₄ synthon.

Scheme XIII



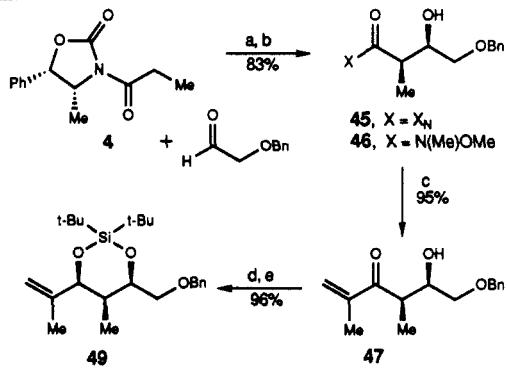
A Highly Stereoselective Osmylation Reaction. Two approaches to the construction of the C₄ stereocenter were considered. As outlined in Scheme XIII, osmylation of the α,β -unsaturated lactone of general structure **A** was expected to proceed with good facial selectivity to afford the desired C₄ and C₅ carbinol stereocenters. Alternatively, the olefin oxidation involving the illustrated acyclic allylic ether was envisioned as a more speculative approach to the incorporation of the C₃ and C₄ oxygens. In the former route, the stereochemical outcome of the osmylation of **A** was unambiguous, but the subsequent refunctionalizations appeared cumbersome. On the other hand, in the oxidation of **B**, the disposition of the oxygen protecting groups is ideally suited for further elaboration. The major uncertainty in this route lay with the lack of precedent for the stereochemical outcome of the osmylation. By way of background, analogies for the stereoselective osmylation of both 1,2-disubstituted⁵⁴ and *E* trisubstituted⁵⁵ allylic alcohol derivatives may be found in the literature. The observed diastereoselectivities in these reactions exhibit considerable substrate variability; nonetheless, this body of data formed the basis of our study on the osmylation of allylic alcohol derivatives such as **B** in Scheme XIII.

Olefin **49**, which might eventually serve as the C₃–C₈ synthon in a projected synthesis of this portion of cytovaricin, was selected as a model substrate for the osmylation study. The stereoselective synthesis of this compound is illustrated in Scheme XIV. Addition

(54) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* 1983, 24, 3943–3946 and 3947–3950; *Tetrahedron*, 1984, 40, 2247–2255. (b) Brimacombe, J. S.; Hanna, R.; Kabir, M. S.; Bennett, F.; Taylor, I. D. *J. Chem. Soc., Perkin Trans. 1* 1986, 815–828.

(55) (a) Stork, G.; Kahn, M. *Tetrahedron Lett.* 1983, 24, 3951–3954. (b) Bernardi, A.; Cardani, S.; Scolastico, C.; Villa, R. *Tetrahedron* 1988, 44, 491–502. (c) Hatakeyama, S.; Sakurai, K.; Numata, H.; Ochiai, N.; Takano, S. *J. Am. Chem. Soc.* 1988, 110, 5201–5203.

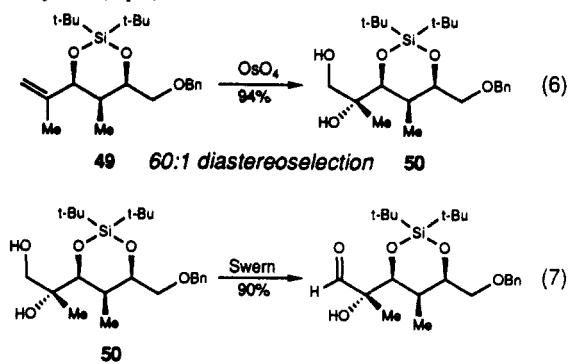
Scheme XIV



(a) 4, Bu_2BOTf , Et_3N , 0 °C; $BnOCH_2CHO$, CH_2Cl_2 , -78 °C; H_2O_2 ; (b) Me_3Al , $MeONHMe-HCl$, THF, 0 °C; (c) 2-lithiopropene, Et_2O -THF, -78 °C; (d) Et_2BOMe , THF - $MeOH$, -70 °C; $NaBH_4$; (e) $(t-Bu)_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2 , 65 °C

of the di-*n*-butylboryl enolate derived from imide 4 to α -(benzyloxy)acetaldehyde⁵⁶ provided aldol adduct 45 in greater than 99% diastereomeric purity as determined by GC analysis. Purification by recrystallization then afforded an 87% yield of stereochemically homogeneous 45. Transamination of this imide to the "Weinreb amide"²⁸ was followed by the construction of ketone 47. Addition of 2.5 equiv of 2-lithiopropene to the *N*-methoxy-*N*-methylamide 46 proceeded smoothly to afford a 92% overall yield of enone 47. Selective reduction of 47 to afford the syn 1,3-diol was achieved through application of the Sandoz procedure ($NaBH_4$, $MeOBu_2$).⁵⁷ As advertised, formation of the presumed boron chelate with methoxydiethylborane followed by external hydride delivery cleanly afforded the desired syn diol with greater than >100:1 facial selectivity. Finally, silylene formation at elevated temperature⁵² served to provide the C_3-C_{14} synthon 49 in 96% yield for the two steps.

It was with some gratification that osmylation of olefin 49 proceeded with the desired stereochemical outcome with >60:1 diastereoselectivity to afford diol 50 in excellent yield (eq 6).⁵⁸ Through subsequent work, we have demonstrated that the osmylation of 1,1-disubstituted allylic alcohol derivatives is a stereoregular process of some scope.⁵⁹ Finally, it was found that the required oxidation of this diol to the C_3 aldehyde could be achieved without selective protection of the tertiary alcohol. Thus, Swern oxidation of 50 cleanly provided the anticipated aldehyde in 90% yield (eq 7).



The three transformations that we viewed to be pivotal to the assemblage of the polyol glycoside subunit are shown in Scheme XV. It was anticipated that the illustrated C_8-C_9 aldol bond construction between aldehyde 52 and the chiral glycolate enolate should proceed in the illustrated manner on the basis of prior

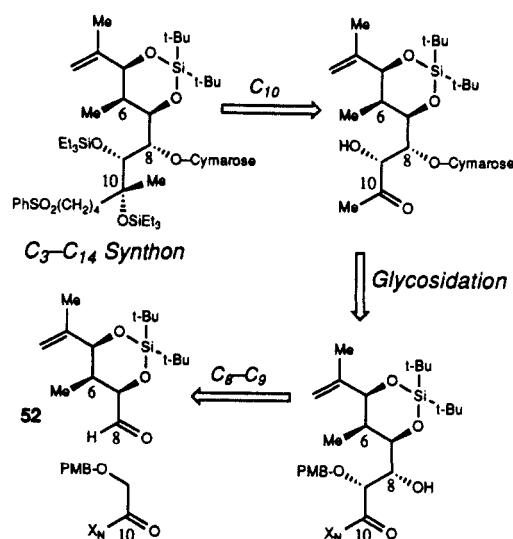
(56) Prepared by ozonolysis of the bis-benzyl ether of 1,4-butene diol employing an indicator dye (ref 72) in 80% yield. For an alternative procedure, see: Garner, P.; Park, J. M. *Syn. Commun.* 1987, 17, 189-194.

(57) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. *J. Tetrahedron Lett.* 1987, 28, 155-158.

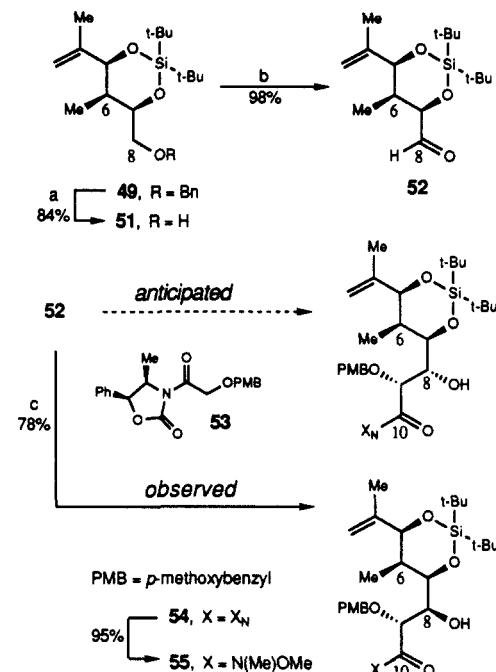
(58) Proof of stereochemistry was achieved by correlation with authentic tetrol obtained from the cyclic osmylation variant illustrated in Scheme XIII. (See ref 59).

(59) Evans, D. A.; Kaldor, S. W. *J. Org. Chem.* 1990, 55, 1698-1700.

Scheme XV



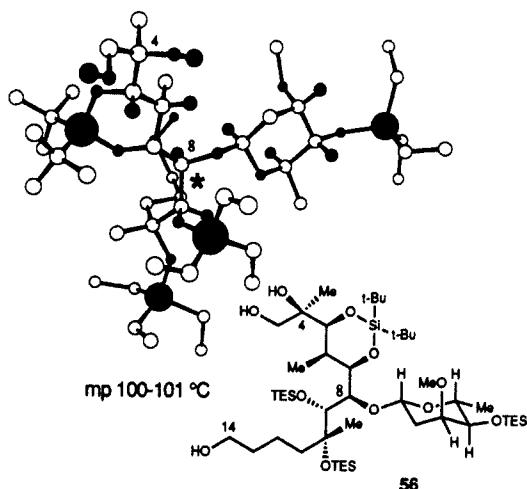
Scheme XVI



(a) Ca , NH_3 , THF , -63 to -45 °C; (b) $(COCl)_2$, $DMSO$, CH_2Cl_2 , -78 °C; Et_3N , -78 to -22 °C; (c) imide 53, nBu_2BOTf , Et_3N , toluene, -50 °C; aldehyde 52; H_2O_2 ; (d) $AlMe_3$, $MeONHMe-HCl$, THF , 0 °C.

precedent established in this laboratory.¹⁵ This intermediate, with its C_8 hydroxyl moiety unprotected, is ideally disposed for successive glycosidation and elaboration to the illustrated C_{10} methyl ketone. Final creation of the C_{10} stereocenter through the chelate-controlled addition of [4-(phenylthio)-1-butyl]magnesium bromide should complete the synthesis of the C_3-C_{14} polyl synthon. Attempts to reduce this plan to practice are discussed below.

A Highly Stereoselective Anti Aldol. The C_8-C_9 syn aldol bond construction between aldehyde 52 and the boron enolate derived from carboximide 53 was anticipated to be unexceptional in stereochemical outcome since we had recorded numerous examples of such double stereodifferentiating reactions in prior work (Scheme XVI).¹⁵ In all such documented cases, reaction stereodifferentiation was completely controlled by the enolate chirality, irrespective of the chirality of the aldehyde. We were therefore surprised to discover that this reaction proceeded with complete stereocontrol to yield the anti aldol adduct 54 in 78% yield as a single diastereomer.⁶⁰ In fact, it was only through conversion

**Figure 3.** Crystal structure of triol **56**.

of this aldol adduct to 8-*epi*-cytovaricin that this errant stereocenter was ultimately discovered.⁶¹ That this aldol adduct was actually the unanticipated anti aldol product was subsequently determined by X-ray crystallographic analysis of triol **56**, a derivative of a more advanced synthetic intermediate containing all of the stereocenters in the polyol glycoside subunit (Figure 3).^{62,63} Because of the history of reliability of these aldol reactions, we committed the cardinal error of not immediately confirming the stereochemical outcome of the reaction between **52** and **53**.

The unexpected reversal of stereochemistry in this reaction is unprecedented with this chiral enolate reagent. It appears that the Felkin–Ahn⁶⁴ diastereofacial bias at the trigonal carbon in silylene aldehyde **52** is sufficiently large to override the inherent β selectivity of the aldol addition reaction as conferred by the pericyclic transition state. As a consequence, the chirality in the enolate defines the C₉ stereocenter, while the C₈ center is controlled by the chirality in the aldehyde reaction partner. This experiment suggests that other nucleophiles should also react in a highly stereoselective manner with **52**. Not surprisingly, organometallic reagents such as methylolithium and methylmagnesium bromide add to the same carbonyl diastereoface with greater than 20:1 selectivity. From a pragmatic standpoint, surmounting this undesired stereochemical bias offered a real challenge. All attempts to obtain the desired syn aldol adduct in even trace quantities through an aldol bond construction met with failure. Ironically, all three of the undesired aldol diastereomers could be obtained as major products by variation of reaction conditions.⁶⁵ The eventual solution to this problem involved the productive utilization of the inherent stereochemical bias in the substrate at the C₈ carbon (Scheme XVII). A one-pot procedure was developed in which Dess–Martin oxidation⁵⁰ of the transaminated anti aldol adduct **55** was immediately followed by *in situ* reduction of the

(60) Heathcock has recently discovered a variant of our asymmetric carboximide aldol methodology using an excess of Lewis acid, chemistry that provides an anti aldol adduct with good stereoselection. However, the anti aldol adduct formed in all cases is of opposite stereochemistry to **67**: Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* 1990, 55, 173–181.

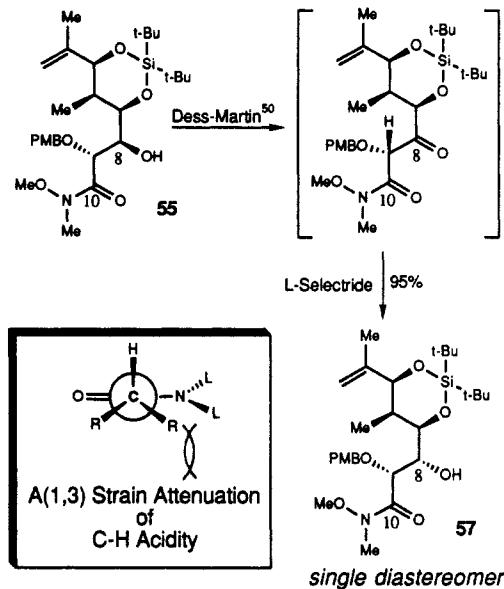
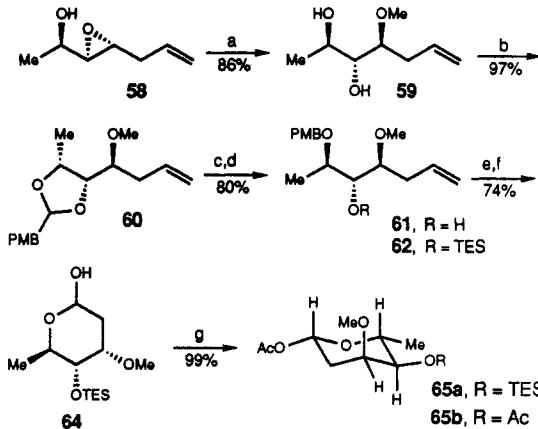
(61) For a complete description of the synthesis of 8-*epi*-cytovaricin the reader is referred to the Supplementary Material.

(62) Clardy, J.; Stout, T.; Cornell University. Unpublished results. Crystals of triol **56** were grown from acetonitrile, and a large flat plate was sealed in a Lindemann capillary with mother liquor. The crystals belonged to the monoclinic space group *P2*₁ with *a* = 14.498 (4), *b* = 13.502 (2), *c* = 16.446 (5) Å, and β = 105.70 (1) $^\circ$. A total of 4438 unique reflections with $2\theta \leq 116^\circ$ were collected using CuK α radiation and variable speed 0.20 scans. A total of 3429 reflections were judged observed ($|F_o| \geq 4.0\sigma(F_o)$) and used in subsequent calculations. The structure was solved uneventfully and refined by full-matrix least-squares techniques with anisotropic nonhydrogen atoms and fixed isotropic hydrogens to a conventional residual of 0.068. Additional crystallographic details can be found in the Supplementary Material deposited with this article.

(63) The synthesis of triol **56** is detailed in the Supplementary Material.

(64) See Ahn, N. T.; Eisenstein, O. *Nouv. J. Chim.* 1977, 1, 61–70 and references cited therein.

(65) A variety of metal enolates (B, Li, Ti, Zr, Mg) were surveyed. Stoichiometry, solvent, and auxiliary were also varied to no avail.

Scheme XVII**Scheme XVIII**

(a) MeOH, CSA, 50 °C; (b) *p*-MeOC₆H₄CH(OMe)₂, CSA, DMF; (c) DIBAI-H, CH₂Cl₂, -70 to -10 °C; (d) TESOTf, Et₃N, CH₂Cl₂, 0 °C; (e) O₃, MeOH, CH₂Cl₂, -78 °C; DMS, -78 °C to 25 °C; (f) DDQ, CH₂Cl₂, H₂O, 10 °C; (g) Ac₂O, pyridine, CH₂Cl₂

resulting β -ketoamide with lithium tri-*sec*-butylborohydride (L-Selectride).⁶⁶ With this reagent, hydride addition occurred exclusively from the *re* face of the carbonyl, effecting near quantitative formation of the desired alcohol **57** as a single diastereomer. It is noteworthy that no C₉ epimerization is observed in this reaction sequence, despite the intermediasity of an oxygenated 1,3-dicarbonyl species. Apparently, A(1,3) strain is sufficient to attenuate the potential acidifying effect of the C₁₀ amide carbonyl.⁶⁷

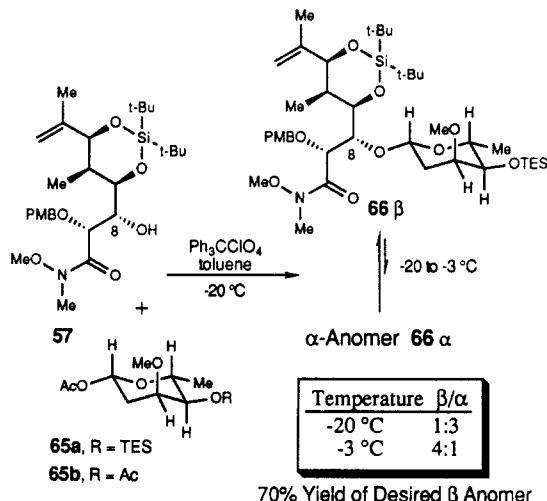
Synthesis of D-Cymarose. In designing a suitable coupling partner for hydroxy amide **57**, we were interested in the utilization of an equatorial-selective glycosidation directly on the deoxysugar in contrast to the usual protocol of relying upon a C-2 controller substituent to dictate the stereochemical course of the glycosidation.⁶⁸ The synthesis of the required sugar, D-cymarose, fol-

(66) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* 1972, 94, 7159–7161.

(67) Johnson, F. *Chem. Rev.* 1968, 68, 375–413. Allylic strain arguments are also used in rationalizing the stability of chiral β -ketoimides: Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* 1984, 106, 1154–1156.

(68) A considerable body of literature exists on the use of oxygen director groups (e.g. acetates). For a general review see: Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* 1986, 25, 212–235. For more recent methodology, with specific reference to non-oxygen controller groups, see: Nicholaou, K. C.; Ladduwahetty, T.; Randall, J. L.; Chucholowski, A. *J. Am. Chem. Soc.* 1986, 108, 2466–2467, and references cited therein.

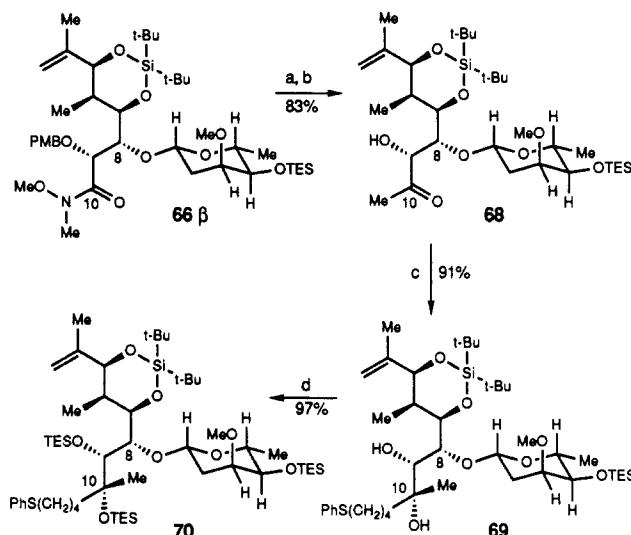
Scheme XIX



lowed a modified strategy for the synthesis of 2,6-dideoxyhexoses reported by Roush and Brown (Scheme XVIII).⁶⁹ Sharpless asymmetric epoxidation methodology was employed to oxidize 1-butadienyl methylcarbinol with attendant kinetic resolution to give the epoxy alcohol **58** in 96% ee,⁷⁰ which was then transformed into the diol methoxy ether **59** with methanolic acid. Formation of the *p*-methoxybenzylidene acetal (97%) was followed by DIBA1H-mediated acetal cleavage, securing the desired *p*-methoxybenzyl ether alcohol **61** in 83% yield. This reductive cleavage proceeds with 7.9:1 regioselectivity in a contrastive sense, implying a chelated intermediate may be responsible for the observed product distribution.⁷¹ After conversion of alcohol **61** to the triethylsilyl (TES) ether (98%), ozonolysis of the monosubstituted olefin in the presence of an indicator dye⁷² provided the sensitive β -methoxy aldehyde (78%). Immediate submission of this aldehyde to oxidative deprotection (DDQ) then afforded the crystalline lactol **64** (95%) as a mixture of anomers.⁷³ Finally, activation of **64** to provide an intermediate amenable to glycosidation was achieved by acetylation, providing exclusively the equatorial acetoxy glycoside **65a** in excellent yield (99%).

Acid-Catalyzed Glycosidation. During the course of the glycosidation of hydroxy amide **57**, a number of methods were surveyed.⁷⁴ The most successful protocol for achieving the desired bond construction involved the use of the activator trityl perchlorate (Scheme XIX).⁷⁵ A cooled (-20°C) solution of alcohol **57** and acetoxy glycoside **65a** in toluene was treated with a catalytic amount (ca. 5%) of trityl perchlorate, and the resulting heterogeneous mixture was monitored by thin-layer chromatography and NMR analysis of quenched aliquots. A high-yielding, rapid reaction was observed at -20°C to afford a 1:3 distribution

Scheme XX



(a) MeLi , THF, -78°C ; (b) DDQ, CH_2Cl_2 , H_2O , 10 to 25°C ; (c) $\text{PhS}(\text{CH}_2)_4\text{MgBr}$, THF, -40 to -25°C ; (d) $n\text{-BuLi}$, THF, -40°C ; TESOTf , -40 to -10°C .

of glycosides favoring the undesired axial anomer **66alpha**. However, upon warming the reaction mixture to -3°C , anomer equilibration was effected to give a 4:1 equilibrium mixture in favor of the desired β glycoside **66beta**. The minor diastereomer, **66alpha**, was then recycled by resubmission to the reaction conditions to afford the 4:1 distribution of glycosides favoring **66beta**. Through the application of this equilibration procedure, a 70% yield of the desired equatorial anomer **66beta** could be achieved.⁷⁶ It was surprising to note that the success of this anomer equilibration critically depended on the nature of the protecting group at the C_4 alcohol. For example, the use of 1,4-bisacetoxy glycoside **65b** as a coupling partner for alcohol **57** provided an initial kinetic mixture in which the two anomeric products were formed in equal amounts. Subsequent warming of the reaction mixture to 0°C did not affect this ratio, and further warming to 25°C resulted only in decomposition. Furthermore, isolation and resubmission of either of the two product anomers to the reaction conditions resulted in no detectable equilibration. We tentatively conclude that destabilization of the oxonium ion derived from **65b** could be stereoelectronic in nature with the mixing of antiperiplanar $\sigma\text{C=O}$ and $\sigma^*\text{C=OAc}$ states effectively transmitting electron withdrawal to the oxonium ion site.

The mechanism of this trityl perchlorate catalyzed reaction is intriguing. Control experiments have established that in the presence of 4-Å molecular sieves or 2,6-di-*tert*-butylpyridine no reaction takes place, implying that the actual catalyst is not trityl perchlorate, but perchloric acid.⁷⁷ In support of this conclusion, we have found that catalytic amounts of a strong Bronsted acid such as either triflic or perchloric acid are indeed sufficient to catalyze the glycosidation between **57** and **65a** in the absence of trityl perchlorate.

Synthesis of the C_3 - C_{14} Subunit (70). The last significant bond construction to be addressed in this portion of the molecule was the elaboration of the C_{10} stereocenter (Scheme XX). Treatment of the *N*-methoxy-*N*-methylamide **66beta** with methylolithium (95%) followed by a DDQ-mediated deprotection of the *p*-methoxybenzyl ether served to reveal methyl ketone **68** (86%), which was anticipated to be a good substrate for chelation-controlled Grignard addition. Despite the seminal work of Cram on chelation-controlled additions to α -hydroxy ketones, such substrates are seldom used in synthesis.⁷⁸ In the event, addition of 3 equiv of the

(69) Roush, W. R.; Brown, R. J. *J. Org. Chem.* 1983, 48, 5093–5101.
 (70) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* 1987, 109, 5765–5780. Kinetic resolution of this diene alcohol was accomplished with the more bulky dicyclododecyl tartrate ligand to afford the desired epoxy alcohol **58** in >96% ee as determined by Mosher ester analysis (Roush performed this kinetic resolution with diisopropyl tartrate, obtaining 90% ee).

(71) A recent report documents similar findings in polyoxygenated systems: Takano, S.; Kurotaki, A.; Sekiguchi, Y.; Satoh, S.; Hirama, M.; Ogasawara, K. *Synthesis* 1986, 811–817.

(72) Veysoglu, T.; Mitschler, L. A.; Swazey, J. K. *Synthesis* 1980, 807–810.

(73) Lactol **64** was converted to D-(+)-cymarose by treatment with buffered pyridinium hydrofluoride. Data for the synthetic material matched literature data for the natural product in all respects (^1H NMR, IR, rotation, TLC).

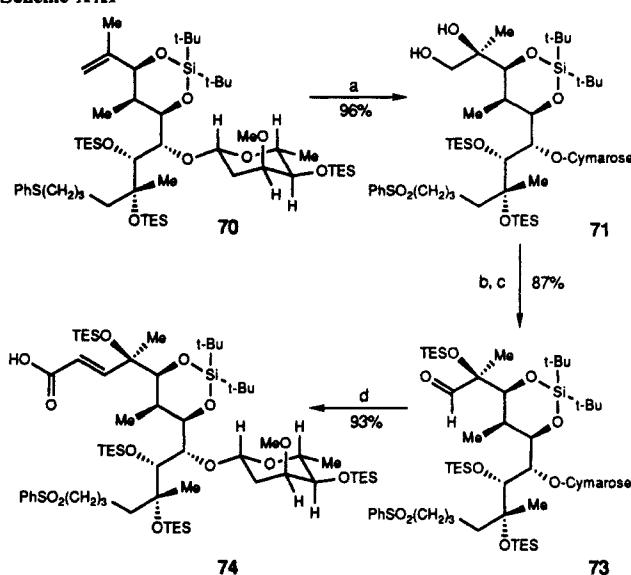
(74) Trichloroacetimidates: Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* 1986, 25, 212–235. Thiophenyl glycosides: Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* 1983, 105, 2430–2434. Enol ethers: Theim, J.; Karl, H.; Schwentner, J. *Synthesis* 1978, 696–698. Glycosyl fluorides: Matsumoto, J.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* 1988, 29, 3567–3570. Glycosyl sulfoxides: Kahne, D.; Walker, S.; Cheng, Y.; Engen, D. V. *J. Am. Chem. Soc.* 1989, 111, 6881–6882.

(75) Mukaiyama, T.; Kobayashi, S.; Shoda, S. *Chem. Lett.* 1984, 907–910.

(76) The protocol developed is a substantial modification of the Mukaiyama procedure (ref 75) which employs stoichiometric trityl perchlorate in ether. The use of solvents in which trityl perchlorate was readily solubilized (e.g. CH_2Cl_2 or CH_3CN) resulted in complete decomposition of **57** and **65a**.

(77) An analogous observation has been made by Kishi in the total synthesis of the mitomycins: Kishi, Y. *J. Nat. Prod.* 1979, 42, 549–568.

Scheme XXI



(a) Cat. OsO₄, NMO, H₂O, THF, acetone, 25 °C; (b) (COCl)₂, DMSO, CH₂Cl₂, -78 °C; Et₃N, -78 to -30 °C; (c) TESOTf, 2,6-lutidine, CH₂Cl₂, 0 °C;
 (d) (EIO₂)POCH₂COOTMS, *n*-BuLi, THF, 25 °C. ⁷³

Grignard reagent derived from 1-bromo-4-(phenylthio)butane⁷⁹ cleanly provided diol **69** as the only detectable diastereomer (91%). Bis-silylation of this highly encumbered diol was then achieved through bis-lithiation with *n*-butyllithium and subsequent silylation with triethylsilyl triflate, affording a 97% yield of the fully protected sulfide olefin **70**.

From olefin **70**, only four synthetic operations were required to complete the synthesis of the sulfone acid **74** (Scheme XXI). Treatment of **70** with a catalytic amount of osmium tetroxide in the presence of 4 equiv of *N*-methylmorpholine *N*-oxide achieved bis-hydroxylation to give diol sulfone **71** as a single diastereomer in excellent yield (96%). Whereas osmylation of this 1,1-disubstituted olefin was fully expected to proceed with high diastereoselectivity on the basis of our earlier work (eq 6), the concomitant catalytic oxidation of the sulfide functionality to the sulfone had little literature precedent.⁸⁰ In 1965 Henbest demonstrated that, whereas oxidation of sulfoxides to the corresponding sulfones with osmium tetroxide was found to be a facile process at room temperature, treatment of dibenzyl or diphenyl sulfide with OsO₄ under stoichiometric conditions in refluxing ether for 48 h resulted in complete recovery of starting sulfide.⁸¹ It thus appears that tertiary amine catalysis is responsible for the successful sulfone oxidation of sulfide **70**.⁸² In terms of relative rates of oxidation, **70** was oxidized first to the corresponding sulfone olefin in a very rapid process (20 min, 25 °C, 93%), with osmylation of the 1,1-disubstituted olefin occurring in a relatively slow subsequent step (12 h, 25 °C). Diol sulfone **71** was next subjected to a Swern oxidation to provide the highly oxygen-sensitive aldehyde **72**⁸³ (87%) which was immediately silylated to afford the fully protected C₁-C₄ synthon **73** (96%). Formation of sulfone acid **74** was

(78) Cram, D. J.; Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828-5835.

(79) Bakuzis, P.; Bakuzis, M. L. F.; Fortes, C. C.; Santos, R. J. *Org. Chem.* 1976, 41, 2769-2770.

(80) One piece of evidence in favor of the desired transformation may be found in a footnote in a paper by Hauser, in which it was noted that a sulfide olefin was osmylated to the corresponding diol sulfone in the presence of an amine oxide cooxidant: Hauser, F. M.; Ellenberger, S. R.; Clardy, J. C.; Bass, L. S. *J. Am. Chem. Soc.* 1984, 106, 2458-2459.

(81) Henbest, H. B.; Khan, S. A. *J. Chem. Soc., Chem. Commun.* 1968 1036.

(82) In a control experiment, excess *N*-methylmorpholine *N*-oxide in the absence of catalyst gave no reaction after 14 h at 25 °C. *N*-oxides are known to oxidize sulfoxides to sulfones under more drastic conditions (sulfuric acid, 195 °C): Biffin, M. E. C.; Miller, J.; Paul, D. B. *Tetrahedron Lett.* 1969, 1015-1018.

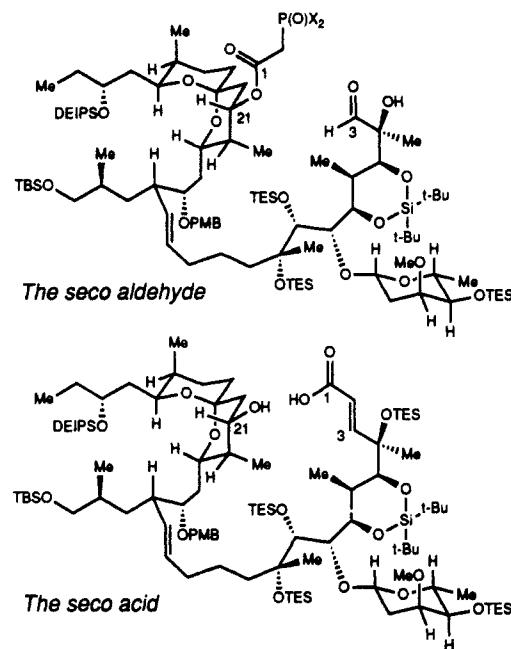
(83) Formation of the ketone derived from "deformylation" of 72 was observed.

achieved by treatment of aldehyde **73** with an excess of the lithium enolate derived from diethyl $\{[(\text{trimethylsilyl})\text{oxy}]\text{carbonyl}\}$ -methanephosphonate (25°C , 20 h)⁸⁴ to give the desired α,β -unsaturated acid (93%), thus completing the synthesis of the polyol glycoside subunit.

With syntheses of both halves of cytovaricin in hand, the final stages of the synthesis were now ready to be tested. The Julia-Lythgoe coupling²¹ of sulfone acid 74 with the spiroketal aldehyde 37 was examined first.

Assemblage and Macrocyclization

The C₃-C₁₄ subunit **70**, when united with the spiroketal moiety **37**, provided us with sufficient versatility to test both illustrated carbomacrocyclization and macrolactonization options during the development of the synthesis. In our initial efforts, which resulted in the synthesis of *8-epi*-cytovaricin, the Horner-Emmons macrocyclization of the "seco aldehyde" could never be induced to provide greater than a 35% yield of the 22-membered lactone. On the basis of these disappointing results, we then elected to evaluate the illustrated seco acid as a cyclization precursor. To enhance the convergency of the assemblage process, the α,β -unsaturated acid moiety was incorporated into the polyol glycoside fragment prior to the Julia-Lythgoe olefination (*vide supra*). In order to render this functional group and the associated vulnerable C₄ oxygen substituent inert to the reductive conditions necessary for the β -acetoxy sulfone elimination,⁸⁵ the unprotected acid, as its derived carboxylate salt, was carried through the olefination sequence.



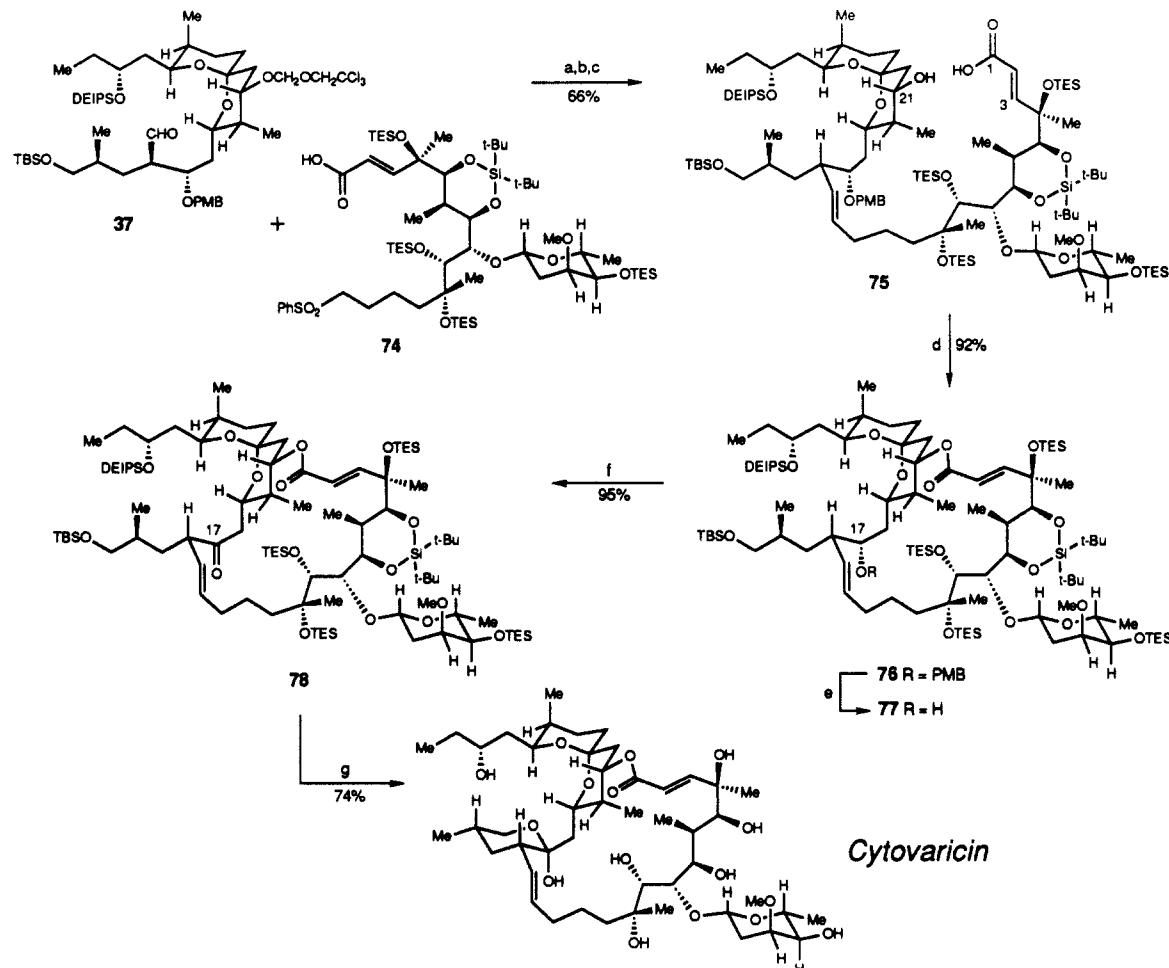
Julia-Lythgoe Olefination. The addition of sulfone anions to aldehydes can be a capricious process. A number of reports in the literature document problems in achieving bond constructions of this sort, especially in polyoxygenated systems.⁸⁶ A problem commonly observed is incomplete reaction either as a result of partial formation of the sulfone anion in the initial deprotonation step, or because the potential equilibrium between product alkoxyl

(84) Lombardo, L.; Taylor, R. J. K. *Synthesis* 1978, 131-132. Use of dianion chemistry resulted in complete decomposition of 73; Coutrot, P.; Snoussi, M.; Savignac, P. *Synthesis* 1978, 133-134.

(85) When a model α,β -unsaturated ester containing an allylic tertiary carbinol was submitted to 6% Na/Hg in MeOH/THF at -60 °C, complete deconjugative cleavage was observed within 10 min. Tanner has also attempted a Julia-Lythgoe coupling sequence on a system containing similar functionality with only modest success (30% yield after optimization) in a synthesis of ingramycin: Tanner, D.; Somfai, P. *Tetrahedron* 1987, 43, 4395-4406.

(86) For a recent example, see: Hanessian, S.; Ugolini, A.; Hodges, P. J.; Beaulieu, P.; Dube, D.; Andre, C. *Pure Appl. Chem.* 1987, 59, 299-316.

Scheme XXII



(a) 74, LiNEt₂, THF, -78 to -55 °C; 37, -78 °C; (b) Ac₂O, DMAP, CH₂Cl₂, 25 °C; (c) NaHCO₃, MeOH-THF, -40 °C; 6% Na-Hg, -40 to -30 °C. (d) DMAP-HCl, DMAP, DCC, CHCl₃, 61 °C; syringe pump addition of 75 over 21 h. (e) DDO, CH₂Cl₂, H₂O, 25 °C; (f) Dess-Martin periodinane, pyridine, CH₂Cl₂, 25 °C; (g) HF-pyr, pyridine, THF, 25 °C.

sulfone and starting materials is displaced in favor of the latter. In the formation of the bis-metallated sulfone acid 37, it was essential to use the more kinetically competent base lithium diethylamide, as opposed to lithium diisopropylamide, to insure complete dianion formation. Interestingly, the sulfone could be used as its own internal titration indicator in metering in the 2 equiv of base required for dianion formation.⁸⁷ Treatment of 74 with sufficient lithium diethylamide to effect complete carboxylate formation was marked by the initial appearance of the canary yellow sulfone anion. Subsequent addition of another equivalent of lithium diethylamide followed by introduction of spiroketal aldehyde 37 resulted in complete coupling of the two halves, forming a nearly statistical mixture of hydroxy sulfones (Scheme XXII). Submission of the unpurified product mixture to a concentrated solution of acetic anhydride containing a large excess of (*N,N*-dimethylamino)pyridine (18 h, 25 °C) provided the acetoxy sulfones in quantitative yield. Without further purification, the mixture of acetoxy sulfones was treated with an excess of sodium bicarbonate in a methanol/THF mixture at -50 °C to transform the carboxylic acid moiety to the sodium carboxylate. Subsequent addition of a large excess of pulverized 6% sodium amalgam to the reaction mixture effected both reductive elimination of the acetoxy sulfone to the trans olefin and concomitant cleavage of the C₂₁ (2,2,2-trichloroethoxy)methoxy protecting group on the spiroketal to afford a 66% overall yield of the desired trans olefin. The convergent nature of this coupling protocol provided the added benefit of directly providing us with our hydroxy acid macrolactonization substrate.

(87) This feature of the reaction proved especially useful in small-scale exploratory work on this coupling chemistry.

Macrocyclization. In contemplating the macrolactonization of hydroxy acid 75, we elected to use an in situ activation method.⁸⁸ Specifically, two procedures were of interest to us on the basis of documented successes in complex natural product syntheses: Mukaiyama's *N*-methyl-2-chloropyridinium iodide chemistry,⁸⁹ and Keck's DMAP-hydrochloride modification of the Steglich esterification process.⁹⁰ For our first attempt at macrocyclization, we employed the Mukaiyama procedure under conditions that had proven highly successful for closure of a 34-membered lactone during the course of White's synthesis of aplasmomycin.⁹¹ Unfortunately, hydroxy acid 75 proved more reluctant to lactonize under these reaction conditions, and less than 5% of a reaction product, tentatively identified as the desired macrocycle, was obtained. We next examined Keck's carbodiimide macrocyclization methodology which had worked quite well in the Stork-Rychovsky dihydroerythronolide A synthesis.⁹² By delivering hydroxy acid 75 by syringe pump over 21 h to a refluxing chloroform solution containing a large excess of reagents, we were gratified to obtain the desired macrocycle in 92% yield (Scheme XXII).

Lactol Formation and Final Deprotection. In direct analogy with our earlier model and correlation work on the spiroketal

(88) For leading references on macrocyclization in macrolide synthesis see: (a) Paterson, I.; Mansuri, M. M. *Tetrahedron* 1985, 41, 3569-3624. (b) Boeckman, R. K., Jr.; Goldstein, S. W. In *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley: New York, 1988; Vol. 7, pp 1-139.

(89) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* 1976, 49-50.

(90) Boden, E. P.; Keck, G. E. *J. Org. Chem.* 1985, 50, 2394-2395.

(91) White, J. D.; Vedananda, T. R.; Kang, M.; Choudhry, S. C. *J. Am. Chem. Soc.* 1986, 108, 8105-8107.

(92) Stork, G.; Rychovsky, S. D. *J. Am. Chem. Soc.* 1987, 109, 1565-1567.

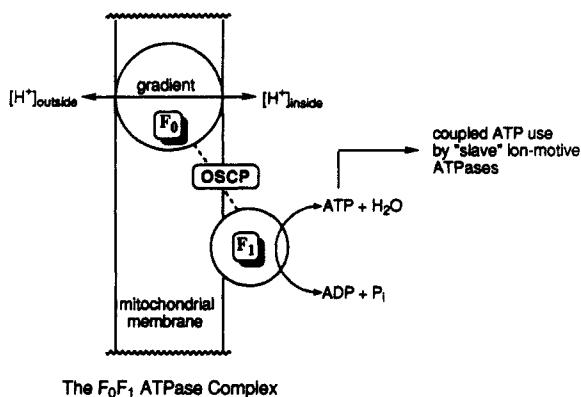
The F_0F_1 ATPase Complex

Figure 4. The oligomycins. Potent inhibitors of oxidative phosphorylation.

subunit, we hoped to employ oxidative deprotection of the C_{17} PMB ether, Swern oxidation to the corresponding C_{17} ketone, and buffered pyridinium fluoride deprotection to reveal cytovaricin. As anticipated, oxidative deprotection (DDQ) of the macrolactone 76 to reveal the C_{17} alcohol 77 proceeded in excellent yield (98%). However, attempted oxidation of 77 provided a disquieting result: complete decomposition of the starting alcohol was observed under oxidation conditions identical with those used with success in earlier model work. After attempts to improve this reaction met with failure, other oxidants were examined. Again, the Dess–Martin periodinane reagent⁵⁰ proved to be the reagent of choice for this transformation. Treatment of alcohol 77 with an excess of the periodinane reagent under mildly basic conditions afforded the desired β,γ -unsaturated ketone 78 in 95% yield, with no apparent epimerization or olefin conjugation (Scheme XXII). Final deprotection to the natural product was then achieved by treatment of 78 with buffered pyridinium hydrofluoride (25 °C, 60 h), providing a single product by TLC analysis which coeluted with natural cytovaricin in a number of solvent systems. Interestingly, several of the partially desilylated intermediates observed on the way to the final product were significantly more polar than the natural product, implying that a hydrogen-bonding network may be present in cytovaricin which is disrupted in partially protected precursors.⁹³ Synthetic cytovaricin thus obtained (74%) crystallized in orthorhombic crystals on slow evaporation from acetonitrile and proved identical in all respects (1H , COSY-90, and ^{13}C NMR; IR; TLC; $[\alpha]_D$; HRMS; analysis; melting point⁹⁴) with natural cytovaricin. It was satisfying to find that less than 5% dienol ether formation was observed in the final deprotection step.

Proposed Mode of Action for Cytovaricin

The oligomycin–rutamycin family of spiroketal macrolides (Scheme I) is an interesting group of compounds that has attracted considerable attention from the biological research community. While a recent Chemical Abstracts search of cytovaricin produced only four papers on the compound, all emanating from Isono's group,^{2–5} the corresponding search on oligomycin afforded over 600 references spanning a broad range of journals.⁶ The oligomycins are a class of cytotoxic compounds that inhibit oxidative phosphorylation in mitochondria. Although these compounds do not possess clinical utility due to the indiscriminate nature of their cytotoxicity, their use as H^+ -ATPase inhibitors has contributed greatly to our current understanding of the mechanism of oxidative phosphorylation.^{95,96}

(93) The X-ray structure determined by Isono indicates several potential hydrogen bonds. See ref 3.

(94) The primary material isolated from the heated melting point capillary corresponded to a decomposition product tentatively ascribed to cytovaricin dienol ether aglycone. "Thermal deglycosidation" is a documented process for steroid glycosides: Higuchi, R.; Kitamura, Y.; Komori, T. *Liebigs Ann. Chem.* 1986, 638–646.

(95) (a) Lardy, H. A.; Johnson, D.; McMurray, W. C. *Arch. Biochem. Biophys.* 1958, 78, 587–596. (b) Tyler, D. D. In *Membrane Structure and Function*; Bittar, E. E., Ed.; Wiley: New York, 1984; Vol. V, pp 117–179.

The proton motive ATPases in mammalian cells, located in the inner membrane of mitochondria, consist of two basic subunits, termed F_0 and F_1 . These two subunits work in concert to accomplish the task of packaging external energy into the biologically usable energy form of ATP. The F_0 subunit consists of a membrane-spanning proton channel used in electrochemical proton gradient formation across the membrane. The water soluble F_1 subunit, on the other hand, is loosely bound to the inside of the mitochondrial membrane and is responsible for catalysis of ATP synthesis (Figure 4).⁹⁷ The two subunits act in a coupled fashion to complete the catalytic cycle: It is proposed that proton gradient formation from F_0 induces a conformational change in F_1 responsible for ATP release from the bound $ATP-F_1$ complex.⁹⁸

It has been concluded that the oligomycins act by decoupling the F_0 and F_1 subunits of the F_0F_1 proton motive ATPase complex, thus inhibiting ATP synthesis. It is now thought that there is a physical association of oligomycin with the F_0 membrane-spanning section of the complex that is strong enough to displace the linker protein, OSCP (oligomycin sensitivity conferring protein), responsible for holding the two subunits in a working union.⁹⁹ This competitive binding of oligomycin to F_0 effectively inhibits oxidative phosphorylation in the cell, ultimately killing the organism.

We were initially attracted to the oligomycins because of their spiroketal subunit, which bears a striking resemblance to the spiroketal portion of cytovaricin, especially in the case of the two rutamycins (see Scheme I). However, further comparison of the structures also revealed significant differences. Cytovaricin is a 22-membered macrolide, while all oligomycins possess significantly larger 26-membered rings. The oligomycins lack the lactol and glycoside of cytovaricin, but contain an ethyl side chain and diene missing in cytovaricin. Finally, the extent of functionalization and substitution pattern of the polyoxygenated regions of the two macrolides differ markedly.

In spite of the apparent discrepancies between the two classes of compounds in two-dimensional space, a comparison of their crystal structures reveals otherwise.^{100,101} A rigid superposition of the two X-ray structures produce an overlay indicative of a high degree of similarity (Figure 5). As expected, the two spiroketal moieties are essentially superimposable. Further sources of homology come from unexpected sources. Although the ring sizes of the two macrolides are quite different, the larger 26-membered lactone ring in rutamycin A appears to fold back upon itself to nicely coalign with the smaller 22-membered ring of cytovaricin. While rutamycin A lacks the lactol moiety found in cytovaricin, its ethyl side chain occupies the corresponding conformational space. Perhaps most surprisingly, oxygen and methyl substituents in the polyol region map onto each other with remarkable consistency, in many cases occupying the same volume in space. The one nonoverlapping entity in this overlay is cytovaricin's cymarose appendage. It is thus with some interest that we note that phthoramycin, the recently isolated addition to the cytovaricin family, lacks just this pendant structural feature (Scheme I).⁸

To the best of our knowledge, no mode of action has been proposed to date to explain cytovaricin's cytotoxic effects. From the preceding discussion, we conclude that cytovaricin and the oligomycins bear sufficient homology to propose an analogous mode of action. This similarity, in turn, strongly suggests that

(96) For an introduction to ATPases with leading references see: Pedersen, P. L.; Carafoli, E. *TIBS* 1987, 12, 146–150.

(97) ATPases in aerobic organisms are typically run predominantly in the direction of ATP synthesis. However, catalysis of hydrolysis of ATP is also possible.

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(99) See: Dupuis, A.; Vignais, P. V. *Biochemistry* 1987, 26, 410–418 and references cited therein.

(100) (a) Reference 3 (cytovaricin). (b) Arnoux, B.; Garcia-Alvarez, M. C.; Marazano, C.; Das, B. C.; Pascard, C.; Merienne, C.; Staron, T. *J. Chem. Soc., Chem. Commun.* 1978, 318–319 (rutamycin A).

(101) Superpositions were performed on an Evans and Sutherland PS 390 graphics terminal. In the literature, the rutamycin A structure (absolute configuration undetermined) is arbitrarily drawn in a form antipodal to that of cytovaricin. An inversion routine was thus applied on the rutamycin A crystal structure before overlay was attempted.

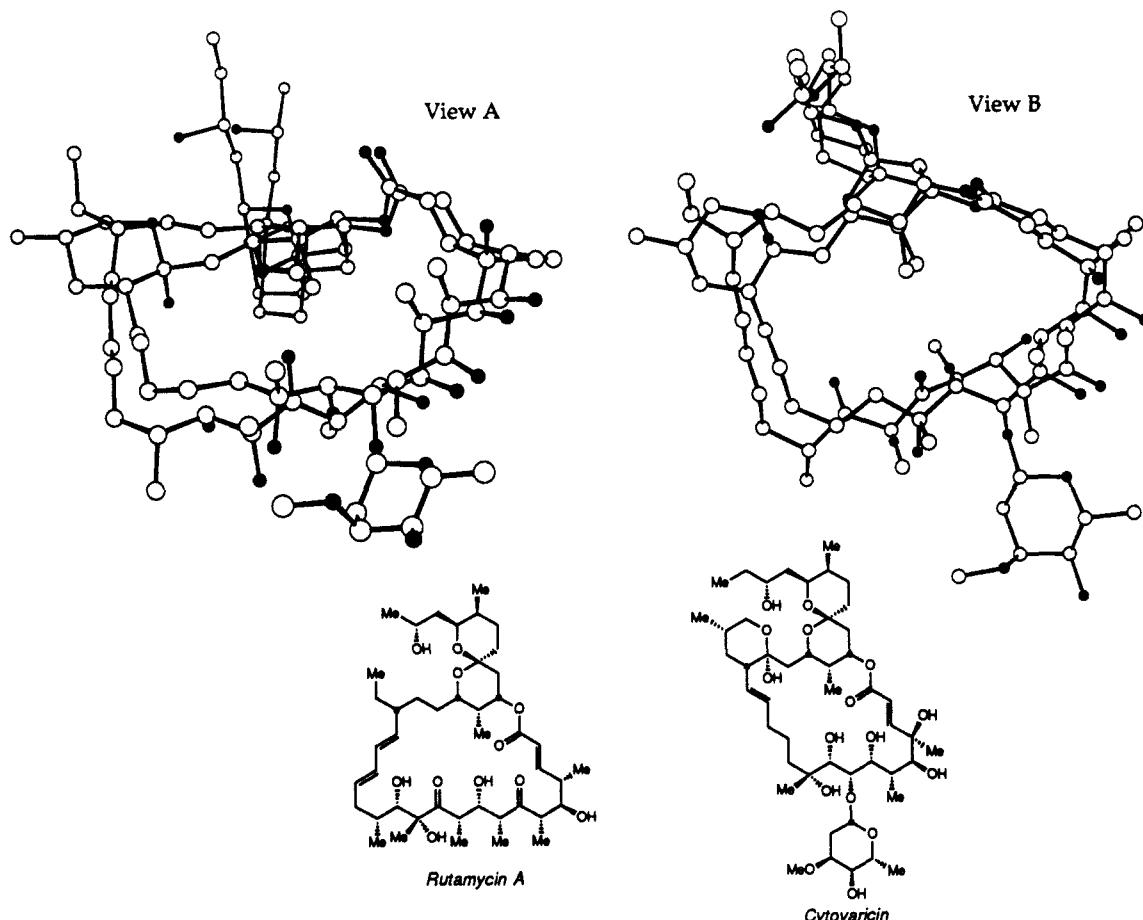


Figure 5. Superposition of rutamycin A and cytovaricin.

cytovaricin should be assayed for its decoupling potential as an inhibitor of oxidative phosphorylation.

Experimental Section

General. Melting points and boiling points are uncorrected. Mass spectra (MS) were determined on a Kratos MS-50 spectrometer operating at 70 eV. ¹H and ¹³C NMR spectra were recorded on Bruker AM-500, AM-300, or AM-250 spectrometers at ambient temperature. When employed in ¹H NMR assignments, numbered carbons refer to the cytovaricin numbering of Isono et al.² Analytical and preparative thin-layer chromatography (TLC) was performed on EM Reagents 0.25-mm silica gel 60-F plates. Liquid chromatography was performed by using forced flow (flash chromatography)¹⁰² of the indicated solvent system on EM Reagents silica gel 60 (230–400 mesh). Analytical high-performance liquid chromatography was carried out on a Hewlett-Packard HP 1090 chromatograph equipped with a diode array detector using a Dupont Zorbax column (4.6 × 25 cm, 5-μm silica gel). Capillary GLC analyses were performed on a Hewlett-Packard 5880A chromatograph equipped with fused-silica capillary columns (50-m × 0.32-mm) wall coated with DB-1, DB-1701, or DB-5 (J & W Scientific). THF, diethyl ether, and toluene were distilled from sodium metal/benzophenone ketyl. Dichloromethane and other amines were distilled from calcium hydride. DMF and DMSO were distilled under reduced pressure from calcium hydride and were stored over 4-Å molecular sieves under an argon atmosphere. 2-Propanol was dried over 4-Å molecular sieves and degassed with argon just prior to use in samarium diiodide-catalyzed reductions. Ethanol-free chloroform for macrolactonization reactions was produced by repeated extraction of Mallinckrodt chloroform (0.75% ethanol) with water, followed by distillation from P₂O₅ into a receiver containing 4-Å molecular sieves and was used within 2 h after purification.¹⁰³ Organolithium reagents (*n*-butyllithium, methylolithium, 2-lithiopropene,¹⁰⁴

lithium diisopropylamide, and lithium diethylamide) were titrated by use of the Britton modification of the method of Brown.¹⁰⁵ 4-(Phenylthio)butylmagnesium bromide was synthesized according to the method of Bakuzis⁹ and was titrated with 1,10-phenanthroline as an indicator.¹⁰⁶ Samarium diiodide,¹⁰⁷ di-*n*-butylboron triflate,¹⁰⁸ stannous triflate,¹⁰⁹ methoxydiethylborane,¹¹⁰ tri-*n*-butyltin hydride,¹¹¹ diethyl(isopropylsilyl)chlorosilane,³⁷ bromomethyl 2,2,2-trichloroethyl ether,⁴¹ diethyl [[(trimethylsilyl)oxy]carbonyl]methanephosphonate,⁸⁴ 4-methoxybenzaldehyde dimethyl acetal,¹¹² and triphenylmethyl perchlorate¹¹³ were all prepared according to literature procedures. The Dess–Martin periodinane was formed with use of a modification of the literature procedure¹¹⁴ in which the hydroxyiodinane oxide intermediate was heated at 80 °C with acetic anhydride and acetic acid only until dissolution was complete (ca. 10 min). Typically, all nonorganometallic, commercially obtained reagents were purified by distillation or recrystallization before use.

4α,26α-Didehydro-26α-deoxycytovaricin (2). A solution of 3.0 mg (3.3 μmol) of cytovaricin in 0.4 mL of “100.0 atom percent” deuterio-dichloromethane at 24 °C was periodically monitored by NMR spec-

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(114) See ref 50. Use of a blast shield in preparing this reagent is advised because of the potential for explosion.

troscopy until dienol formation was >95% complete (ca. 12 h).¹¹⁵ Essentially quantitative formation of the highly UV-active dienol ether **2** was observed, with no evidence of deglycosidation.¹¹⁶ Data for **2**: $[\alpha]^{23}_{D46} -9.5^\circ$ (*c* 0.60, CH_2Cl_2); IR (thin film) 3600–3200, 3050, 2970, 2930, 1720, 1655, 1625, 1510, 1460, 1380, 1310, 1270, 1175, 1090, 980, 935, 905, 870, 740, 705 cm^{-1} ; ^1H NMR (CD_2Cl_2 , 500 MHz with COSY-90) δ 6.80 (d, 1 H, *J* = 15.5 Hz, $\text{C}_3\text{-H}$), 6.33 (d, 1 H, *J* = 15.3 Hz, $\text{C}_2\text{-H}$), 5.28 (s, 1 H, OH), 5.26–5.21 (m, 2 H, $\text{C}_{14}\text{-H}$ and $\text{C}_{21}\text{-H}$), 5.10 (s, 1 H, OH), 4.80 (dd, 1 H, *J* = 9.8 and 1.8 Hz, $\text{C}_1\text{-H}$), 4.13–4.06 (m, 2 H), 4.00–3.92 (m, 2 H including $\text{C}_{24}\text{-H}_{\text{eq}}$), 3.81–3.73 (m, 2 H), 3.75–3.70 (m, 2 H, including $\text{C}_5\text{-H}$), 3.65–3.63 (m, 1 H, $\text{C}_3\text{-H}$), 3.44 (t, 1 H, *J* = 10.1 Hz, $\text{C}_{24}\text{-H}_{\text{ax}}$), 3.43 (s, 3 H, $\text{C}_3\text{-OCH}_3$), 3.24–3.18 (m, 1 H, $\text{C}_4\text{-H}$), 3.07–3.03 (m, 2 H), 2.93 (t, 1 H, *J* = 12.8 Hz, one of $\text{C}_{18}\text{-CH}_2$), 2.53–2.47 (m, 1 H, one of $\text{C}_{13}\text{-CH}_2$), 2.46–2.25 (m, 4 H, including $\text{C}_2\text{-H}_{\text{eq}}$), 2.23–2.18 (m, 1 H, one of $\text{C}_{18}\text{-CH}_2$), 2.16–2.08 (m, 1 H) 2.04–1.98 (m, 1 H, $\text{C}_{20}\text{-H}$), 1.97–1.86 (m, 18 H), 1.33 (s, 3 H, $\text{C}_4\text{-CH}_3$), 1.30 (d, 3 H, *J* = 6.8 Hz, $\text{C}_5\text{-CH}_3$), 1.22–1.15 (m, 2 H), 1.11 (s, 3 H, $\text{C}_{10}\text{-CH}_3$), 0.95 (t, 3 H, *J* = 7.4 Hz, $\text{C}_{34}\text{-CH}_3$), 0.94 (d, 3 H, *J* = 7.2 Hz, CHCH_3), 0.93 (d, 3 H, *J* = 7.0 Hz, CHCH_3), 0.87 (d, 3 H, *J* = 7.0 Hz, CHCH_3), 0.78 (d, 3 H, *J* = 7.0 Hz, $\text{C}_{20}\text{-CH}_3$); ^{13}C NMR (CD_2Cl_2 , 75.5 MHz) δ 165.1, 149.2, 147.8, 129.0, 124.9, 109.1, 100.1, 98.3, 86.7, 79.5, 77.7, 77.4, 75.3, 75.2, 74.3, 72.3, 72.2, 71.7, 70.7, 68.8, 67.6, 67.4, 57.4, 40.8, 38.3, 36.1, 35.8, 34.8, 34.1, 32.9, 32.0, 31.5, 31.4, 29.9, 29.8, 28.7, 27.6, 27.1, 22.4, 22.2, 18.1, 17.2, 11.3, 10.4, 5.9, 4.8; TLC R_f = 0.13 (4% MeOH/ CH_2Cl_2); MS (70 eV, FAB with *m*-nitrobenzyl alcohol) *m/e* 882 (5, M^+), 739 (8, $\text{M}^+ - \text{glycoside}$).

26 α -O-Methylcytovaricin (3). To a cooled (0 °C) solution of 3.8 mg (4.2 μmol) of natural cytovaricin (**1**) in 1 mL of methanol were added ca. 40 beads of Dowex 50X 8–200 ion-exchange resin. After 1.4 h, the mixture was treated with 4 drops of triethylamine and was filtered through a plug of cotton (CH_2Cl_2 rinses). Concentration by rotary evaporation provided 3.8 mg (100%) of the desired ketal **3** as an amorphous powder. This material was employed without further purification in subsequent reactions. Data for **3**: IR (thin film/trace CH_2Cl_2) 3600–3200, 3060, 2940, 1717, 1650 (wk), 1460, 1420, 1385, 1310, 1265, 1230, 1170, 1090, 1070, 1005, 980, 895, 870, 740, 705 cm^{-1} ; ^1H NMR (500 MHz, acetonitrile- d_3) δ 6.84 (d, 1 H, *J* = 15.6 Hz, $\text{C}_3\text{-H}$), 5.97 (d, 1 H, *J* = 15.7 Hz, $\text{C}_2\text{-H}$), 5.38 (dd, 1 H, *J* = 6.7 and 15.9 Hz, $\text{C}_{15}\text{-H}$), 5.32–5.27 (m, 1 H, $\text{C}_{21}\text{-H}$), 5.23 (dt, 1 H, *J* = 15.9 and 4.8 Hz, $\text{C}_{14}\text{-H}$), 4.88 (br s, 1 H), 4.80 (dd, 1 H, *J* = 9.6 and 1.4 Hz, $\text{C}_1\text{-H}$), 4.42 (br s, 1 H), 4.03 (dm, 1 H, *J* = 7.9 Hz, $\text{C}_{30}\text{-H}$), 3.92–3.88 (m, 1 H, $\text{C}_{19}\text{-H}$), 3.78–3.60 (m, 4 H), 3.34 (s, 3 H, $\text{C}_3\text{-OCH}_3$), 3.14 (s, 3 H, $\text{C}_{17}\text{-OCH}_3$), 3.13 (m, 1 H, $\text{C}_{16}\text{-H}$), 3.12 (t, 1 H, *J* = 11.1 Hz, $\text{C}_{24}\text{-H}_{\text{ax}}$), 3.04 (dd, 1 H, *J* = 6.7 and 8.0 Hz), 2.79 (dd, 1 H, *J* = 11.1 and 7.5 Hz), 2.55 (s, 1 H, $\text{C}_{10}\text{-OH}$ or $\text{C}_4\text{-OH}$), 2.35–2.26 (m, 2 H, $\text{C}_{13}\text{-CH}_2$), 2.05–1.23 (m, 29 H), 1.23 (s, 3 H, $\text{C}_4\text{-CH}_3$), 1.18 (d, 3 H, *J* = 6.8 Hz, $\text{C}_5\text{-CH}_3$), 1.06 (s, 3 H, $\text{C}_{10}\text{-CH}_3$), 0.96 (t, 3 H, *J* = 7.4 Hz, $\text{C}_{34}\text{-CH}_3$), 0.92 (d, 3 H, *J* = 7.0 Hz, one of CHCH_3), 0.89 (d, 3 H, *J* = 6.9 Hz, one of CHCH_3), 0.88 (d, 3 H, *J* = 6.8 Hz, one of CHCH_3), 0.76 (d, 3 H, *J* = 6.6 Hz, $\text{C}_{23}\text{-CH}_3$); ^{13}C NMR (125.5 MHz, acetonitrile- d_3) 165.9, 151.6, 133.0, 132.5, 120.3, 100.6, 100.4, 98.3, 83.3, 80.0, 78.3, 77.8, 76.2, 75.6, 73.5, 73.2, 72.0, 71.1, 70.3, 69.3, 67.8, 67.7, 57.7, 47.5, 46.3, 42.3, 41.4, 37.1, 36.9, 36.4, 36.3, 36.2, 34.7, 34.4, 34.3, 31.9, 31.7, 30.8, 30.5, 27.8, 27.2, 24.9, 24.1, 18.5, 11.6, 10.7, 6.4, 5.8; TLC R_f = 0.10 (4% methanol/ CH_2Cl_2); MS (70 eV, FAB, *m*-nitrobenzyl alcohol) *m/e* 914 (5, M^+), 883 (47, $\text{M}^+ - \text{CH}_3\text{OH}$), 739 ($\text{M}^+ - \text{CH}_3\text{OH}$ – glycoside).

[4S]-4-Methyl-5-[[1,1-dimethylethyl]dimethylsilyloxy]-1-pentanol (9). To a solution of 5.50 g (25.6 mmol) of olefin **8**¹⁵ in 20 mL of THF was added 77.0 mL (0.5 M in THF, 37.5 mmol) of 9-borabicyclo[3.3.1]nonane (9-BBN) over a 3-min period. After 2 h, the solution was cooled to 0 °C, and 30 mL of 3.0 N sodium hydroxide (90 mmol) was introduced, followed by the dropwise addition of 60 mL of 30% aqueous hydrogen peroxide over a 15-min period. The resulting mixture was stirred at 0 °C for 2.5 h, warmed to ambient temperature, stirred for an additional 1 h, and diluted with 300 mL of 3:1 hexane/ CH_2Cl_2 . Upon separation of the biphasic mixture, the aqueous layer was washed with 1 × 150 mL of CH_2Cl_2 , and the combined organic extracts were successively washed with 1 × 100 mL of water and 1 × 100 mL of 0.05 N aqueous phosphate buffer, dried (Na_2SO_4), filtered, and concentrated. The resulting milky-white oil was purified by flash chromatography (8 × 18 cm of silica gel, 20% EtOAc/hexane), affording 5.79 g (97%) of **9** as a viscous oil: $[\alpha]^{23}_{D46} -12.5^\circ$ (*c* 1.14, CH_2Cl_2); IR (thin film) 3340 (br), 2960, 2935, 2860, 1470, 1465, 1390, 1360, 1255, 1150, 1095, 1060, 1005, 940, 835, 815, 775, 665 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 3.61

(115) Commercial grade CD_2Cl_2 typically possessed sufficient acid to catalyze dienol ether formation without further prompting. For more rapid dienol ether formation, a drop of anhydrous CDCl_3 was added.

(116) More acidic conditions (e.g. HF/ $\text{CH}_3\text{CN}/\text{H}_2\text{O}$) caused concomitant deglycosidation.

(t, 2 H, *J* = 6.4 Hz, CH_2OH), 3.15–3.35 (m, 2 H, CH_2OTBS), 1.71 (s(br), 1 H, OH), 1.65–1.05 (m, 5 H, $\text{HOCH}_2\text{CH}_2\text{CHCH}_3$), 0.88 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.87 (d, 3 H, *J* = 5.9 Hz, CHCH_3), 0.02 (s, 6 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 68.2, 63.2, 35.5, 30.2, 29.2, 25.9, 18.3, 16.7, -5.4; TLC R_f = 0.16 (20% EtOAc/hexane). Anal. Calcd for $\text{C}_{12}\text{H}_{31}\text{O}_2\text{Si}$: C, 62.01; H, 12.14. Found: C, 61.77; H, 11.95.

[4S]-4-Methyl-5-[[1,1-dimethylethyl]dimethylsilyloxy]pentanoic Acid (10). To a clear solution of 15.1 g (269 mmol) of potassium hydroxide and 16.7 g (61.6 mmol) of potassium persulfate in 2.3 L of water was added 403 mg (1.54 mmol) of ruthenium trichloride trihydrate, rapidly producing an dark-green solution which turned light-orange over ca. 15 min. To this orange solution was added 3.58 g (15.4 mmol) of alcohol **9** dissolved in 780 mL of *tert*-butyl alcohol over a 2-min period producing a muddy brown-green solution. After 1 h, an additional 50 mg (0.19 mmol) of ruthenium trichloride trihydrate catalyst was introduced, and the solution lightened over 0.75 h to afford a light-orange solution. After the mixture was stirred for a total of 2.5 h at room temperature, 75 mL of saturated sodium sulfite was added, immediately producing a dark-green mixture. The dark suspension was extracted with 2 × 1.1 L of diethyl ether, the combined ethereal extracts were washed with 1 × 500 mL of 0.5 N potassium hydroxide, and the combined aqueous extracts were acidified to pH 2.5 with approximately 90 mL of 3.6 M aqueous sulfuric acid in the presence of 1 L of EtOAc. The aqueous layer was washed with 1 × 0.9 L of EtOAc, and the combined EtOAc extracts were washed with 0.8 L of brine, dried (Na_2SO_4), filtered, and concentrated to afford 2.99 g (79%) of the lactonization-prone acid **10** as a clear oil. This material was azetropically dried with 3 × 10 mL of toluene and employed without hesitation in the formation of imide **11**. Data for acid **10**: IR (thin film) 3500–2350 (OH), 1715, 1472, 1465, 1415, 1285, 1255, 1095, 835, 775 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 9.70–8.80 (b s, 1 H, COOH), 3.39 (d, 2 H, *J* = 7.0 Hz, CH_2OSi) 2.48–2.30 (m, 2 H, CH_2COOH), 1.84–1.38 (m, 3 H, $\text{CH}_3\text{CHCH}_2\text{CH}_2\text{COOH}$), 0.88 (d, 3 H, *J* = 6.9 Hz, CHCH_3), 0.87 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.02 (s, 6 H, $\text{Si}(\text{CH}_3)_2$); TLC R_f = 0.05–0.30 (60% EtOAc/hexane).

[3(4S),4R,5S]-3-[4-Methyl-5-[[1,1-dimethylethyl]dimethylsilyloxy]-1-oxopentyl]-4-methyl-5-phenyl-2-oxazolidinone (11). To a cooled (-78 °C) solution of 2.80 g (11.4 mmol) of acid **10** in 85 mL of diethyl ether was added 1.66 mL (1.21 g, 11.9 mmol) of triethylamine followed by 1.40 mL (1.37 g, 11.4 mmol) of pivaloyl chloride. Triethylamine hydrochloride immediately began to precipitate and after 5 min the cooling bath was removed. The slurry was warmed to 0 °C over 30 min and was held at 0 °C for an additional 1 h. Meanwhile, a separate solution of 2.01 g (11.4 mmol) of [4R,5S]-4-methyl-5-phenyl-2-oxazolidinone in 18 mL of THF was prepared. After the oxazolidinone was cooled to -78 °C, 7.01 mL (1.62 M in hexane, 11.4 mmol) of *n*-butyllithium was added by syringe over 5 min, resulting in a pale, orange-red solution which was stirred for 10 min at -78 °C. The flask containing the mixed anhydride was in turn cooled to -78 °C, and the lithiated oxazolidinone was transferred via cannula to the slurry. After the resultant slurry was stirred for 15 min at -70 °C, the reaction mixture was warmed to 0 °C over ca. 20 min and was held at that temperature for an additional 30 min before quenching with 80 mL of water with simultaneous warming to room temperature. The layers were separated, and the aqueous layer was washed with 2 × 20 mL of EtOAc. The combined organic extracts were washed with 100 mL of 0.1 N aqueous NaHSO₄, 100 mL of saturated aqueous NaHCO₃, and 100 mL of brine, dried (Na_2SO_4), filtered, and concentrated. Purification of the concentrate by flash chromatography (8 × 24 cm of silica gel, linear gradient of 7–15% EtOAc/hexane) provided 4.32 g (94%) of imide **11** as a low-melting solid: $[\alpha]^{23}_{D46} + 27.3^\circ$ (*c* 1.79, CH_2Cl_2); IR (thin film) 3065, 2960, 2940, 2900, 2860, 1795, 1705, 1500, 1470, 1460, 1385, 1350, 1310, 1255, 1210, 1200, 1150, 1120, 1090, 1070, 1035, 1005, 990, 960, 840, 815, 770, 730, 700, 665, 640 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.48–7.28 (m, 5 H, ArH), 5.67 (d, 1 H, *J* = 7.3 Hz, OCHAr), 4.77 (quintet, *J* = 6.6 Hz, 1 H, NCHCH_3), 3.57–3.35 (m, 2 H, COCH_2O), 3.13–2.82 (highly structured multiplet, 2 H, $\text{CH}_2\text{C=O}$), 1.90–1.40 (m, 3 H, $\text{CH}_2\text{CH}_2\text{C=O}$ and CHCH_3), 0.93 (d, *J* = 6.6 Hz, 3 H, CHCH_3), 0.90 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.87 (d, *J* = 6.8 Hz, 3 H, CH_2CHN), 0.05 (s, 6 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (75.5 MHz, CDCl_3) δ 173.2, 152.9, 133.5, 128.7, 128.6, 125.7, 78.9, 68.0, 54.7, 35.4, 33.4, 27.9, 25.9, 18.3, 16.5, 14.5, -5.4; TLC R_f = 0.20 (10% EtOAc/hexane). Anal. Calcd for $\text{C}_{22}\text{H}_{35}\text{NO}_5\text{Si}$: C, 65.15; H, 8.70. Found: C, 65.43; H, 8.99.

[3(2R,3S),4R,5S]-3-[3-Hydroxy-5-[(4-methoxyphenyl)methoxy]-2-methyl-1-oxopentyl]-4-methyl-5-phenyl-2-oxazolidinone (12). To a cooled (-15 °C) solution of 7.78 g (33.4 mmol) of imide **4**²³ in 60 mL of CH_2Cl_2 was added 9.14 mL (10.1 g, 36.7 mmol) of di-*n*-butylboron triflate¹⁰⁸ followed by 5.58 mL (4.05 g, 40.0 mmol) or triethylamine. The solution turned yellow upon addition of the triflate and exothermed to +10 °C upon addition of triethylamine. After stirring at 0 °C for 15 min, the solution was cooled to -78 °C and 6.17 g (31.8 mmol) of 3-(*p*-meth-

oxybenzyloxy)propanal²⁷ in 5 mL of CH_2Cl_2 (plus a 5 mL rinse) was added via cannula. The resulting pale yellow solution was stirred at -78°C for 1.5 h, then warmed to 0°C over 30 min, and stirred at 0°C for 30 min. The reaction was quenched by the addition of 33 mL of pH 7 phosphate buffer followed by 120 mL of methanol, resulting in a homogeneous solution. After 5 min, 33 mL of 30% aqueous hydrogen peroxide in 50 mL methanol was added dropwise over a 30-min period (*caution*: initial reaction is highly exothermic). After stirring for 1 h at 0°C , the reaction mixture was concentrated by rotary evaporation. The resulting mixture was extracted with 3×100 mL of EtOAc. The individual organic extracts were washed with 100 mL of 5% aqueous NaHCO_3 and 100 mL of brine. The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The resulting semisolid was recrystallized from 1:3 diethyl ether/hexane to provide 8.80 g (65%) of aldon adduct **12**. The mother liquors were concentrated and chromatographed (5 cm \times 20 cm column, 2:1 hexane/EtOAc) to provide 3.00 g (22%) of additional product. The total yield was 11.80 g (87%) of aldon adduct **12**: mp 101–102 $^\circ\text{C}$ (diethyl ether/hexane); $[\alpha]^{24}_{546} +1.0^\circ$ (*c* 1.84, CH_2Cl_2); IR (CHCl_3) 3500 (OH), 3040, 3018, 2970, 2945, 2920, 2875, 2850, 1785, 1698, 1618, 1592, 1519, 1510, 1455, 1385, 1370, 1345, 1250, 1198, 1185, 1175, 1150, 1125, 1095, 1070, 1035, 990, 962, 825 cm^{-1} ; ^1H NMR (300 MHz , CDCl_3) δ 7.43–7.25 (m, 7 H, ArH), 6.87 (d, *J* = 6.8, 2 H, ArH), 5.63 (d, *J* = 7.2, 1 H, PhCHO), 4.76 (quint, *J* = 6.8, 1 H, CH_3CHN), 4.46 (s, 2 H, ArCH_2O), 4.17–4.10 (m, 1 H, HCOH), 3.87–3.78 (m, 1 H, CHCH_3), 3.79 (s, 3 H, CH_3O), 3.68–3.63 (m, 2 H, $\text{CH}_2\text{OCH}_2\text{Ar}$), 3.33 (d, *J* = 2.4, 1 H, OH), 1.98–1.70 (br m, 2 H, $\text{CH}_2\text{CH}_2\text{OCH}_2\text{Ar}$), 1.25 (d, *J* = 7.0, 3 H, $\text{CH}_3\text{CHC=O}$), 0.88 (d, *J* = 6.5, 3 H, CH_3CHN); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 176.1, 159.1, 152.4, 133.2, 130.1, 129.1, 128.5, 125.4, 113.6, 78.6, 72.6, 70.3, 67.7, 55.0, 54.6, 42.5, 33.7, 14.1, 11.0; TLC R_f = 0.32 (1:1 hexane/EtOAc). Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{NO}_6$: C, 67.43; H, 6.84. Found: C, 67.46; H, 6.77.

[2R,3S]-N-Methoxy-N,2-dimethyl-5-[(4-methoxyphenyl)methoxy]-3-[(triethylsilyl)oxy]pentanamide (14). To a suspension of 7.94 g (81.4 mmol) of *N,O*-dimethylhydroxylamine hydrochloride in 41 mL of THF at 0°C was added 41.0 mL (82.0 mmol) of 2.0 M trimethylaluminum in toluene over a 5-min period (*caution*: vigorous gas evolution). After the addition was complete, the cooling bath was removed and the clear solution was stirred for 30 min at room temperature. The solution was recooled to -15°C , and a solution of 11.6 g (27.1 mmol) of imide **12** in 41 mL of THF (plus a 5 mL rinse) was added via cannula. The cloudy reaction mixture was stirred at -10°C to 0°C , at which temperature gas evolved steadily and the mixture slowly cleared. After 2.5 h the solution was transferred by cannula into a mixture of 200 mL of CH_2Cl_2 and 400 mL 0.5 N aqueous HCl at 0°C . The resulting two-phase mixture was stirred at 0°C for 1 h. The layers were separated, and the aqueous layer was extracted with 4×300 mL of CH_2Cl_2 . The individual organic extracts were washed with 2×100 mL of brine, combined, dried (Na_2SO_4), filtered, and concentrated. The unpurified alcohol/oxazolidinone mixture was dissolved in 40 mL of dry dimethylformamide, and 5.01 mL (4.49 g, 29.8 mmol) of chlorotriethylsilane followed by 3.70 g (54.3 mmol) of imidazole was added. After the mixture was stirred for 30 min, 200 mL of water was added and the reaction mixture was extracted with 4×200 mL of EtOAc. The individual organic extracts were washed with 100 mL of 0.5 N aqueous NaHSO_4 and 100 mL of brine, then combined, dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by chromatography (10 cm \times 19 cm column, 2:1 hexane/EtOAc, followed by pure EtOAc) gave 10.46 g (91% for two steps) of amide **14** as a colorless oil, followed by 4.70 g (98%) of oxazolidinone auxiliary. Data for amide **14**: $[\alpha]^{23}_{546} -7.6^\circ$ (*c* 0.78, CH_2Cl_2); IR (film) 3040, 2960, 2945, 2920, 2885, 2860, 1665, 1618, 1590, 1520, 1465, 1420, 1390, 1305, 1250, 1175, 1105, 1090, 1005, 850, 825, 755, 745 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.24 (d, *J* = 8.8, 2 H, ArH), 6.85 (d, *J* = 8.8, 2 H, ArH), 4.40 (s, 2 H, ArCH_2O), 4.02 (dt, *J* = 7.6, 5.5, 1 H, CHOTES), 3.80 (s, 3 H, CH_3OAr), 3.60 (s, 3 H, CH_3ON) δ 3.57–3.45 (highly structured m, 2 H, $\text{CH}_2\text{OCH}_2\text{Ar}$), 3.14 (s, 3 H, CH_3N), 3.05–2.95 (br m, 1 H, CHCH_3), 2.92–2.72 (m, 2 H, $\text{CH}_2\text{CH}_2\text{O}$), 1.14 (d, *J* = 6.9, 3 H, CHCH_3), 0.95 (t, *J* = 7.9, 9 H, $(\text{CH}_3\text{CH}_2)_3\text{Si}$), 0.59 (q, *J* = 7.9, 6 H, $(\text{CH}_3\text{CH}_2)_3\text{Si}$); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 176.1, 159.1, 130.7, 129.2, 113.7, 72.5, 71.6, 66.4, 61.2, 55.2, 41.6, 35.8, 32.2, 14.3, 6.9, 5.1; TLC R_f = 0.33 (2:1 hexane/EtOAc). Anal. Calcd for $\text{C}_{22}\text{H}_{39}\text{NO}_5\text{Si}$: C, 62.08; H, 9.24. Found: C, 61.98; H, 9.36.

[3(2R,3S,4E),4R,5S]-3-(3-Hydroxy-2-methyl-1-oxo-4-heptenyl)-4-methyl-5-phenyl-2-oxazolidinone (15). To a cooled (-15°C) solution of 25.2 g (108 mmol) of imide **4**²³ in 200 mL of CH_2Cl_2 was added 29.6 mL (32.6 g, 119 mmol) of di-*n*-butylboron triflate¹⁰⁸ via syringe followed by 18.1 mL (13.1 g, 130 mmol) of triethylamine. The solution turned yellow upon addition of the triflate and exothermed to 10°C upon addition of triethylamine. After stirring at 0°C for 15 min, the solution was cooled to -78°C and 10.6 mL (9.09 g, 108 mmol) of *trans*-2-pen-

tenal in 10 mL (plus a 5 mL rinse) of CH_2Cl_2 was added via cannula. The resulting pale yellow solution was stirred at -78°C for 1.5 h, warmed to 0°C over 30 min, and stirred at 0°C for 30 min. The reaction was quenched by addition of 100 mL of pH 7 phosphate buffer followed by 450 mL of methanol to result in a homogeneous solution. After 5 min, 100 mL of 30% aqueous hydrogen peroxide in 150 mL of methanol was added dropwise over 30 min (*caution*: initial reaction is highly exothermic). After stirring for 1 h at 0°C , the reaction mixture was concentrated by rotary evaporation. The resulting mixture was extracted with 3×200 mL of EtOAc. The individual organic extracts were washed with 200 mL of 5% aqueous NaHCO_3 and 200 mL of brine. The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The resulting semisolid was recrystallized from 1:3 diethyl ether/hexane to provide 27.0 g (79%) of aldon adduct **15**. The mother liquors were concentrated and chromatographed (8 \times 20 cm column, 3:1 hexane/EtOAc) to provide 4.60 g (13%) of additional product. The total yield was 31.6 g (92%) of aldon adduct **15**: mp 95.5–96 $^\circ\text{C}$ (hexane/diethyl ether); $[\alpha]^{24}_{546} +4.82^\circ$ (*c* 1.98, CH_2Cl_2); IR (CDCl_3) 3530, 3038, 3018, 2990, 2975, 2880, 1783, 1695, 1500, 1448, 1385, 1368, 1345, 1300, 1235, 1195, 1150, 1125, 1092, 1069, 1030, 1002, 990, 970, 960, 910, 700 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.46–7.30 (m, 5 H, ArH), 5.82 (ddt, *J* = 15.4, 6.2, 1.2, 1 H, $\text{CH}_2\text{CH=CH}$), 5.67 (d, *J* = 6.8, 1 H, ArCHO), 5.48 (ddt, *J* = 15.4, 6.3, 1.5, 1 H, $\text{CH}_2\text{CH=CH}$), 4.79 (quint, *J* = 6.8, 1 H, CHN), 4.83–4.75 (m, 1 H, CHO), 3.87 (qd, *J* = 7.0, 3.6, 1 H, $\text{CH}_3\text{C=O}$), 2.78 (d, *J* = 3.0, 1 H, OH), 2.09 (quint, *J* = 7.2, 2 H, CH_2CH_3), 1.23 (d, *J* = 7.0, 3 H, $\text{CH}_3\text{CHC=O}$), 1.02 (t, *J* = 7.2, 3 H, CH_2CH_3), 0.89 (d, *J* = 6.8, 3 H, CH_3CHN); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 176.3, 152.7, 134.9, 133.2, 128.7, 128.6, 128.1, 125.6, 78.9, 72.8, 54.8, 42.9, 25.2, 14.3, 13.3, 11.0. TLC R_f = 0.25 (3:1 hexane/EtOAc). Anal. Calcd for $\text{C}_{24}\text{H}_{23}\text{NO}_4$: C, 68.12; H, 7.30. Found: C, 68.09; H, 7.26.

[2S,3S,4E]-2-Methyl-4-heptene-1,3-diol (16). To a solution of 15.0 g (47.4 mmol) of aldon adduct **15** in 150 mL of THF was added 4.07 mL (42.7 g, 71.1 mmol) of acetic acid followed by 12.8 mL (9.56 g, 52.1 mmol) of tri-*n*-butylborane. The solution exothermed to $+30^\circ\text{C}$. After stirring at 20°C for 1.25 h, the solution was cooled to 0°C and 47.7 mL (2 M in THF, 94.8 mmol) of lithium borohydride was added via an addition funnel. The resulting colorless solution was stirred at 0°C for 1.25 h, then quenched by addition of 175 mL of methanol (*caution*: vigorous, exothermic hydrogen evolution). After 5 min at 0°C , 100 mL of pH 7 phosphate buffer was added followed by dropwise addition of 90 mL of 30% aqueous hydrogen peroxide (*caution*: initial reaction is highly exothermic). After stirring for 1 h at 20°C the reaction mixture was concentrated by rotary evaporation. The resulting mixture was extracted with 5×150 mL of CH_2Cl_2 . The individual organic extracts were washed with 100 mL of brine. The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in approximately 150 mL of hot 2:1 EtOAc/hexane. Upon cooling, 4.10 g (49%) of the oxazolidinone auxiliary crystallized and was filtered from the solution. The mother liquor was concentrated and chromatographed twice (8 cm \times 20 cm column, 2:1 CH_2Cl_2 /EtOAc) to provide an additional 3.40 (40%) of auxiliary and 6.04 g (85%) of diol **16**. The diol was contaminated with 2–5% (NMR analysis) of the oxazolidinone. Kugelrohr distillation provided a sample contaminated with less than 1% of the oxazolidinone: bp 130 $^\circ\text{C}$ (0.05 mm); $[\alpha]^{23}_{546} -5.12^\circ$ (*c* 0.61, CH_2Cl_2); IR (film) 3350, 2975, 2940, 2885, 1670, 1460, 1380, 1110, 1080, 1030, 1010, 970, 895, 845 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 5.73 (dt, *J* = 15.4, 6.2, 1 H, $\text{CH}_2\text{CH=CH}$), 5.53 (dd, *J* = 15.4, 6.9, 1 H, $\text{CH}_2\text{CH=CH}$), 4.24–4.22 (m, 1 H, CHO), 3.72–3.58 (m, 2 H, CH_2OH), 2.51–2.35 (br m, 2 H, 2OH), 2.08 (quint, *J* = 7.0, 2 H, CH_2CH_3), 1.98–1.90 (m, 1 H, CHCH_3), 1.00 (t, *J* = 7.7, 3 H, CH_2CH_3), 0.86 (d, *J* = 7.0, 3 H, CHCH_3); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 134.5, 129.2, 75.8, 66.1, 40.2, 25.2, 13.5, 11.4; TLC R_f = 0.23 (2:1 CH_2Cl_2 /EtOAc), 0.24 (4:1 diethyl ether/hexane); oxazolidinone R_f 0.30, 0.10, respectively.

[2S,3S,4E]-2-Methyl-1-[tris(1-methylethyl)siloxy]-4-hepten-3-ol (17). To a clear solution of 6.04 g (41.9 mmol) of diol **16** in 50 mL of CH_2Cl_2 ¹¹⁷ was added 5.75 g (47.0 mmol) of (*N,N*-dimethylamino)pyridine followed by 9.14 mL (8.24 g, 42.7 mmol) of chlorotriisopropylsilane. After the mixture was stirred at 20°C for 12 h, 50 mL of aqueous 0.25 M potassium dihydrogen phosphate was added. The resulting mixture was partitioned between 50 mL of water and 50 mL of CH_2Cl_2 . The aqueous layer was extracted with 5 \times 50 mL of CH_2Cl_2 . The organic layers were combined, dried (Na_2SO_4), filtered, concentrated, and chromatographed (7 \times 20 cm column, 15:1 hexane/EtOAc), to afford 1.4 g (8%) of disilylated diol, 1.1 g (20%) of recovered diol **16**, and 8.0

(117) Complete removal of the oxazolidinone from this diol is crucial. Subsequent experiments employing purer diol showed considerable reduction of unreacted diol and disilylation.

g (63%) of silyl ether **17**. The disilylated material was desilylated with 2.45 g (9.19 mmol, 3 equiv) of tetra-*n*-butylammonium fluoride trihydrate in 9 mL of THF. After stirring at 25 °C for 2 h, the reaction was quenched with 20 mL of water. The yellow mixture was extracted with 5 × 20 mL of CH₂Cl₂. The organic layers were combined, dried (Na₂SO₄), filtered, and concentrated. The unpurified diol was chromatographed (3 × 20 cm column, 2:1 CH₂Cl₂/EtOAc), combined with the recovered diol described above, and resubjected to the above silylation conditions to afford 2.52 g (64%) of silyl ether **17**. The total yield of silyl ether **17** was 9.60 g (83%); bp 120 °C (0.01 mm); [α]²⁴₅₄₆ -1.3° (c 1.75, CH₂Cl₂); IR (film) 3450, 2870, 2850, 2900, 2875, 1465, 1395, 1385, 1250, 1105, 1070, 1015, 998, 970, 920, 885, 785, 735, 680 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 5.74 (ddt, *J* = 15.3, 6.3, 1.2, 1 H, CH₂CH=CH), 5.50 (ddt, *J* = 15.3, 6.3, 1.5, 1 H, CH₂CH=CH), 4.25–4.15 (m, 1 H, CHO), 3.80–3.70 (m, 2 H, CH₂OTIPS), 3.42 (d, *J* = 5.1, 1 H, OH), 2.07 (pm, *J* = 7.5, 2 H, CH₂CH₃), 1.97–1.89 (m, 1 H, CH₃), 1.18–1.02 (br m, 21 H, ((CH₃)₂CH₂Si)), 1.00 (t, *J* = 7.5, 3 H, CH₂CH₃), 0.87 (d, *J* = 7.7, 3 H, CHCH₃); ¹³C NMR (CDCl₃, 75.5 MHz) δ 133.7, 129.2, 75.8, 67.7, 40.2, 25.4, 18.0, 13.6, 11.8, 11.5; MS (70 eV) *m/e* 257 (M⁺ - C₃H₇, 17), 131 (53), 119 (100), 103 (17), 75 (15), 61 (10); TLC *R*_f = 0.25 (15:1 hexane/EtOAc). Anal. Calcd for C₁₇H₃₆O₂Si: C, 67.94; H, 12.07. Found: C, 67.86; H, 12.14.

[2S,2(4R,6S)]-[2-(2,2-Dimethyl-4-ethyl-1,3-dioxan-6-yl)propyl]-oxytris(1-methylethyl)silane (**18**). A cooled (4 °C), mechanically stirred solution of 13.7 g (45.6 mmol) of allylic alcohol **17** in 85 mL of THF and 285 mL of aqueous 0.25 M potassium dihydrogen phosphate was treated with 34.7 g (137 mmol) of iodine dissolved in 200 mL of THF in one portion. After the dark purple solution was stirred at 4 °C for 2 h, saturated aqueous sodium sulfite was added until the reaction turned white. The resulting mixture was extracted with 5 × 400 mL of EtOAc. The individual organic extracts were washed with 100 mL of brine, combined, dried (Na₂SO₄), filtered, and concentrated. The clear yellow residue (*R*_f (iodide) = 0.14, *R*_f (allyl alcohol) = 0.44, 6:1 hexane/EtOAc) was immediately dissolved in 100 mL of toluene and 14.7 mL (15.9 g, 54.7 mmol) of freshly distilled tri-*n*-butyltin hydride was added. The resulting colorless solution was stirred at 25 °C overnight (12 h), concentrated by rotary evaporation and chromatographed (*R*_f (iodide) = 0.48, *R*_f (diol) = 0.22, 8 cm × 30 cm column, 4:1 hexane/EtOAc) to remove most of the tin species. The resulting pale yellow oil was dissolved in 100 mL of 2,2-dimethoxypropane, and 3 mg of toluenesulfonic acid monohydrate was added. The clear solution was stirred at 25 °C for 1.5 h, then concentrated by rotary evaporation and chromatographed (8 × 22 cm column, 97:3 hexane/EtOAc) to afford 8.12 g (67%) of acetonide **18**: bp 110 °C (0.04 mm); [α]²⁴₅₄₆ -20.1° (c 0.870, CH₂Cl₂); IR (film) 2990, 2970, 2950, 2900, 2885, 1458, 1380, 1370, 1228, 1180, 1160m, 1140, 1105, 1068, 1045, 1030, 1015, 995, 950, 920, 905, 885, 970, 795, 680, 660 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 3.82 (dt, *J* = 9.8, 6.2, 1 H, CH₂CHOC(CH₃)), 3.69–3.55 (m, 3 H, CH₂O, CH₂CHOCH₂), 1.81–1.71 (m, 1 H, one of CHOC₂CHO), 1.66–1.36 (m, 4 H, one of CHOCH₂CHO, CHCH₃, CH₂CH₃), 1.32 (s, 6 H, (CH₃)₂C), 1.13–1.02 (m, 21 H, ((CH₃)₂CH₂Si)), 0.95 (d, *J* = 6.8, 3 H, CH₃CH), 0.91 (t, *J* = 7.3, 3 H, CH₃CH₂); ¹³C NMR (CDCl₃, 75.5 MHz) δ 99.9, 68.3, 67.0, 65.0, 40.8, 36.2, 28.9, 24.7, 24.5, 18.0, 12.2, 12.0, 9.69; *R*_f = 0.25 (97:3 hexane/EtOAc). Anal. Calcd for C₂₀H₄₂O₃Si: C, 66.98; H, 11.80. Found: C, 66.92; H, 11.93.

[2S,2(4R,6S)]-2-(2,2-Dimethyl-4-ethyl-1,3-dioxan-6-yl)propan-1-ol (**19**). To a solution of 8.97 g (25.0 mmol) of silyl ether **18** in 33 mL of THF was added 15.8 g (50.0 mmol) of tetra-*n*-butylammonium fluoride trihydrate in 50 mL of THF in one portion. The clear yellow solution was stirred at 25 °C for 1 h before adding 125 mL of water. The reaction mixture was extracted with 4 × 200 mL of EtOAc. The organic layers were combined, dried over potassium carbonate, filtered, concentrated, and chromatographed (7 cm × 22 cm column; 8:1:1 CH₂Cl₂/EtOAc/hexane) to afford 5.00 g (99%) of alcohol **19**. (Note: This alcohol was not stable on storage due to facile acetonide migration): [α]²⁴₅₄₆ -50.6° (c 1.70, CH₂Cl₂); IR (film) 3400, 2990, 2970, 2940, 2895, 1460, 1380, 1228, 1180, 1155, 1130, 1100, 1035, 995, 950, 900, 860 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 3.94 (ddd, *J* = 9.9, 6.1, 4.5, 1 H, CH₂CHOC(CH₃)), 3.75–3.60 (m, 2 H, CH₂OH), 3.60–3.48 (m, 1 H, CH₂CHOCH₂), 3.70 (br s, 1 H, OH), 1.95–1.83 (m, 2 H, CHOCH₂CHO), 1.60–1.37 (m, 3 H, CHCH₃, CH₂CH₃), 1.33 (s, 3 H, one of (CH₃)₂C), 1.32 (s, 3 H, one of (CH₃)₂C), 0.90 (t, *J* = 7.4, 3 H, CH₃CH₂), 0.88 (d, *J* = 7.2, 3 H, CH₃CH); ¹³C NMR (CDCl₃, 75.5 MHz) δ 100.3, 69.5, 68.4, 65.7, 38.8, 34.0, 28.8, 24.7, 11.5, 9.7; TLC *R*_f = 0.21 (8:1 CH₂Cl₂/EtOAc); MS (70 eV) *m/e* 188 (10), 187 (M⁺ - 15, 100), 143 (10), 109 (28), 85 (10), 69 (10), 59 (36).

[2R,2(4R,6S)]-2-(2,2-Dimethyl-4-ethyl-1,3-dioxan-6-yl)propanal (**20**). To a solution of 3.71 mL (5.39 g, 42.5 mmol) of oxalyl chloride in 75 mL of CH₂Cl₂ at -78 °C was added dropwise a solution of 5.32 mL (5.86 g, 75.0 mmol) of dimethyl sulfoxide in 75 mL of CH₂Cl₂. After 15 min,

a solution of 5.00 g (24.7 mmol) of alcohol **19** in 50 mL (plus a 5 mL rinse) of CH₂Cl₂ was added via cannula at a rate to maintain the internal temperature below -60 °C. After 1 h at -78 °C, 14.0 mL (10.1 g, 100 mmol) of triethylamine was added over a 3-min period. The reaction was allowed to warm to -30 °C over a 1-h period, and the resulting mixture was poured into a mixture of 300 mL of hexane and 300 mL of 0.5 N aqueous NaHSO₄. The aqueous layer was extracted with 3 × 200 mL of 9:1 CH₂Cl₂/hexane. The organic layers were washed with 100 mL of saturated aqueous NaHCO₃ and 100 mL of brine. The combined organic layers were dried (Na₂SO₄), filtered, concentrated, and chromatographed (5 cm × 20 cm column, 2:1 hexane/EtOAc) to afford 4.90 g (99%) of aldehyde **20** as an oil: [α]²³₅₄₆ -106° (c 1.33, CH₂Cl₂); IR (film) 2995, 2975, 2940, 2880, 2720, 1730, 1460, 1385, 1230, 1180, 1140, 1045, 1025, 995, 950, 850, 805 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 9.63 (d, *J* = 1.1, 1 H, CHO), 4.06 (dt, *J* = 9.5, 6.2, 1 H, CH₂CHOCH₂), 3.63–3.51 (m, 1 H, CH₂CHOCH₃), 2.40–2.31 (m, 1 H, CHCH₃), 1.70–1.30 (m, 4 H, CHOCH₂CHO, CH₂CH₃), 1.23 (s, 3 H, one of (CH₃)₂C), 1.21 (s, 3 H, one of (CH₃)₂C), 1.00 (d, *J* = 7.0, 3 H, CH₃CH), 0.80 (t, *J* = 7.4, 3 H, CH₃CH₂); ¹³C NMR (CDCl₃, 75.5 MHz) δ 203.5, 100.2, 67.9, 66.0, 50.3, 35.2, 28.5, 24.4, 9.5, 8.5; TLC *R*_f = 0.28 (8:1 hexane/EtOAc); MS (70 eV) *m/e* 201 (M⁺ + 1, 40), 185 (19), 141 (43), 100 (14), 96 (12), 95 (20), 85 (32), 59 (100), 58 (50), 57 (36), 56 (14), 55 (38).

2-Chloro-N-methoxy-N-methylacetamide (20a). To a slurry of 21.4 g (219 mmol) of *N,O*-dimethylhydroxylamine hydrochloride in 400 mL of CH₂Cl₂ at 0 °C was added 35.5 mL (34.7 g, 439 mmol) of pyridine followed by dropwise addition of 15.9 mL (22.5 g, 199 mmol) of chloroacetyl chloride over 30 min. The resulting slurry was stirred for 15 min at 0 °C followed by warming to 20 °C. After the mixture was stirred at room temperature for 18 h, 300 mL of saturated aqueous NaHCO₃ was added. The two-phase mixture was stirred for 40 min, the layers were separated, and the aqueous layer was extracted with 3 × 300 mL of CH₂Cl₂. The organic layers were individually washed with 300 mL of 6 N HCl and 300 mL of brine, combined, dried (Na₂SO₄), filtered, concentrated to a yellow solid, and distilled to provide 20.7 g (75%) of amide **20a**: mp 39.5–40.5 °C, bp 94–95 °C (9 mm); IR (film) 3000, 2975, 2940, 2910 w, 2820, 1680, 1465, 1440, 1420, 1385, 1260, 1175, 1150, 1120, 1095, 1000, 930, 920, 785, 765, 730, 645 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 4.24 (s, 2 H, CICH₂), 3.74 (s, 3 H, CH₃O), 3.23 (s, 3 H, CH₃N); ¹³C NMR (CDCl₃, 75.5 MHz) δ 166.9, 61.2, 40.4, 32.2. TLC *R*_f = 0.60 (8:1 CH₂Cl₂/EtOAc). Anal. Calcd for C₄H₈NO₂Cl: C, 34.92; H, 5.86. Found: C, 34.87; H, 5.92.

N-Methoxy-N-methyl-2-(triphenylphosphoranylidene)acetamide (20b). To a solution of 20.7 g (150 mmol) of chloroacetamide **20a** in 200 mL of acetonitrile was added 40.2 g (153 mmol) of triphenylphosphine. The resulting solution was heated at reflux for 15 h, cooled to room temperature, and concentrated by rotary evaporation. The resulting viscous residue was dissolved in 500 mL of CH₂Cl₂ and washed with 2 × 200 mL of 2 N potassium hydroxide and 200 mL of brine. The aqueous layers were extracted with 200 mL of CH₂Cl₂. The organic layers were combined, dried (Na₂SO₄), filtered, and concentrated to provide a thick oil which solidified on standing. The residue was recrystallized twice from 1:1 hexane/EtOAc to provide 45.8 g (84%) of phosphorane **20b** as pale yellow crystals: mp 183–185 °C. Analytical data from Challenger¹⁸ (mp 176–177 °C); IR (CHCl₃) 3000, 1550, 1440, 1408; ¹H NMR (CDCl₃, 300 MHz) δ 7.41–7.71 (m, 15 H, ArH), 3.73 (s, 3 H, CH₃O), 3.53 (br d, *J*_{HP} = 23, 1 H, C=CH=O), 3.08 (s, 3 H, CH₃N); ¹³C NMR (CDCl₃, 75.5 MHz) δ 176.5 (d, *J*_{CP} = 11), 133.0 (d, *J*_{CP} = 10.7), 131.5 (d, *J*_{CP} = 2.6), 128.5 (d, *J*_{CP} = 12.5), 128.2 (d, *J*_{CP} = 91), 60.9, 35.6, 33.3 (d, *J*_{CP} = 126.2). Anal. Calcd for C₂₂H₂₁NO₂P: C, 72.91; H, 5.84. Found: C, 72.81; H, 6.04.

[2E,4S,4(4R,6S)]-N-Methoxy-N-methyl-4-(2,2-dimethyl-4-ethyl-1,3-dioxan-6-yl)pent-2-enamide (21). A solution of 4.90 g (24.5 mmol) of aldehyde **20** and 18.2 g (50.0 mmol) of phosphorane **20b** in 35 mL of CH₂Cl₂ was stirred at 25 °C for 12 h, then concentrated and chromatographed (7 × 18 cm column, 3:1 hexane/EtOAc) to afford 6.68 g (95%) of amide **21**: [α]²³₅₄₆ -57.9° (c 1.76, CH₂Cl₂); IR (CHCl₃) 2990, 2970, 2945, 2885, 1670, 1640, 1445, 1415, 1380, 1228, 1180, 1130, 1125, 1045, 995, 950, 885, 855, 835, 800, 710; ¹H NMR (CDCl₃, 300 MHz) δ 6.90 (dd, *J* = 15.5, 7.9, 1 H, C=CHCH), 6.42 (dd, *J* = 15.5, 0.7, 1 H, C=CHCO), 3.70 (s, 3 H, CH₃ON), 3.69–3.60 (m, 2 H, 2 CHO), 3.24 (s, 3 H, CH₃N), 2.42 (hex, *J* = 7.9, 1 H, CHCH₃), 1.69–1.36 (br m, 4 H, 2-CH₂), 1.34 (s, 3 H, one of (CH₃)₂C), 1.33 (s, 3 H, one of (CH₃)₂C), 1.10 (d, *J* = 7.7, 3 H, CH₃CH), 0.88 (t, *J* = 7.4, 3 H, CH₃CH₂); ¹³C NMR (CDCl₃, 75.5 MHz) δ 166.5, 148.0, 118.9, 100.0, 69.2, 67.9, 61.4, 41.6, 36.0, 32.1, 28.5, 24.4, 24.3, 15.5, 9.4; TLC *R*_f = 0.20 (3:1 hexane/EtOAc); capillary GC analysis (DB1701, 50 m,

8 psi, 200 °C isothermal) showed the amide to be a 97:3 mixture of olefin isomers (t_R , (cis) = 2.97 min; t_R (trans) = 4.02 min). Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.13, H, 9.54. Found: C, 63.10; H, 9.51.

[4S,4(4S,6R)]-N-Methoxy-N-methyl-4-(2,2-dimethyl-6-ethyl-1,3-dioxan-4-yl)pentanamide (22). A solution of 6.68 g (23.4 mmol) of amide 21 and 0.350 g of 5% Pd/C in 78 mL of EtOAc was stirred vigorously under 1 atm of hydrogen. The solution was stirred at 25 °C until capillary gas chromatographic analysis showed the disappearance of starting material (6 h, DB-1701, 50 m, 8 psi, 200 °C isothermal t_R (olefin) = 4.02 min, t_R (alkane) = 3.46 min), then filtered through Celite, and concentrated to afford 6.25 g (93%) of amide 22: $[\alpha]^{23}_{D46}$ -44.4° (c 1.57, CH_2Cl_2); IR (CHCl₃) 2995, 2975, 2950, 2890, 1675, 1470, 1420, 1382, 1230, 1180, 1155, 1140, 1050, 1030, 1000, 950, 875; ¹H NMR (CDCl₃, 300 MHz) δ 3.68 (s, 3 H, CH₃ON), 3.67–3.60 (m, 1 H, CH₂CHOCH₂), 3.57 (dt, J = 9.7, 6.4, 1 H, CH₂CHOCHCH₃), 3.17 (s, 3 H, CH₃N), 2.47–2.40 (m, 2 H, CH₂CO), 1.88–1.65 (m, 2 H, CH₂), 1.55–1.32 (m, 5 H, 2 CH₂, CHCH₃), 1.32 (s, 3 H, one of (CH₃)₂C), 1.31 (s, 3 H, one of (CH₃)₂C), 0.92 (d, J = 6.6, 3 H, CH₃CH), 0.90 (t, J = 7.4, 3 H, CH₃CH₂); ¹³C NMR (CDCl₃, 75.5 MHz) δ 174.5, 99.8, 69.8, 68.1, 61.0, 37.3, 35.6, 32.2, 29.5, 28.7, 26.8, 24.6, 24.3, 14.7, 9.5; TLC R_f = 0.20 (3:1 hexane/EtOAc). Anal. Calcd for $C_{15}H_{29}NO_4$: C, 62.69; H, 10.17. Found: C, 62.47; H, 10.28.

[5S,5(4S,6R)]-5-(2,2-Dimethyl-6-ethyl-1,3-dioxan-4-yl)-2-hexanone (23). To a cooled (~78 °C) solution of 5.46 g (19.0 mmol) of amide 22 in 125 mL of THF was added 16.1 mL (20.9 mmol) of methyl lithium (1.30 M, halide-free in diethyl ether) over a 10-min period. After 15 min, the reaction mixture was transferred via cannula into a well-stirred mixture of 350 mL of saturated aqueous NH₄Cl and 100 mL of diethyl ether at 0 °C. The mixture was extracted with 4 × 200 mL of EtOAc. The organic layers were combined, dried (Na₂SO₄), filtered, concentrated, and chromatographed (8 × 26 cm column, 4:1 hexane/EtOAc) to afford 4.26 g (93%) of ketone 23 as a clear fluid oil: $[\alpha]^{24}_{D46}$ -53.0° (c 1.99, CH_2Cl_2); IR (film) 2990, 2970, 2940, 2885, 1725, 1465, 1415, 1380, 1320, 1230, 1180, 1140, 1045, 990, 950, 900, 870 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 3.70–3.55 (m, 2 H, 2HCO), 2.58–2.35 (m, 2 H, CH₂C=O), 2.16 (s, 3 H, CH₃C=O), 1.84–1.38 (m, 7 H), 1.35 (s, 6 H, (CH₃)₂C), 0.93 (t, J = 7.4, 3 H, CH₂CH₃), 0.90 (d, J = 7.0, 3 H, CHCH₃); ¹³C NMR (CDCl₃, 75.5 MHz) δ 199.7, 99.9, 69.9, 68.2, 41.3, 37.1, 35.6, 29.7, 28.7, 25.8, 24.6, 24.4, 14.8, 9.7; TLC R_f = 0.36 (4:1 hexane/EtOAc). Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.40; H, 10.90.

Identical material was obtained by hydrogenation of 1.53 g (6.36 mmol) of enone 21a in EtOAc as described for unsaturated amide 21 providing 1.52 g (99%) of ketone 23.

[5S,5(4S,6R)]-5-(2,2-Dimethyl-6-ethyl-1,3-dioxan-4-yl)-2-hexanone Dimethylhydrazone (24). To a cooled (0 °C) solution of 3.85 g (16.0 mmol) of ketone 23 in 12 mL of CH₂Cl₂ was added 12.2 mL (160 mmol) of freshly distilled 1,1-dimethylhydrazine.¹⁵ Chlorotrimethylsilane (4.08 mL, 32.0 mmol) was then introduced dropwise over a 10-min period, maintaining the reaction temperature below 7 °C. The resulting white slurry was recooled to 0 °C and then was allowed to warm to ambient temperature. After 50 min at 21 °C, the slurry was recooled to 0 °C and was poured onto ca. 80 g of ice. The mixture was partitioned between 80 mL of water and 80 mL of CH₂Cl₂, the aqueous layer was extracted with 3 × 100 mL of CH₂Cl₂, and the combined organic extracts were dried (Na₂SO₄), filtered, and concentrated to afford 4.50 g (99%) of hydrazone 24 as a 4:1 E/Z mixture: IR (thin film) 2990, 2960, 2940, 2885, 2860, 2820, 2780, 1645, 1470, 1380, 1370, 1230, 1180, 1140, 1045, 1025, 990, 950 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 3.65–3.59 (m, 1 H, CH₂CHOCH₂), 3.54 (dt, J = 9.7, 6.3, 1 H, CH₂CHOCH₂), 2.41 (s, 4.8 H, (CH₃)₂N), 2.38 (s, 1.2 H, (CH₃)₂N), 2.32–2.10 (m, 2 H, CH₂CH₂), 1.93 (s, 2.4 H, CH₃C=N), 1.90 (s, 0.6 H, CH₃C=N), 1.75–1.40 (m, 6 H), 1.31 (s, 6 H, (CH₃)₂C), 1.35–1.20 (m, 1 H), 1.05–0.85 (highly structured m, 6 H, CHCH₃, CH₂CH₃); ¹³C NMR (CDCl₃, 75.5 MHz) δ 167.2, 99.7, 69.6, 68.0, 47.2, 46.7, 37.2, 36.4, 35.7, 28.9, 28.6, 24.4, 24.2, 16.1, 14.6, 9.5. The minor isomer had additional signals at 69.7, 69.1, 37.4, 35.5, 28.8, 22.8, 14.4; TLC R_f = 0.18 (2:1 hexane/EtOAc).

[3S,4R,6Z,10S,10(4R,6S)]-10-(2,2-Dimethyl-4-ethyl-1,3-dioxan-6-yl)-7-(2,2-dimethylhydrazino)-1-[(4-methoxyphenyl)methoxy]-4-methyl-3-(triethylsiloxy)-6-undecen-5-one (25a). To a solution of 2.79 mL (2.01 g, 19.9 mmol) of diisopropylamine in 8 mL of THF at -30 °C was added 12.0 mL (17.7 mmol) of methyl lithium (1.48 M in diethyl ether, halide-free) over a 45-s period. The resulting colorless solution was warmed to 0 °C, stirred until methane evolution ceased (ca. 5 min), and was recooled to -5 °C. In a separate flask, 4.50 g (15.8 mmol) of hydrazone 24 was azeotropically dried by addition and evaporation of 2 × 10 mL of toluene. The hydrazone was dissolved in 4 mL of THF and was transferred by cannula into the lithium diisopropylamide solution over a 7-min period (1 mL of THF rinse). The resulting bright yellow solution

was stirred for 35 min at 0 °C and was cooled to -78 °C.

In a third flask, 7.41 g (17.4 mmol) of amide 14 was azeotropically dried by addition and evaporation of 2 × 10 mL of toluene. The amide was dissolved in 12 mL of THF and was cooled to -55 °C. The cooled (-78 °C) hydrazone enolate solution was then transferred by cannula into the cooled amide solution over a 4-min period, and the resulting yellow solution was stirred for 19.5 h at -45 °C. The reaction mixture was further cooled to -78 °C and was transferred by cannula into a rapidly stirred, 0 °C biphasic mixture consisting of 100 mL of saturated aqueous NH₄Cl and 100 mL of diethyl ether. After stirring for 10 min, the mixture was warmed to room temperature and was separated. The aqueous layer was extracted with 3 × 100 mL of EtOAc, and the combined organic extracts were dried (Na₂SO₄), filtered, concentrated, and purified by flash chromatography (8 × 26 cm of silica gel, linear gradient of 18–25% EtOAc/hexane) to give 9.22 g (90%) of the vinylogous amide 25a as a yellow oil: $[\alpha]^{23}_{D46}$ -78.6° (c 2.36, CH_2Cl_2); IR (thin film) 2995, 2960, 2940, 2920, 2880, 2790, 1610, 1575, 1518, 1460, 1380, 1370, 1305, 1250, 1230, 1175, 1095, 1045, 920, 850, 820, 735 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 11.24 (s, 1 H, NH), 7.27 (d, J = 7.8, 2 H, ArH), 6.86 (d, J = 7.8, 2 H, ArH), 4.86 (s, 1 H, C=C), 4.40 (s, 2 H, CH₂Ar), 4.03–3.99 (m, 1 H, CHOTES), 3.80 (s, 3 H, CH₃OAr), 3.75–3.45 (m, 4 H, CH₂OAr, 2 CHO), 2.52 (s, 6 H, (CH₃)₂N), 2.45–2.35 (m, CH₂C=C), 2.30–2.20 (m, 1 H, CHC=O), 1.90–1.38 (m, 9 H), 1.33 (s, 3 H, one of (CH₃)₂C), 1.32 (s, 3 H, one of (CH₃)₂C), 1.10 (d, J = 6.8, 3 H, CH₂CHC=O), 0.93 (t, J = 7.7, 9 H, (CH₃CH₂)₂Si), 0.95–0.85 (m, 6 H, CH₂CHCH₃, CH₂CH₃), 0.56 (q, J = 7.7, 6 H, (CH₃CH₂)₂Si); ¹³C NMR (CDCl₃, 75.5 MHz) δ 199.6, 167.2, 159.2, 130.9, 129.1, 113.8, 100.0, 92.5, 72.5, 72.4, 69.8, 68.3, 67.0, 55.2, 50.9, 48.7, 37.6, 35.8, 35.6, 31.2, 29.5, 28.9, 24.7, 24.5, 14.8, 13.3, 9.7, 6.9, 5.2; TLC R_f = 0.25 (3:1 hexane/EtOAc). Anal. Calcd for $C_{36}H_{64}N_2O_6Si$: C, 66.62; H, 9.94. Found: C, 66.65; H, 9.87.

[2S,3R,6R,8S,8(2R),9S]-3,9-Dimethyl-8-(2-hydroxybutyl)-2-[2-[(4-methoxyphenyl)methoxyethyl]-1,7-dioxaspiro[5.5]undecan-4-one (26). To a solution of 81 mL of 95:5 acetonitrile/concentrated aqueous hydrofluoric acid (47%) was added 9.0 mL of deionized water. This solution was added to 9.22 g (14.7 mmol) of vinylogous amide 25a and the resulting clear solution was stirred at room temperature for 16.5 h. The reaction was quenched by cautious addition of 80 mL of saturated aqueous NaHCO₃ and was partitioned between 200 mL of water and 300 mL of EtOAc. The aqueous layer was extracted with 3 × 150 mL of EtOAc, and the combined organic extracts were washed with 200 mL of brine, dried (Na₂SO₄), filtered, and concentrated. Purification of the residue by flash chromatography (10 × 20 cm of silica gel, linear gradient of 25–30% EtOAc/hexane) afforded 5.67 g (92%) of spiroketal 26 as a clear oil: $[\alpha]^{23}_{D46}$ -108° (c, 2.44, CH_2Cl_2); IR (film) 3550, 2970, 2940, 2890, 2840, 1720, 1618, 1590, 1520, 1510, 1465, 1410, 1390, 1375, 1305, 1255, 1220, 1180, 1155, 1095, 1060, 1040, 985, 960, 915, 850, 820, 735 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.27 (d, J = 7.7, 2 H, ArH), 6.90 (d, J = 7.7, 2 H, ArH), 4.49 (d, J = 8.0, 1 H, one of CH₂Ar), 4.48 (d, J = 8.0, 1 H, one of CH₂Ar), 4.24–4.19 (m, 1 H, ArOCH₂CH₂CHO), 3.95 (dm, J = 9.5, 1 H, HOCH₂CH₂CHO), 3.80 (s, 3 H, CH₃OAr), 3.76–3.70 (m, 1 H, one of ArOCH₂), 3.62–3.52 (m, 1 H, HOCH₂), 3.45–3.35 (m, 1 H, one of ArOCH₂), 3.42 (d, J = 4.5, 1 H, OH), 2.51 (d, J = 14.8, 1 H, CH_{ax}H_{eq}C=O), 2.32 (d, J = 14.8, 1 H, CH_{ax}H_{eq}C=O), 2.35–2.25 (m, 1 H, CH₂CHC=O), 2.15–2.05 (m, 1 H, (RO)₂CH₂CH_{eq}H_{ax}), 1.98–1.85 (m, 1 H, one of ArOCH₂CH₂CHO), 1.78–1.68 (m, 1 H, one of ArOCH₂CH₂CHO), 1.68–1.22 (br m, 7 H), 1.17 (dd, J = 10.6, 1.2, 1 H, one of HOCH₂CH₂CHO), 1.07 (d, J = 7.2, 3 H, CH₃CHC=O), 0.89 (d, J = 7.0, 3 H, CH₃CHCH₂CH₂), 0.83 (t, J = 7.4, 3 H, CH₃CH₂); ¹³C NMR (CDCl₃, 75.5 MHz) δ 210.0, 159.5, 129.8, 113.9, 98.9, 72.6, 68.3, 68.0, 66.1, 65.5, 55.2, 48.3, 47.6, 40.8, 31.3, 30.8, 30.5, 29.5, 26.7, 11.0, 10.4, 9.98; TLC R_f = 0.25 (9:1 CH₂Cl₂/acetone). Anal. Calcd for $C_{25}H_{38}O_6$: C, 69.10; H, 8.81. Found: C, 68.95; H, 8.76.

[2S,3R,6R,8S,8(2R),9S]-3,9-Dimethyl-8-[2-[(1-methylethyl)dioethylsilyloxy]butyl]-2-[2-(4-methoxyphenyl)methoxyethyl]-1,7-dioxaspiro[5.5]undecan-4-one (28). To a cooled (0 °C) solution of 5.66 g (13.0 mmol) of spiroketal alcohol 26 and 1.33 g (19.5 mmol) of imidazole in 24 mL of CH₂Cl₂ was added 2.68 g (16.3 mmol) of chlorodiethylsilylpropylsilane¹⁷ over a 1-min period. The resulting white slurry was warmed to room temperature and stirred for 2.6 h. After the solution was diluted with 100 mL of water and 100 mL of 3:1 hexane/CH₂Cl₂ and separated, the aqueous layer was extracted with 2 × 50 mL of 3:1 hexane/CH₂Cl₂, and the combined organic extracts were washed with 200 mL of brine, dried (Na₂SO₄), filtered, and concentrated. Purification of the residue by flash chromatography (8 × 25 cm of silica gel, linear gradient of 12–15% EtOAc/hexane) provided 7.19 g (98%) of silyl ether 28 as a clear, viscous oil: $[\alpha]^{23}_{D46}$ -75.0° (c 2.35, CH_2Cl_2); IR (thin film) 2960, 2940, 2880, 1725, 1615, 1590, 1515, 1460, 1380, 1300, 1245, 1090, 1040, 1010, 980, 880, 820, 730 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz)

7.24 (d, 2 H, $J = 8.6$ Hz, ArH), 6.86 (d, 2 H, $J = 8.6$ Hz, ArH), 4.45 (d, 1 H, $J = 11.6$ Hz, one of CH_2Ar), 4.42 (d, 1 H, $J = 11.6$ Hz, one of CH_2Ar), 4.06–4.00 (ddd, 1 H, $J = 7.5, 4.7$, and 2.9 Hz, $\text{C}_{19'}\text{-H}$), 3.79 (s, 3 H, ArOCH₃), 3.68–3.48 (m, 4 H, ArCH₂OCH₂, C₃₀-H, and C₃₂-H), 2.50 (d, 1 H, $J = 14.6$ Hz, C₂₅-H_{ax}), 2.30 (dq, 3 H, $J = 7.2$ Hz and 2.9 Hz, C₂₀-H), 2.24 (d, 1 H, $J = 14.6$ Hz, C₂₅-H_{eq}), 2.12–1.22 (m, 12 H), 1.09 (d, 3 H, $J = 7.2$ Hz, C₂₀-CH₃), 1.00–0.89 (m, 15 H), 0.84 (t, 3 H, $J = 7.4$ Hz, C₃₄-H₃), 0.58 (q, 4 H, $J = 7.7$ Hz, Si(CH₂CH₃)₂); ¹³C NMR (CDCl₃, 75.5 MHz) δ 209.9, 159.2, 130.4, 129.1, 113.8, 99.1, 72.7, 71.6, 70.1, 67.7, 67.1, 55.2, 48.3, 48.0, 39.8, 31.9, 29.9, 29.4, 29.3, 26.4, 17.4, 13.2, 11.0, 10.8, 9.0, 7.1, 4.1, 4.0; TLC $R_f = 0.30$ (20% EtOAc/hexane). Anal. Calcd for C₃₂H₅₄O₆Si: C, 68.29; H, 9.69. Found: C, 68.39; H, 9.60.

[2S,3R,4S,6R,8S,8(2R),9S]-3,9-Dimethyl-8-[2-[(1-methylethyl)diethylsilyloxy]butyl]-2-[2-[(4-methoxyphenyl)methoxyethyl]-1,7-dioxaspiro[5.5]undecan-4-ol (54) and [2S,3R,4R,6R,8S,8(2R),9S]-3,9-Dimethyl-8-[2-[(1-methylethyl)diethylsilyloxy]butyl]-2-[2-[(4-methoxyphenyl)methoxyethyl]-1,7-dioxaspiro[5.5]undecan-4-ol (29). A flask containing 3.00 g (20.0 mmol) of samarium powder was thoroughly purged with argon, and a solution of 2.80 g (10.0 mmol) of thiosulfate-washed 1,2-diidoethane in 100 mL of freshly distilled THF was added to the powder by cannula over an 8-min period with vigorous stirring. The dark-blue slurry thus obtained was stirred for an additional 1 h, stirring was terminated, and the dark-blue solution was employed within 2 h in ketone reductions.¹⁰⁷

To an argon-blanketed flask containing 6.32 g (11.2 mmol) of a solution of ketone 28 in 38 mL of THF at 23 °C was added 8.60 mL (6.75 g, 112 mmol) of freshly distilled and argon-degassed isopropyl alcohol, followed by 16.8 mL (assumed 0.10 M in THF, 1.68 mmol) of samarium diiodide. After 3 h, the dark-blue solution was diluted with 300 mL of diethyl ether and was extracted with 200 mL of saturated aqueous NaHCO₃. The aqueous layer was extracted with 2 × 100 mL of diethyl ether, and the combined organic layers were sequentially washed with 150 mL of saturated aqueous sodium sulfite and 150 mL of brine, dried (Na₂SO₄), filtered, concentrated, and purified by flash chromatography (10 × 28 cm of silica gel, linear gradient of 10–20% EtOAc/CH₂Cl₂) to afford 92.5 mg (1.5%) of axial alcohol 30, followed by 6.20 g (98%) of the desired equatorial alcohol 29 (67:1 ratio of 29/30). Data for equatorial alcohol 29: [α]_D²³ -53.5° (c 1.80, CH₂Cl₂); IR (thin film) 3620–3140, 2960, 2870, 1615, 1585, 1515, 1460, 1385, 1305, 1250, 1170, 1090, 1040, 1015, 980, 730 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.25 (d, 2 H, $J = 8.0$ Hz, ArH), 6.87 (d, 2 H, $J = 8.0$ Hz, ArH), 4.46 (d, 1 H, $J = 11.5$ Hz, one of CH₂Ar), 4.40 (d, 1 H, $J = 11.5$ Hz, one of CH₂Ar), 4.25–4.15 (m, 1 H, C₂₁-H), 3.80 (s, 3 H, ArOCH₃), 3.75–3.44 (m, 5 H, ArCH₂OCH₂, C₃₀-H, C₁₉-H, and C₃₂-H), 2.10–1.30 (m, 15 H), 1.02–0.83 (m, 22 H), 0.61 (q, 4 H, $J = 8.2$ Hz, Si(CH₂CH₃)₂); ¹³C NMR (CDCl₃, 75.5 MHz) δ 159.2, 130.7, 129.1, 113.8, 97.5, 77.2, 72.6, 71.8, 69.4, 68.1, 67.7, 67.2, 55.2, 40.2, 39.1, 38.2, 32.9, 30.0, 29.9, 29.7, 26.5, 17.4, 13.2, 11.1, 9.1, 7.1, 4.13, 4.07; TLC $R_f = 0.10$ (10% EtOAc/CH₂Cl₂). Anal. Calcd for C₃₂H₅₆O₆Si: C, 68.04; H, 9.99. Found: C, 68.05; H, 10.04.

Data for axial alcohol 30: [α]_D²³ -38.7° (c 3.00, CH₂Cl₂); IR (thin film) 3570–3460 (OH, H-bonded), 2960, 2980, 2940, 2880, 1615, 1585, 1515, 1460, 1385, 1300, 1245, 1170, 1125, 1045, 970, 725 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.24 (d, 2 H, $J = 8.7$ Hz, ArH), 6.87 (d, 2 H, $J = 8.7$ Hz, ArH), 4.46 (d, 1 H, $J = 11.5$ Hz, one of CH₂Ar), 4.42 (d, 1 H, $J = 11.5$ Hz, one of CH₂Ar), 4.28 (d, 1 H, $J = 9.7$ Hz, OH), 4.13–4.06 (m, 1 H, C₁₉-H), 3.79 (s, 3 H, ArOCH₃), 3.77–3.50 (m, 5 H, ArCH₂OCH₂, C₃₀-H, C₂₁-H, and C₃₂-H), 2.10–1.34 (m, 14 H), 1.02–0.83 (m, 19 H), 0.86 (t, 3 H, $J = 7.1$ Hz, C₃₄-CH₃), 0.60 (q, 4 H, $J = 8.2$ Hz, Si(CH₂CH₃)₂); ¹³C NMR (CDCl₃, 75.5 MHz) δ 159.2, 130.7, 129.1, 113.8, 98.3, 72.5, 71.2, 70.7, 69.7, 67.6, 63.5, 55.2, 39.8, 37.9, 35.8, 32.9, 29.8, 29.6, 29.4, 25.9, 17.4, 13.2, 10.9, 10.8, 8.9, 7.1, 4.12, 4.08; TLC $R_f = 0.37$ (10% EtOAc/CH₂Cl₂). Anal. Calcd for C₃₂H₅₆O₆Si: C, 68.04; H, 9.99. Found: C, 68.18; H, 9.87.

[1(2S,3R,4S,6R,8S,9S),2R]-1-[3,9-Dimethyl-2-[(4-methoxyphenyl)methoxyethyl]-4-[(2,2,2-trichloroethoxy)methoxy]-1,7-dioxaspiro[5.5]undecan-8-yl]-2-butoxy)(1-methylethyl)diethylsilane 31. To a cooled (0 °C) solution of 6.20 g (11.0 mmol) of spiroketal alcohol 29 and 5.18 g (24.2 mmol) of 1,8-bis(dimethylamino)naphthalene (proton sponge) in 34 mL of acetonitrile was added 2.22 mL (3.99 g, 16.5 mmol) of bromomethyl trichloroethyl ether.⁴¹ The resulting pale yellow solution was stirred at 0 °C for 3 min and was warmed to room temperature. The amine hydrobromide salt slowly precipitated as the reaction progressed. After 18.5 h at room temperature, the reaction mixture was quenched by addition of 40 mL of saturated aqueous NaHCO₃, and the biphasic mixture was stirred for 10 min. After diluting with 150 mL of CH₂Cl₂, the mixture was acidified to pH 2 with 0.1 N aqueous NaHSO₄, and the phases were separated. The aqueous layer was washed with 2 × 30 mL of CH₂Cl₂, and the combined organic extracts were washed with 100 mL

of brine, dried (Na₂SO₄), filtered, concentrated, and purified by flash chromatography (10 × 300 cm of silica gel, linear gradient of 7–10% EtOAc/hexane), affording 7.70 g (97%) of the ether 31: [α]_D²³ -56.1° (c 2.73, CH₂Cl₂); IR (thin film) 2960, 2880, 1615, 1585, 1515, 1460, 1385, 1300, 1250, 1170, 1160, 1120, 1080, 1030, 990, 965, 930, 810, 720 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.25 (d, 2 H, $J = 8.7$ Hz, ArH), 6.87 (d, 2 H, $J = 8.7$ Hz, ArH), 4.93 (s with satellites, 2 H, OCH₂O), 4.45 (d, 1 H, $J = 11.5$ Hz, one of CH₂Ar), 4.40 (d, 1 H, $J = 11.5$ Hz, one of CH₂Ar), 4.24–4.16 (m, 1 H, C₂₁-H), 4.17 (s, 2 H, OCH₂CCl₃), 3.80 (s, 3 H, ArOCH₃), 3.77–3.44 (m, 5 H, ArCH₂OCH₂, C₃₀-H, C₁₉-H, and C₃₂-H), 2.08–1.83 (m, 5 H), 1.77 (dd, 1 H, $J = 12.6$ and 4.6 Hz, C₂₅-H_{ax}), 1.75–1.35 (m, 8 H including C₂₅-H_{eq}), 1.04–0.83 (m, 22 H), 0.61 (q, 4 H, $J = 8.2$ Hz, Si(CH₂CH₃)₂); ¹³C NMR (CDCl₃, 75.5 MHz) δ 159.2, 130.7, 129.1, 113.8, 97.4, 94.0, 78.9, 73.7, 72.6, 71.8, 69.4, 67.9, 67.3, 55.3, 40.2, 36.7, 35.8, 32.9, 30.1, 29.9, 29.8, 26.5, 17.4, 13.3, 11.1, 9.1, 7.2, 4.8, 4.2, 4.1; TLC $R_f = 0.56$ (30% EtOAc/hexane). Anal. Calcd for C₃₅H₅₉Cl₃O₆Si: C, 57.88; H, 8.19. Found: C, 58.05; H, 8.26.

[2(2S,3R,4S,6R,8(2R),9S)-1-[3,9-Dimethyl-4-[(2,2,2-trichloroethoxy)methoxy]-8-[2-[(1-methylethyl)diethylsilyloxy]butyl]-1-yl]-1,7-dioxaspiro[5.5]undecan-2-yl]-1-ethanol (32). A solution of 7.60 g (10.5 mmol) of ether 31 in 83 mL of CH₂Cl₂ was treated with 4.7 mL of deionized water, and the resulting biphasic mixture was cooled to 7 °C with vigorous stirring. Solid 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 3.09 g, 13.6 mmol) was then introduced in one portion, immediately affording a black slurry intermingled with orange water droplets. After stirring for 1.1 h at 8 °C, the reaction mixture was quenched with 80 mL of saturated aqueous NaHCO₃, 200 mL of water was added, and this mixture was extracted with 3 × 200 mL of CH₂Cl₂. The combined organic extracts were washed with 300 mL of brine, dried (Na₂SO₄), filtered, and concentrated to provide a clear oil. Flash chromatography of this material (7 × 28 cm of silica gel, linear gradient of 1.8–2.5% diethyl ether/CH₂Cl₂) gave 5.98 g (94%) of the desired primary alcohol 32: [α]_D²³ -74.7° (c 1.90, CH₂Cl₂); IR (thin film) 3600–3200, 2940, 2880, 1460, 1385, 1240, 1230, 1160, 1120, 1080, 1025, 965, 810, 725 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 4.92 (s with satellites, 2 H, OCH₂O), 4.26–4.16 (dt, 1 H, $J = 11.9$ and 4.8 Hz, C₂₁-H), 4.16 (s, 2 H, OCH₂CCl₃), 3.91 (dt, 1 H, $J = 10.7$ and 2.3 Hz, C₃₀-H), 3.80–3.65 (m, 4 H, C₁₈-CH₂, C₁₉-H, and C₃₂-H), 2.87 (d, 1 H, $J = 5.4$ Hz, OH), 2.00–1.87 (m, 3 H including C₂₀-H), 1.80 (dd, 1 H, $J = 12.8$ and 4.6 Hz, C₂₅-H_{ax}), 1.70–1.37 (m, 10 H including C₂₅-H_{eq}), 1.00–0.86 (m, 22 H), 0.61 (q, 4 H, $J = 8.3$ Hz, Si(CH₂CH₃)₂); ¹³C NMR (CDCl₃, 75.5 MHz) δ 97.9, 93.9, 79.9, 73.4, 72.0, 70.5, 69.1, 61.4, 40.6, 36.7, 36.3, 35.1, 30.0, 29.9, 26.6, 17.4, 13.3, 11.0, 9.4, 7.1, 5.0, 4.3, 4.2; TLC $R_f = 0.20$ (3% diethyl ether/CH₂Cl₂). Anal. Calcd for C₂₇H₅₁Cl₃O₆Si: C, 53.50; H, 8.48. Found: C, 53.38; H, 8.50.

[2(2S,3R,4S,6R,8(2R),9S)-1-[3,9-Dimethyl-4-[(2,2,2-trichloroethoxy)methoxy]-8-[2-[(1-methylethyl)diethylsilyloxy]butyl]-1-yl]-1,7-dioxaspiro[5.5]undecan-2-yl]ethanal (33). To a solution of 325 μ L (473 mg, 3.73 mmol) of oxalyl chloride in 7.5 mL of CH₂Cl₂ at -78 °C was added dropwise 462 μ L (509 mg, 6.51 mmol) of dimethyl sulfoxide over a 5-min period. The clear solution was stirred for 10 min, and a solution of 1.13 g (1.86 mmol) of alcohol 32 in 6 mL of CH₂Cl₂ was added dropwise by cannula over a 10-min period (1.5 mL rinse, internal temperature maintained below -69 °C). After stirring for 30 min at -78 °C, the slurry was treated with 1.81 mL (1.31 g, 13.0 mmol) of triethylamine over a 1.5-min period, and the resulting clear solution was stirred for 15 min at -78 °C before being warmed to -30 °C over a 5-min period. After 5 min at -30 °C, the slurry was quenched by addition of 18 mL of 0.05 N aqueous pH 7 phosphate buffer with simultaneous removal of the cooling bath. The mixture was partitioned between 100 mL of 4:1 hexane/CH₂Cl₂ and 50 mL of water and the aqueous layer was washed with 2 × 30 mL of 4:1 hexane/CH₂Cl₂. The combined organic extracts were then extracted successively with 100 mL of 0.1 N aqueous NaHSO₄, 100 mL of saturated aqueous bicarbonate, and 100 mL of brine, and were dried (Na₂SO₄), filtered, and concentrated to afford a malodorous oil. This material was purified by flash chromatography (5 × 20 cm of silica gel, 10% EtOAc/hexane), yielding 1.04 g (94%) of the desired aldehyde 33 as a clear oil: IR (thin film) 2950, 2880, 2730, 1732, 1460, 1385, 1260, 1120, 1080, 1025, 990, 965, 810, 720 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 9.81 (dd, 1 H, $J = 2.7$ and 1.7 Hz, CHO), 4.94 (s, 2 H, OCH₂O), 4.32–4.25 (m, 2 H, C₁₉-H and C₂₁-H), 4.17 (s, 2 H, OCH₂CCl₃), 3.75–3.67 (m, 2 H, C₃₀-H and C₃₂-H), 2.70 (ddd, 1 H, $J = 16.2$, 3.9, and 1.7 Hz, one of C₁₈-CH₂), 2.36 (ddd, 1 H, $J = 16.2$, 3.9, and 1.7 Hz, one of C₁₈-CH₂), 2.05–1.96 (m, 1 H, C₂₀-H), 1.96–1.87 (m, 1 H), 1.81 (dd, 1 H, $J = 12.8$ and 4.7 Hz, C₂₅-H_{eq}), 1.68–1.32 (m, 9 H including C₂₅-H_{ax}), 1.05–0.86 (m, 22 H), 0.61 (q, 4 H, $J = 8.6$ Hz, Si(CH₂CH₃)₂); TLC $R_f = 0.24$ (10% EtOAc/hexane).

[**3[2R,2[1S,3R,4S,6R,8S,8(2R),9S],4S,5S]-3-[2-[3,9-Dimethyl-4-[(2,2,2-trichloroethoxy)methoxy]-8-[2-[(1-methylethyl)diethylsilyl]oxy]but-1-yl]-1,7-dioxaspiro[5.5]undecan-2-yl]-1-hydroxyeth-1-yl]-3-[4-methyl-5-[(1,1-dimethylethyl)dimethylsilyl]-1-oxopentyl]-4-methyl-5-phenyl-2-oxadimineone (34).** To a cooled (-78°C) solution of 3.87 g (9.54 mmol) of imide 11 in 37 mL of CH_2Cl_2 was added 1.47 mL (1.06 g, 10.6 mmol) of triethylamine followed by 2.32 mL (2.54 g, 9.28 mmol) of di-n-butylboron triflate.¹⁰⁸ The resulting slurry was briefly warmed to -60°C , affording a homogeneous solution which was immediately recooled to -78°C and stirred for 0.5 h. After warming to 0°C over a 10-min period, the reaction mixture was stirred at 0°C for 0.8 h and recooled to -78°C before introducing a solution of 5.10 g (8.44 mmol) of aldehyde 33 in 15 mL of CH_2Cl_2 over a 7-min period (3 mL wash). The resulting solution was stirred for 1.2 h at -78°C , warmed to 0°C and stirred for an additional 0.5 h at this temperature before quenching with 12 mL of 0.05 N aqueous pH 7 phosphate buffer. After the solution was diluted with 100 mL of methanol, 10 mL of 30% aqueous hydrogen peroxide was cautiously added over 5 min while maintaining the reaction temperature below 7°C . The mixture thus produced was stirred for 50 min at 0°C . Volatiles were removed by rotary evaporation at room temperature, and the residue was diluted with 100 mL of water and extracted with 3 \times 200 mL of EtOAc. The combined organic extracts were washed with 300 mL of brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (10 \times 28 cm of silica gel, 1:1 hexane/ CH_2Cl_2 with 1% diethyl ether for 4 L, 1:2 hexane/ CH_2Cl_2 with 1% diethyl ether for 5 L, then linear gradient of 1.2–1.5% diethyl ether/ CH_2Cl_2), giving 7.40 g (87%) of the desired aldol adduct 34 as the only discernible diastereomer: $[\alpha]^{23}_{D46} -45.3^{\circ}$ (*c* 1.34, CH_2Cl_2); IR (thin film) 3600–3300, 2980–2860, 1785, 1700, 1450, 1340, 1190, 1020, 880, 840, 810, 770, 700, 665 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.45–7.25 (m, 5 H, ArH), 5.63 (d, 1 H, *J* = 7.1 Hz, ArCHO), 4.93 (d, 1 H, 7.1 Hz, one of OCH_2O), 4.90 (d, 1 H, *J* = 7.1 Hz, one of OCH_2O), 4.83 (quint, 1 H, *J* = 6.6 Hz, NCH_3), 4.45–4.35 (m, 1 H, $\text{C}_{21}\text{-H}$), 4.28–4.16 (m, 1 H, $\text{C}_{32}\text{-H}$), 4.16 (d, 1 H, *J* = 10.6 Hz, one of OCH_2CCl_3), 4.13 (d, 1 H, *J* = 10.6 Hz, one of OCH_2CCl_3), 4.15–4.05 (m, 1 H, $\text{C}_{17}\text{-H}$), 3.97 (dm, 1 H, *J* = 10.7 Hz, $\text{C}_{19}\text{-H}$), 4.88–4.73 (m, 1 H, $\text{C}_{16}\text{-H}$), 4.78–4.70 (tm, 1 H, *J* = 4.5 Hz, $\text{C}_{30}\text{-H}$), 3.50–3.43 (m, 2 H, $\text{C}_{24}\text{-CH}_2$), 3.40 (d, 1 H, *J* = 3.5 Hz, $\text{C}_{17}\text{-OH}$), 2.15–1.30 (m, 17 H), 1.01–0.85 (m, 37 H), 0.70–0.60 (q, *J* = 8.1 Hz, Si(CH_2CH_3)₂), 0.05 (s, 3 H, one of Si(CH_3)₂), 0.04 (s, 3 H, one of Si(CH_3)₂); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 175.2, 153.3, 133.4, 128.7, 125.7, 97.3, 93.9, 79.8, 78.8, 73.7, 73.6, 70.0, 69.2, 67.5, 66.4, 55.3, 46.3, 40.4, 36.8, 36.6, 36.3, 34.6, 31.7, 30.5, 30.1, 29.8, 26.7, 25.9, 18.3, 17.4, 14.4, 13.4, 11.0, 9.7, 7.1, 4.9, 4.5, 4.3, -5.4; TLC R_f = 0.05 (1:2 hexane/ CH_2Cl_2 + 1.1% diethyl ether). Anal. Calcd for $\text{C}_{49}\text{H}_{84}\text{Cl}_3\text{NO}_{10}\text{Si}_2$: C, 58.29; H, 8.39. found: C, 58.17; H, 8.45.

[**2R,2(1S,2(2S,3R,4S,6R,8S,8(2R),9S)),4S]-2-[2-[3,9-Dimethyl-4-[(2,2,2-trichloroethoxy)methoxy]-8-[2-[(1-methylethyl)diethylsilyl]oxy]but-1-yl]-1,7-dioxaspiro[5.5]undecan-2-yl]-1-hydroxyeth-1-yl]-N,4-dimethyl-5-[(1,1-dimethylethyl)dimethylsilyl]oxy]-N-methoxypentanamide (35). To a suspension of 6.42 g (65.8 mmol) of *N,O*-dimethylhydroxylamine hydrochloride in 12 mL of anhydrous THF at -30°C was added 32.9 mL (65.8 mmol) of 2.0 M trimethylaluminum in toluene over a 5-min period (*caution*: vigorous gas evolution). After the addition was complete, the cooling bath was removed, and the solution was stirred for 15 min at room temperature. The aluminum amide solution was cooled to -10°C , a solution of 7.38 g (7.31 mmol) of aldol adduct 34 in 24 mL of anhydrous THF was slowly added by cannula while maintaining the internal temperature below -8°C (gas evolution), and the resulting solution was warmed to 0°C over a 10-min period. After 2.5 h, the reaction mixture was transferred by cannula into a rapidly stirred mixture of 150 mL of CH_2Cl_2 and 150 mL of 0.1 N aqueous NaHSO_4 at 0°C , and the resulting two-phase mixture was stirred at 0°C for 20 min. After diluting with 500 mL of CH_2Cl_2 and 200 mL of water, the layers were separated, and the aqueous layer was extracted with 3 \times 150 mL of CH_2Cl_2 . The combined organic extracts were washed with 400 mL of brine, dried (Na_2SO_4), filtered, and concentrated. The resulting oil was purified by flash chromatography (10 cm \times 24 cm of silica gel, linear gradient of 12–16% EtOAc/hexane followed by EtOAc), affording 6.40 g (98%) of amide 35 as a viscous oil, followed by 1.25 g (99% recovery) of the oxazolidinone auxiliary. Data for amide 35: $[\alpha]^{23}_{D46} -41.1^{\circ}$ (*c* 1.57, CH_2Cl_2); IR (thin film) 3600–3370, 2960, 2880, 1640, 1460, 1385, 1250, 1155, 1080, 1020, 990, 970, 835, 810, 775, 740, 720 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 4.91 (s, 2 H, OCH_2O), 4.20 (dt, 1 H, *J* = 11.9 and 4.9 Hz, $\text{C}_{21}\text{-H}$), 4.15 (s, 2 H, OCH_2CCl_3), 4.03–3.94 (m, 2 H, including $\text{C}_{19}\text{-H}$), 3.77 (dt, 1 H, *J* = 6.4 and 2.2 Hz, $\text{C}_{30}\text{-H}$), 3.74–3.69 (m, 1 H), 3.71 (s, 3 H, NOCH_3), 3.52 (br s, OH), 3.46 (dd, 1 H, *J* = 9.8 and 5.0 Hz, one of CH_2OTBS), 3.41 (dd, 1 H, *J* = 9.8 and 5.5 Hz, one of CH_2OTBS), 3.20 (s, 3 H, NCH_3), 3.07–3.00 (m, 1 H, $\text{C}_{16}\text{-H}$), 2.05–1.90 (m, 2 H including $\text{C}_{20}\text{-H}$), 1.76 (dd, 1 H, *J* = 12.9 and 4.8 Hz,**

$\text{C}_{25}\text{-H}_{eq}$), 1.74–1.31 (m, 15 H), 0.97 (d, 3 H, *J* = 6.6 Hz, CHCH_3), 0.95–0.86 (m, 19 H), 0.88 (s, 9 H, Si(CH_3)₃), 0.82 (d, 3 H, *J* = 6.9 Hz, CH_3CH), 0.61 (q, 4 H, *J* = 8.1 Hz, Si(CH_2CH_3)₂), 0.03 (s, 6 H, Si(CH_3)₂); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 176.1, 97.3, 97.0, 94.0, 79.9, 73.8, 72.4, 69.4, 69.1, 67.5, 66.7, 61.4, 44.0, 40.3, 38.2, 36.7, 36.6, 34.3, 32.3, 30.1, 29.8, 26.6, 25.9, 18.3, 17.8, 17.4, 13.3, 11.1, 9.3, 7.1, 4.9, 4.2, 4.1, -5.4; TLC R_f = 0.19 (15% EtOAc/hexane). Anal. Calcd for $\text{C}_{41}\text{H}_{80}\text{Cl}_3\text{NO}_9\text{Si}_2$: C, 55.11; H, 9.02. Found: C, 54.99; H, 9.03.

[**2R,2(1S,2(2S,3R,4S,6R,8S,8(2R),9S)),4S]-2-[2-[3,9-Dimethyl-4-[(2,2,2-trichloroethoxy)methoxy]-8-[2-[(1-methylethyl)diethylsilyl]oxy]but-1-yl]-1,7-dioxaspiro[5.5]undecan-2-yl]-1-[(4-methoxyphenyl)methoxy]eth-1-yl]-N,4-dimethyl-5-[(1,1-dimethylethyl)dimethylsilyl]oxy]-N-methoxypentanamide (36a). A cooled (0°C) solution of 3.20 mL (3.55 g, 25.7 mmol) of *p*-methoxybenzyl alcohol in 30 mL of diethyl ether was treated with 35.6 mg (0.89 mmol, 60% dispersion in oil) of sodium hydride. The resulting mixture was stirred at 0°C for 10 min (gas evolution), and 3.00 mL (4.45 g, 30.8 mmol) of freshly distilled trichloroacetonitrile was added dropwise over 2 min, affording a pale-orange solution. After 1 h, the mixture was quenched with 30 mL of saturated aqueous NaHCO_3 and was diluted with 100 mL of ether. The organic layer was dried over anhydrous potassium carbonate, filtered, and concentrated by rotary evaporation. The light-orange oil thus obtained was employed without further purification (TLC R_f = 0.40 in 20% EtOAc/hexane).**

To a solution of 1.72 g (1.92 mmol) of alcohol 35 and 2.18 g (7.70 mmol) of *p*-methoxybenzyl trichloroacetimidate in 5.0 mL of cyclohexane and 0.5 mL of carbon tetrachloride was added 30 μL (5.76 μmol) of a 0.2 M solution of trifluoromethanesulfonic acid in ether. Within 10 min, a precipitate began to form. After 6 h, an additional 70 μL (13 μmol) of ethereal triflic acid was introduced, and the mixture was stirred for another 18 h before diluting with 80 mL of ether and quenching with two 70-mL saturated aqueous bicarbonate extractions. The organic layer was then washed with 60 mL of brine, dried (Na_2SO_4), filtered, and concentrated to afford an oily white solid. Purification of this material by flash chromatography (first flash, 7 \times 24 cm of silica gel, 17% EtOAc/hexane; second flash, 6 \times 24 cm of silica gel, benzene to elute off reagent impurities, then 15–20% EtOAc/hexane) yielded 0.65 g (88% of theoretical recovery) of starting alcohol 35 followed by 1.10 g (57%) of the desired ether 36a. A single recycle provided a total of 1.48 g (77%) of 36a: $[\alpha]^{21}_{D46} -59.0^{\circ}$ (*c* 0.80, CH_2Cl_2); IR (thin film) 2930, 2900, 1665, 1605, 1515, 1465, 1385, 1305, 1250, 1100, 780, 720 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 4.91 (s, 1 H, one of OCH_2O), 4.58 (d, 1 H, *J* = 10.5 Hz, one of CH_2Ar), 4.38 (d, 1 H, *J* = 10.5 Hz, one of CH_2Ar), 4.23–4.19 (m, 1 H, $\text{C}_{21}\text{-H}$), 4.18 (d, 1 H, *J* = 11.5 Hz, one of OCH_2CCl_3), 4.14 (d, 1 H, *J* = 11.5 Hz, one of OCH_2CCl_3), 3.79 (s, 3 H, ArOCH_3), 3.78–3.69 (m, 3 H), 3.64 (s, 3 H, NOCH_3), 3.63–3.51 (m, 2 H), 3.49–3.35 (m, 3 H, including $\text{C}_{24}\text{-CH}_2\text{OTBS}$), 3.17 (s, 3 H, NCH_3), 2.13–1.10 (m, 18 H), 1.00–0.80 (m, 35 H), 0.60–0.50 (m, 4 H, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.033 (s, 3 H, Si(CH_3)₂), 0.027 (s, 3 H, Si(CH_3)₂); ^{13}C NMR (CDCl_3 , 125 MHz) δ 159.1, 130.6, 129.0, 118.7, 97.3, 93.7, 79.6, 73.4, 71.4, 71.2, 69.5, 68.9, 67.9, 61.3, 53.2, 41.8, 40.9, 36.7, 34.1, 32.5, 30.1, 29.9, 29.1, 25.9, 18.3, 17.7, 17.4, 13.2, 11.2, 9.3, 7.2, 4.8, 4.1, 4.0, -5.4; TLC R_f = 0.19 (20% EtOAc/hexane). Anal. Calcd for $\text{C}_{49}\text{H}_{88}\text{Cl}_3\text{NO}_{10}\text{Si}_2$: C, 58.05; H, 8.75. Found: C, 58.19; H, 8.84.

[**2R,2(1S,3R,4S,6R,8S,8(2R),9S),4S]-2-[2-[3,9-Dimethyl-4-[(2,2,2-trichloroethoxy)methoxy]-8-[2-[(1-methylethyl)diethylsilyl]oxy]but-1-yl]-1,7-dioxaspiro[5.5]undecan-2-yl]-1-[(4-methoxyphenyl)methoxy]eth-1-yl]-4-methyl-5-[(1,1-dimethylethyl)dimethylsilyl]oxy]pentanal (37). A cooled (-78°C) solution of 440 mg (0.404 mmol) of amide 36a in 4 mL of THF was treated with 674 μL (1.5 M in toluene, 1.01 mmol) of diisobutylaluminum hydride dropwise over a 3-min period. After 1.1 h, ca. 100 μL of acetone was introduced, and the reaction mixture was transferred by cannula (THF washes) into a rapidly stirred, 0°C mixture of 80 mL of 1:1 0.1 M aqueous sodium–potassium tartrate/diethyl ether. After the solution was warmed to room temperature and stirred for 0.2 h, an additional 100 mL of ether and 80 mL of water were added, and the layers were separated. The aqueous phase was washed with 3 \times 60 mL of ether, and the combined organic extracts were washed with 120 mL of brine, dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by flash chromatography (5 \times 21 cm of silica gel, 7% EtOAc/hexane) provided 354 mg (92%) of the desired PMB aldehyde 37 as a clear oil: IR (thin film) 2960, 2940, 2860, 2720, 1727, 1617, 1590, 1515, 1465, 1385, 1360, 1305, 1250, 1175, 1080, 835, 810, 775, 720 cm^{-1} ; ^1H NMR (benzene-d_6 , 300 MHz) δ 9.92 (d, 1 H, *J* = 1.0 Hz, CHO), 7.31 (d, 2 H, *J* = 8.5 Hz, one of ArH), 6.84 (d, 2 H, *J* = 8.5 Hz, one of ArH), 4.58 (d, 1 H, *J* = 7.1 Hz, one of CH_2Ar), 4.53 (d, 1 H, *J* = 7.1 Hz, one of CH_2Ar), 4.52 (s, 2 H, OCH_2O), 4.35 (apparent dt, 1 H, *J* = 9.5 and 5.0 Hz, $\text{C}_{21}\text{-H}$), 4.14–4.08 (m, 1 H, $\text{C}_{17}\text{-H}$), 4.02–3.80 (m, 3 H), 4.90 (s, 2 H, OCH_2CCl_3), 3.41 (d, 1 H, *J* = 6.8 Hz, $\text{C}_{24}\text{-CH}_2\text{OTBS}$), 3.33 (s, 3 H, ArOCH_3), 2.98–2.91 (m, 1 H, $\text{C}_{20}\text{-H}$),**

2.15–1.20 (m, 17 H), 1.15–0.92 (m, 34 H), 0.78–0.65 (m, 4 H, Si(CH₂CH₃)₂), 0.06 (s, 6 H, Si(CH₃)₂); TLC *R_f* = 0.24 (10% EtOAc/hexane). Anal. Calcd for C₄₇H₈₃O₉Si₂Cl₃: C, 59.13; H, 8.76. Found: C, 58.91; H, 8.69.

[6*R*-{6*a*[2*S**(*R**)*,3S**],8*B*(2*S***,3S***,5S**),9*B*,10*B*]-*α*-Ethyl-10-hydroxy-3,9-dimethyl-8-[tetrahydro-3-(hydroxymethyl)-2-methoxy-5-methyl-2*H*-pyran-2-yl]-1,7-dioxaspiro[5.5]undecane-2-ethanol (38). Preparation of stock ozone solution: CH₂Cl₂ (2 mL) was cooled to –78 °C and was saturated with ozone, producing a bright-blue solution (assumed concentration = 0.04 M).

A cooled (–78 °C) solution of 3.3 mg (3.61 μmol) of cytovaricin mixed methyl ketal 3 in 1.5 mL of methanol was charged with ca. 8 mg of powdered NaHCO₃, and ozone stock solution was introduced by cannula until a pale blue color persisted (ca. 200 μL). After an additional 2 min at –78 °C, excess ozone was removed by bubbling a stream of nitrogen through the slurry, 4.1 mg (0.108 mmol) of sodium borohydride was added, and the slurry was warmed to room temperature. After an additional 40 min, 15 mg of powdered potassium carbonate was introduced, and the mixture was stirred for 2.5 h. Methanol was removed by rotary evaporation and the residue was taken up in 15 mL of EtOAc and washed with 10 mL of water. The aqueous layer was extracted with 5 mL of EtOAc, and the combined organic layers were washed with 15 mL of brine, dried (Na₂SO₄), filtered, and concentrated. Purification of the remaining oil by flash chromatography (1 × 9 cm of silica gel, 5% methanol/CH₂Cl₂ with 2 drops of triethylamine/10 mL of eluant) gave 1.2 mg (75% from cytovaricin) of the highly acid-sensitive triol mixed methyl ketal 38 as an oil: [α]²¹_D –14° (c 0.20, benzene); IR (thin film) 3600–3150, 2980, 1450, 1390, 1335, 1310, 1240, 1230, 1180, 1160, 1125, 1080, 1025, 970, 860, 815, 725 cm^{–1}; ¹H NMR (500 MHz with COSY-90, benzene-*d*₆) δ 4.25 (apparent dt, 1 H, *J* = 11.0 and 1.6 Hz, C₃₀-*H*), 4.19 (dt, 1 H, *J* = 11.9 and 5.0 Hz, C₂₁-*H*), 3.96–3.92 (m, 1 H, C₁₉-*H*), 3.93–3.88 (m, 1 H, C₃₂-*H*), 3.72 (dd, 1 H, *J* = 11.0 and 3.9 Hz, C₂₄-H_{eq}), 3.67 (dd, 1 H, *J* = 11.0 and 5.9 Hz, one of C₁₅-CH₂OH), 3.52 (dd, 1 H, *J* = 11.0 and 3.0 Hz, one of C₁₅-CH₂OH), 3.47–3.38 (br s, 1 H, OH), 3.08 (apparent t, 1 H, *J* = 11.0 Hz, C₂₄-H_{ax}), 2.93 (s, 3 H, OCH₃), 2.27 (tt, 1 H, *J* = 13.3 and 4.5 Hz, C₂₉-*H*), 2.17 (dd, 1 H, *J* = 14.7 and 3.9 Hz, one of C₁₈-CH₂), 2.13–2.06 (br s, 1 H, OH), 1.98 (dd, 1 H, *J* = 14.7 and 7.8 Hz, one of C₁₈-CH₂), 1.84–1.80 (m, 1 H, C₂₀-*H*), 1.77–1.70 (m, 1 H, C₂₂-*H*), 1.71–1.66 (m, 2 H), 1.63–1.45 (m, 5 H, including C₃₁-CH₂), 1.43–1.21 (m, 5 H, including C₂₈-CH₂), 1.10 (t, 3 H, *J* = 7.4 Hz, C₃₄-CH₃), 0.97 (d, 3 H, *J* = 6.7 Hz, C₂₀-CH₃), 0.90 (d, 3 H, *J* = 7.0 Hz, C₂₉-CH₃), 0.70 (d, 3 H, *J* = 6.6 Hz, C₂₃-CH₃); ¹³C NMR (125.5 MHz, benzene-*d*₆) δ 100.9, 69.0, 67.7, 67.6, 67.5, 67.4, 63.6, 46.9, 43.4, 42.2, 39.2, 38.8, 36.6, 31.4, 31.2, 30.5, 30.2, 27.0, 17.2, 11.5, 10.8, 4.5; TLC *R_f* = 0.10 (60% EtOAc/hexane); MS (70 eV, FAB, *m*/*e* 444 (7, M⁺), 413 (44, M⁺ – CH₂OH), 395 (72), 377 (100).

[2*R*,2(1*S*,2(2*S*,3*R*,4*S*,6*R*,8*S*,8(2*R*),9*S*)),4*S*]-2-[2-[3,9-Dimethyl-4-[(2,2,2-trichloroethoxy)methoxy]-8-[2-[(1-methylethyl)diethylsilyl]oxy]but-1-yl]-1,7-dioxaspiro[5.5]undecan-2-yl]-1-[(4-methoxyphenyl)methoxy]eth-1-yl]-4-methyl-5-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-pentanol (39). To a solution of 198 mg (0.207 mmol) of aldehyde 37 in 2.5 mL of absolute ethanol was added 13 mg (0.34 mmol) of sodium borohydride. After 25 min at ambient temperature, the solution was quenched by pipet transfer into a separatory funnel containing 10 mL of saturated aqueous NH₄Cl, and the mixture was extracted with 2 × 10 mL of 3:1 hexane/CH₂Cl₂. The combined organic layers were washed with 15 mL of brine, dried (Na₂SO₄), filtered, and concentrated, and the resulting oil was purified by flash chromatography (2 × 17 cm of silica gel, linear gradient of 15–30% EtOAc/hexane), yielding 189 mg (95%) of the desired alcohol 39 as a clear oil: [α]²¹_D –65.5° (c 1.00, CH₂Cl₂); IR (thin film) 3600–3300, 2960, 2890, 1620, 1520, 1465, 1390, 1305, 1255, 1180, 1160, 1080, 1040, 990, 975, 840, 810, 780, 725 cm^{–1}; ¹H NMR (CDCl₃, 500 MHz) δ 7.24 (d, 2 H, *J* = 8.6 Hz, two of ArH), 6.87 (d, 2 H, *J* = 8.6 Hz, two of ArH), 4.93 (s with satellites, 2 H, OCH₂O), 4.59 (d, 1 H, *J* = 10.5 Hz, one of CH₂Ar), 4.42 (d, 1 H, *J* = 10.5 Hz, one of CH₂Ar), 4.25–4.21 (m, 1 H, C₂₁-*H*), 4.21 (d, 1 H, *J* = 11.5 Hz, one of OCH₂CCl₃), 4.17 (d, 1 H, *J* = 11.5 Hz, one of OCH₂CCl₃), 3.83–3.81 (m, 1 H, C₁₇-*H*), 3.80 (s, 3 H, OCH₃), 3.75 (d, 1 H, *J* = 10.7 Hz, one of CH₂OH), 3.73–3.61 (m, 3 H, C₃₂-*H*, C₃₀-*H*, and C₁₉-*H*), 3.57 (dd, 1 H, *J* = 10.7 and 4.0 Hz, one of CH₂OH), 3.48–3.37 (m, 2 H, C₂₄-CH₂OTBS), 3.16–3.05 (br s, 1 H, OH), 2.34–2.29 (m, 1 H, C₁₆-*H*), 2.05–1.96 (m, 2 H, including C₂₀-*H*), 1.77 (dd, 1 H, *J* = 12.5 and 4.7 Hz, C₂₅-H_{eq}), 1.74–1.25 (m, 15 H including C₂₅-H_{ax}), 1.02 (m, 1 H), 1.00–0.86 (m, 30 H), 0.83 (d, 3 H, *J* = 6.8 Hz, C₂₀-CH₃), 0.61–0.54 (m, 4 H, Si(CH₂CH₃)₂), 0.03 (s, 6 H, Si(CH₃)₂); TLC *R_f* = 0.22 (20% EtOAc/hexane). Anal. Calcd for C₄₇H₈₃Cl₃O₈Si₂: C, 59.01; H, 8.96. Found: C, 59.09; H, 8.94.

[2*R*,2(1*S*,2(2*S*,3*R*,4*S*,6*R*,8*S*,8(2*R*),9*S*)),4*S*]-[2-[2-[3,9-Dimethyl-4-[(2,2,2-trichloroethoxy)methoxy]-8-[2-[(methylethyl)diethylsilyl]oxy]but-1-yl]-1,7-dioxaspiro[5.5]undecan-2-yl]-1-[(4-methoxyphenyl)meth-

oxy]eth-1-yl]-4-methyl-5-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-pentyl]oxy](1,1-dimethylethyl)dimethylsilane (40). To a solution of 160 mg (0.167 mmol) of alcohol 39 and 49 μL (45 mg, 0.418 mmol) of 2,6-lutidine in 2.5 mL of CH₂Cl₂ at 0 °C was added 50 μL (0.217 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. After 20 min, the reaction was diluted with 30 mL of 3:1 hexane/CH₂Cl₂ and was washed successively with 20 mL of 0.1 N aqueous NaHSO₄ and 20 mL of brine. The organic layer was then dried (Na₂SO₄), filtered, and concentrated, and the resultant residue was purified by flash chromatography (2 × 20 cm of silica gel, 7% EtOAc/hexane) to afford 170 mg (95%) of the bis-TBS ether 40: [α]²¹_D –65.6° (c 0.70, CH₂Cl₂); IR (thin film) 2970, 2860, 1620, 1520, 1465, 1390, 1360, 1305, 1250, 1175, 1160, 1090, 1030, 990, 970, 840, 810, 725 cm^{–1}; ¹H NMR (CDCl₃, 500 MHz) δ 7.26 (d, 2 H, *J* = 8.6 Hz, two of ArH), 6.87 (d, 2 H, *J* = 8.6 Hz, two of ArH), 4.94 (s with satellites, 2 H, OCH₂O), 4.50 (d, 1 H, *J* = 10.8 Hz, one of CH₂Ar), 4.42 (d, 1 H, *J* = 10.8 Hz, one of CH₂Ar), 4.24–4.18 (m, 1 H, C₂₁-*H*), 4.21 (d, 1 H, *J* = 11.6 Hz, one of OCH₂CCl₃), 4.16 (d, 1 H, *J* = 11.6 Hz, one of OCH₂CCl₃), 3.83–3.79 (m, 1 H, C₁₇-*H*), 3.80 (s, 3 H, OCH₃), 3.77–3.61 (m, 4 H, C₃₂-*H*, C₃₀-*H*, C₁₉-*H*, and one of C₁₅-CH₂OTBS), 3.56 (dd, 1 H, *J* = 9.8 and 6.6 Hz, one of C₁₅-CH₂OTBS), 3.48 (dd, 1 H, *J* = 9.6 and 4.2 Hz, C₂₄-CH₂OTBS), 3.37 (dd, 1 H, *J* = 9.6 and 6.5 Hz, C₂₄-CH₂OTBS), 2.07–1.93 (m, 3 H, including C₂₀-*H* and C₁₆-*H*), 1.77 (dd, 1 H, *J* = 12.6 and 4.9 Hz, C₂₅-H_{eq}), 1.74–1.20 (m, 15 H including C₂₅-H_{ax}), 1.04–0.83 (m, 34 H), 0.61–0.56 (m, 4 H, Si(CH₂CH₃)₂), 0.04 (s, 6 H, Si(CH₃)₂), 0.03 (s, 6 H, Si(CH₃)₂); ¹³C NMR (CDCl₃, 125 MHz) δ 132.0, 129.5, 114.5, 94.3, 80.1, 77.5, 73.8, 71.9, 71.8, 70.8, 70.7, 69.7, 68.0, 55.5, 42.0, 41.0, 37.5, 37.0, 35.1, 34.1, 33.0, 31.7, 30.5, 27.0, 26.2, 18.0, 17.9, 16.9, 16.8, 13.5, 11.9, 9.1, 7.7, 6.5, 4.3, 4.2, –5.1; TLC *R_f* = 0.16 (5% EtOAc/hexane). Anal. Calcd for C₅₅H₉₉Cl₃O₈Si₃: C, 59.44; H, 9.32. Found: C, 59.50; H, 9.40.

[1(2*S*,3*R*,4*S*,6*R*,8*S*,8(2*R*),9*S*),2*S*,3*S*]-1-[3,9-Dimethyl-4-[(2,2,2-trichloroethoxy)methoxy]-8-[2-[(1-methylethyl)diethylsilyl]oxy]but-1-yl]-1,7-dioxaspiro[5.5]undecan-2-yl]-3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-5-methyl-6-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-hexanol (41). To a solution of 140 mg (0.131 mmol) of 4-methoxybenzyl ether 40 in 2.0 mL of CH₂Cl₂ was added 0.11 mL of deionized water. The slurry was cooled to 5 °C and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 50 mg, 0.22 mmol) was introduced in one portion, immediately producing a black mixture ringed with an orange aqueous layer which faded completely to an orange slurry (DDQ hydroquinone precipitate) over a 10-min period. After 20 min, the reaction mixture was diluted with 20 mL of CH₂Cl₂ and was extracted with 20 mL of saturated aqueous NaHCO₃. The aqueous layer was washed with 1 × 10 mL of CH₂Cl₂, and the combined organic extracts were dried (Na₂SO₄), filtered, and concentrated. Purification by flash chromatography (3 × 18 cm of silica gel, 1% EtOAc/CH₂Cl₂ followed by 20% EtOAc/hexane) gave 107 mg (78%) of the desired alcohol 41 as a colorless oil, followed by 18 mg of a diol lacking the diethylsilylpropylsilyl (DEIPS) group. Data for 41: [α]²¹_D –38.6° (c 0.35, CH₂Cl₂); IR (thin film) 3700–3150, 2970, 2870, 1480, 1475, 1390, 1360, 1260, 1085, 1025, 990, 970, 840, 810, 780, 740, 735 cm^{–1}; ¹H NMR (CDCl₃, 500 MHz) δ 4.91 (s with satellites, 2 H, OCH₂O), 4.27–4.18 (m, 1 H, C₂₁-*H*), 4.17 (s, 2 H, OCH₂CCl₃), 4.02–3.95 (m, 2 H), 3.81–3.66 (m, 4 H), 3.40 (dd, 1 H, *J* = 9.7 and 5.4 Hz, one of C₂₄-CH₂OTBS), 3.34 (dd, 1 H, *J* = 9.7 and 6.1 Hz, one of C₂₄-CH₂OTBS), 3.17 (d, 1 H, *J* = 5.5 Hz, OH), 2.07–1.93 (m, 3 H, including C₂₀-*H* and C₁₆-*H*), 1.85–1.25 (m, 16 H including C₂₅-H_{ax}), 1.04–0.83 (m, 34 H), 0.61–0.56 (m, 4 H, Si(CH₂CH₃)₂), 0.08 (s, 6 H, Si(CH₃)₂), 0.03 (s, 6 H, Si(CH₃)₂); TLC *R_f* = 0.16 (10% EtOAc/hexane). Anal. Calcd for C₄₅H₉₁Cl₃O₈Si₃: C, 56.84; H, 9.65. Found: C, 57.10; H, 9.80.

[1(2*S*,3*R*,4*S*,6*R*,8*S*,8(2*R*),9*S*),2*S*,3*S*]-1-[3,9-Dimethyl-4-[(2,2,2-trichloroethoxy)methoxy]-8-[2-[(1-methylethyl)diethylsilyl]oxy]but-1-yl]-1,7-dioxaspiro[5.5]undecan-2-yl]-3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-5-methyl-6-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-hexanone (42). Preparation of pyridine-buffered Dess-Martin periodinane⁵⁰ stock solution: 207 mg (0.489 mmol) of the Dess-Martin periodinane was added to an argon-purged flask (glove bag). The solid was taken up in 8 mL of CH₂Cl₂, and 237 μL (232 mg, 2.93 mmol) of pyridine was added, producing a clear solution. This stock solution was employed in oxidations within 20 min.

To a solution of 93.0 mg (0.0978 mmol) of alcohol 41 was added 3.0 mL (1.9 equiv) of freshly prepared periodinane stock solution in one portion. After 0.75 h, the clear solution was diluted with 5 mL of diethyl ether and was quenched by introducing 5 mL of 1:1 saturated aqueous NaHCO₃/sodium bisulfite and stirring the resulting mixture for 5 min. Upon further dilution with 20 mL of ether, the mixture was washed with 2 × 10 mL of saturated aqueous NaHCO₃ and 1 × 10 mL of brine, and the organic layer was dried (Na₂SO₄), filtered, and concentrated. the resulting oily residue was purified by flash chromatography (2 × 20 cm

of silica gel, linear gradient of 3.5–5% EtOAc/hexane) to provide 91.3 mg (98%) of the desired ketone **42**: $[\alpha]^{21}_{546} -36.2^\circ$ (*c* 1.40, CH_2Cl_2); IR (thin film) 2970, 2900, 2870, 1725, 1470, 1390, 1365, 1260, 1160, 1090, 1030, 995, 975, 940, 840, 815, 780, 730 cm^{-1} ; ^1H NMR (benzene-*d*₆, 500 MHz) δ 4.56 (d, 1 H, *J* = 7.1 Hz, one of OCH_2O), 4.54 (d, 1 H, *J* = 6.9 Hz, one of OCH_2O), 4.50 (br d, 1 H, *J* = 8.8 Hz, $\text{C}_{19}\text{-H}$), 4.37–4.33 (m, 1 H, $\text{C}_{21}\text{-H}$), 4.23 (apparent t, 1 H, *J* = 6.6 Hz, $\text{C}_{30}\text{-H}$ or $\text{C}_{32}\text{-H}$), 4.19–4.15 (m, 1 H, $\text{C}_{30}\text{-H}$ or $\text{C}_{32}\text{-H}$), 3.93 (d, 1 H, *J* = 11.5 Hz, one of OCH_2CCl_3), 3.90 (d, 1 H, *J* = 11.4 Hz, one of OCH_2CCl_3), 3.80 (apparent t, 1 H, *J* = 9.7 Hz, one of $\text{C}_{15}\text{-CH}_2\text{OTBS}$), 3.59 (dd, 1 H, *J* = 9.7 and 5.6 Hz, one of $\text{C}_{15}\text{-CH}_2\text{OTBS}$), 3.44–3.37 (m, 2 H, $\text{C}_{24}\text{-CH}_2\text{OTBS}$), 2.96 (dd, 1 H, *J* = 17.5 and 9.0 Hz, one of $\text{C}_{18}\text{-CH}_2$), 2.87–2.81 (m, 1 H, $\text{C}_{16}\text{-H}$), 2.26 (dd, 1 H, *J* = 17.5 and 2.7 Hz, one of $\text{C}_{18}\text{-CH}_2$), 2.18–1.98 (m, 3 H, including one of $\text{C}_{31}\text{-CH}_2$ and $\text{C}_{29}\text{-H}$), 1.93–1.79 (m, 6 H, including $\text{C}_{20}\text{-H}$ and one of $\text{C}_{31}\text{-CH}_2$), 1.73–1.68 (m, 1 H), 1.65–1.60 (m, 1 H), 1.57–1.50 (m, 2 H), 1.42–1.37 (br d, 1 H), 1.31–1.24 (m, 7 H, including $\text{C}_{20}\text{-CH}_3$), 1.20–0.92 (m, 34 H), 0.85–0.75 (m, 4 H, Si(CH_2CH_3)₂), 0.09 (s, 6 H, Si(CH_3)₂), 0.07 (s, 6 H, Si(CH_3)₂); ^{13}C NMR (CDCl_3 , 125 MHz) δ 208.9, 97.7, 94.0, 80.1, 73.6, 72.4, 69.9, 68.6, 66.4, 64.9, 53.6, 45.5, 41.2, 37.1, 36.1, 33.9, 32.2, 30.8, 30.4, 30.1, 26.9, 26.1, 17.8, 16.9, 13.7, 11.4, 9.6, 7.6, 5.5, 4.6, 4.5, –5.3, –5.4; TLC R_f = 0.18 (5% EtOAc/hexane). Anal. Calcd for $\text{C}_{45}\text{H}_{89}\text{Cl}_3\text{O}_8\text{Si}_3$: C, 56.97; H, 9.45. Found: C, 57.05; H, 9.52.

[**6R**-[6a[2S*(*R**)₃S*],8β(2S*,3S*,5S*)₃,9β,10β]]-α-Ethyl-10-[(2,2,2-trichloroethoxy)methoxy]-3,9-dimethyl-8-tetrahydro-3-(hydroxymethyl)-2-methoxy-5-methyl-2*H*-pyran-2-yl]-1,7-dioxaspiro[5.5]undecane-2-ethanol (**44**). To a 2-mL glass shell vial containing 15.0 mg (15.8 μmol) of trisilyl ketone **42** was added 350 μL of pyridinium hydrofluoride buffered with excess pyridine (stock solution prepared from 2.1 g of Fluka HF-pyridine, 20 mL of THF, and 7.0 mL of pyridine). The solution was stirred for 3 h at ambient temperature before diluting with 15 mL of 3:1 hexane/ CH_2Cl_2 and extracting with 10 mL of saturated aqueous NaHCO_3 . The organic layer was dried (Na_2SO_4), several drops of triethylamine were introduced, and the solution was filtered and concentrated by rotary evaporation to afford a colorless oil. This material, a mixture of lactol and keto triol by ^1H NMR analysis, was employed without hesitation in the subsequent step (TLC R_f = 0.01–0.11, 30% EtOAc/hexane).

The lactol obtained from the previous reaction (assumed 15.8 μmol) was dissolved in 1.0 mL of methanol, the clear solution was cooled to 0 °C, and ca. 40 beads of Dowex 50X 8–200 ion-exchange resin were introduced in one portion. After 0.8 h, ca. 40 μL of triethylamine was introduced, and the mixture was filtered through a Celite plug (CH_2Cl_2 washes). Concentration of the filtrate and purification of the residue by flash chromatography (1.5 × 18 cm of silica gel, 30% EtOAc/hexane, 4 drops of triethylamine/100 mL of eluent) gave 8.7 mg (91% for two steps) of the highly acid-labile methyl ketal **44** as an oil: $[\alpha]^{23}_{546} -16^\circ$ (*c* 0.32, benzene); IR (thin film) 3650–3150, 2960, 1460, 1390, 1330, 1310, 1243, 1230, 1180, 1160, 1125, 1080, 1025, 970, 870, 860, 815, 725 cm^{-1} ; ^1H NMR (500 MHz with COSY-90, benzene-*d*₆) δ 4.55 (d, 1 H, *J* = 7.0 Hz, one of OCH_2O), 4.53 (d, 1 H, *J* = 7.0 Hz, one of OCH_2O), 4.44 (dt, 1 H, *J* = 11.9 and 4.7 Hz, $\text{C}_{21}\text{-H}$), 4.28 (dm, 1 H, *J* = 9.4 Hz, $\text{C}_{30}\text{-H}$), 4.08–4.05 (apparent t, 1 H, $\text{C}_{19}\text{-H}$), 3.94 (d, 1 H, *J* = 11.2 Hz, one of OCH_2CCl_3), 3.96–3.90 (m, 1 H, $\text{C}_{32}\text{-H}$), 3.84 (d, 1 H, *J* = 11.2 Hz, one of OCH_2CCl_3), 3.70 (ddd, 1 H, *J* = 10.7, 4.4, and 2.0 Hz, $\text{C}_{24}\text{-H}_{eq}$), 3.64 (dd, 1 H, *J* = 11.0 and 5.3 Hz, one of $\text{C}_{15}\text{-CH}_2\text{OH}$), 3.57 (dd, 1 H, *J* = 11.0 and 3.4 Hz, one of $\text{C}_{15}\text{-CH}_2\text{OH}$), 3.37–3.20 (br s, 1 H, OH), 3.08 (apparent t, 1 H, *J* = 11.1 Hz, $\text{C}_{24}\text{-H}_{ax}$), 2.96 (s, 3 H, OCH_3), 2.28 (m, 1 H), 2.21 (dd, 1 H, *J* = 14.6 and 4.4 Hz, one of $\text{C}_{18}\text{-CH}_2$), 2.15–2.09 (m, 1 H, $\text{C}_{20}\text{-H}$), 2.00 (dd, 1 H, *J* = 14.6 and 7.4 Hz, one of $\text{C}_{18}\text{-CH}_2$), 1.90 (dd, 1 H, *J* = 12.8 and 4.8 Hz, $\text{C}_{25}\text{-H}_{eq}$), 1.87–1.83 (m, 1 H, $\text{C}_{16}\text{-H}$), 1.83–1.74 (m, $\text{C}_{23}\text{-H}$), 1.64 (ddd, 1 H, *J* = 13.0, 11.0 and 1.7 Hz, one of $\text{C}_{31}\text{-CH}_2$), 1.60–1.40 (m, 9 H, including $\text{C}_{25}\text{-H}_{ax}$), 1.29–1.21 (m, 2 H, $\text{C}_{32}\text{-OH}$ and one of $\text{C}_{31}\text{-CH}_2$), 1.08 (t, 3 H, *J* = 7.3 Hz, $\text{C}_{34}\text{-CH}_3$), 1.04 (d, 3 H, *J* = 6.7 Hz, $\text{C}_{20}\text{-CH}_3$), 0.88 (d, 3 H, *J* = 7.0 Hz, $\text{C}_{27}\text{-CH}_3$), 0.68 (d, 3 H, *J* = 6.6 Hz, $\text{C}_{23}\text{-CH}_3$); ^{13}C NMR (125.5 MHz, benzene-*d*₆) 100.8, 97.6, 97.5, 93.2, 79.5, 73.5, 69.0, 67.7, 67.6, 63.7, 46.9, 43.7, 42.1, 36.8, 36.7, 31.44, 31.37, 30.5, 30.3, 26.9, 17.2, 11.5, 10.7, 5.2; TLC R_f = 0.25 (30% EtOAc/hexane). Anal. Calcd for $\text{C}_{27}\text{H}_{47}\text{O}_8\text{Cl}_3$: C, 53.51; H, 7.82. Found: C, 53.61; H, 7.92.

[**6R**-[6a[2S*(*R**)₃S*],8β(2S*,3S*,5S*)₃,9β,10β]]-α-Ethyl-10-hydroxy-3,9-dimethyl-8-[tetrahydro-3-(hydroxymethyl)-2-methoxy-5-methyl-2*H*-pyran-2-yl]-1,7-dioxaspiro[5.5]undecane-2-ethanol (**38** from Synthetic Material). Trichloroether **44** (6.2 mg, 10.2 μmol) was azeotropically dried with two 1-mL portions of toluene and was subsequently dissolved in 0.8 mL of THF. Freshly prepared samarium diiodide (71.2 μmol , 0.72 mL, 0.10 M in THF)¹⁰⁷ was introduced in one portion, affording a dark blue solution. After 35 min at ambient temperature, the reaction was diluted with 15 mL of diethyl ether and was extracted with 10 mL of saturated aqueous potassium carbonate. The aqueous extract

was washed with 10 mL of EtOAc, and the combined organic layers were washed successively with 15 mL of saturated aqueous sodium sulfite and 15 mL of brine, dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by flash chromatography (1 × 18 cm, linear gradient of 60–80% EtOAc/hexane) yielded 3.2 mg (71%) of the desired triol mixed methyl ketal **38** as a clear oil. This material proved identical in all respects (^1H NMR, rotation, TLC, GC cojunction, MS) with natural material.

GC analysis [DB-1, 235 °C, 15psi: $t_{\text{enol ether}} = 3.06 \text{ min}$, $t_{\text{methyl ketal}} = 3.60 \text{ min}$]. Coinjection of synthetic **38** with authentic triol derived from cytovaricin produced no doubling of peaks.

[**3(2R,3R),4R,5S**]-3-[3-Hydroxy-2-methyl-1-oxo-4-(phenylmethoxybutyl)-4-methyl-5-phenyl-2-oxazolidinone (**45**). To a solution of 11.7 g (50.0 mmol) of the imide **42**²³ in 100 mL of CH_2Cl_2 at 0 °C was added 13.8 mL (15.1 g, 55.0 mmol) of di-*n*-butylboron triflate,¹⁰⁸ followed within one minute by 8.4 mL (6.1 g, 60 mmol) of triethylamine. The resulting solution was stirred for 30 min at 0 °C. Upon cooling to –78 °C, a solution of 8.26 g (55.0 mmol) of α -benzyloxyacetaldehyde in 15 mL of CH_2Cl_2 was introduced over a 3-min period by cannula. The reaction was stirred for 45 min at –78 °C, warmed to 0 °C over a 15-min period, and then quenched by addition of 90 mL of 0.05 N pH 7 phosphate buffer in 200 mL of methanol. After 5 min, the quenched reaction mixture was further cooled to –10 °C and 90 mL of 30% hydrogen peroxide in 200 mL of methanol was added over 15 min (*caution*: initial reaction is highly exothermic). The resultant clear solution was stirred for 1 h at 0 °C, during which time a white precipitate formed. Concentration to a total volume of 200 mL afforded a white slurry, which was diluted with 100 mL of water and extracted with 4 × 700 mL of diethyl ether. The combined organic extracts were washed successively with 500 mL of 5% aqueous NaHCO_3 and 700 mL of brine, dried over anhydrous magnesium sulfate, and concentrated to yield a white crystalline mass. Recrystallization from 30% pentane/ether provided two crops of aldon adduct **45** as long needles (13.8 g, 0.95 g). The mother liquors were concentrated, and the residue was purified by flash chromatography (8 cm × 18 cm of silica gel, 25% EtOAc/hexane). The solid thus obtained was recrystallized (30% pentane/ether) to provide an additional 1.95 g of product. The total yield of aldon adduct **45** was 16.7 g (87%): mp 115.5–115.8 °C; $[\alpha]^{24}_{546} -3.8^\circ$ (*c* 1.00, CH_2Cl_2); IR (C₂H₂Cl₂) 3575 (br), 3070, 3040, 3000, 2980, 2920, 2880, 1782, 1700, 1500, 1460, 1370, 1345, 1235, 1200, 1123, 1070, 1030, 960 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.45–7.25 (m, 10 H, ArH), 5.47 (d, 1 H, *J* = 7.2 Hz, ArCHO), 4.67 (dq, 1 H, *J* = 7.2 and 6.6 Hz, NCHCH₃), 4.56 (s, 2 H, ArCH₂O), 4.18 (m, 1 H, $\text{C}_7\text{-H}$), 3.96 (dq, 1 H, *J* = 7.0 and 5.1 Hz, $\text{C}_6\text{-H}$), 3.56 (d with satellites, 2 H, *J* = 5.4 Hz, ArCH₂OCH₂), 2.74 (d, 1 H, *J* = 4.1 Hz, OH), 1.27 (d, 3 H, *J* = 7.0 Hz, $\text{C}_7\text{-CH}_3$), 0.87 (d, 3 H, *J* = 6.6 Hz, NCHCH₃); ^{13}C (CDCl₃, 75.5 MHz) δ 175.8, 152.6, 138.1, 133.4, 128.7 (3), 128.6 (7), 128.4, 127.7, 125.6, 78.8, 73.4, 72.0, 71.0, 54.8, 40.5, 14.3, 12.1; TLC R_f = 0.14 (30% EtOAc/hexane). Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_5$: C, 68.91; H, 6.57. Found: C, 69.00; H, 6.49.

[**2R,3R**]-3-Hydroxy-N-methoxy-*N*-dimethyl-4-(phenylmethoxy)butanamide (**46**). To a suspension of 24.9 g (255 mmol) of *N,O*-dimethylhydroxylamine hydrochloride in 100 mL of anhydrous THF at –10 °C was added 128 mL of 2.0 M trimethylaluminum in toluene over a 20-min period (*caution*: vigorous gas evolution). After completing the addition, the cooling bath was removed, and the solution was stirred for 10 min at 0 °C and 15 min at room temperature. The aluminum amide solution was recooled to –10 °C, and a solution of 32.6 g (85.0 mmol) of imide **45** in 80 mL of THF and 100 mL of CH_2Cl_2 was added by cannula. The cloudy reaction mixture was warmed to 0 °C over a 10-min period, whereupon gas evolution was clearly evident and the mixture slowly cleared. After 3 h, the solution was transferred by cannula into a rapidly stirred mixture of 250 mL of CH_2Cl_2 and 250 mL of 0.5 N aqueous HCl at 0 °C. The resulting two-phase mixture was stirred at 0 °C for 1 h, the layers were separated, and the aqueous layer extracted with 4 × 500 mL of CH_2Cl_2 . The combined organic extracts were washed with 800 mL of brine, dried (Na_2SO_4), filtered, and concentrated. Upon concentration from three, 100-mL portions of 20% EtOAc/hexane, the oxazolidinone auxiliary crystallized, producing a crystal-impregnated oil. The majority (12.1 g, 80% recovery) of the byproduct oxazolidinone was removed by recrystallization from ca. 300 mL of 30% EtOAc/hexane. Concentration of the supernatant afforded an oil which was purified by flash chromatography (10 cm × 26 cm of silica gel, linear gradient from 70% to 77% *tert*-butyl methyl ether/hexane, then 65% EtOAc/hexane), providing 21.8 g (96%) of amide **46** as a golden oil, followed by 2.20 g oxazolidinone (combined 95% recovery). Data for amide **46**: $[\alpha]^{24}_{546} -18.3^\circ$ (*c* 1.53, CH_2Cl_2); IR (thin film) 3440 (br), 3025, 2970, 2935, 2860, 1650, 1495, 1450, 1385, 1175, 1114, 990, 735, 695 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.38–7.23 (m, 5 H, ArH), 4.57 (d with satellites, 1 H, *J* = 11.9 Hz, one of ArCH₂O), 4.51 (d with satellites, 1 H, *J* = 11.9 Hz, one of ArCH₂O), 4.06 (ddd, 1 H, *J* = 3.3, 5.5, and 2.1

Hz, C₇-H), 3.67 (s, 3 H, NOCH₃), 3.52 (d with satellites, 1 H, *J* = 2.1 Hz, one of ArCH₂OCH₂), 3.50 (d with satellites, *J* = 2.1 Hz, one of ArCH₂OCH₂), 3.40 (d, 1 H, *J* = 3.1 Hz, OH), 3.17 (s, 3 H, NCH₃), 3.17–3.08 (br m, 1 H, C₆-H), 1.19 (d, 3 H, *J* = 7.1 Hz, C₇-CH₃); ¹³C (75.5 MHz, CDCl₃) δ 177.1, 160.1, 138.1, 128.3, 127.6, 73.5, 71.5, 71.0, 61.4, 37.0, 32.0 (br), 11.7; TLC *R*_f = 0.16 (80% *tert*-butyl methyl ether/hexane). Anal. Calcd for C₁₄H₂₁NO₄: C, 62.90; H, 7.92. Found: C, 62.97; H, 7.87.

[4*R*,5*R*]-5-Hydroxy-4-methyl-2-methylene-6-(phenylmethoxy)hexan-3-one (**47**). A dry flask was charged with 22.9 g (82.5 mmol) of a 25% dispersion of lithium (1% sodium content) in oil under an argon atmosphere, and the oil was removed by washing twice with 40 mL of diethyl ether. The oil-free lithium was suspended in 250 mL of diethyl ether, and after cooling to 0 °C, a solution of 22.2 mL (30.2 g, 250 mmol) of 2-bromopropene in 50 mL of diethyl ether was cautiously added by cannula over 20 min while maintaining the reaction temperature below 25 °C. An induction period of approximately 10 min was characteristically observed before the strongly exothermic reaction initiated. The reaction mixture was held at 0 °C for 30 min and was then stirred at ambient temperature for 14 h. Stirring was terminated, the remaining lithium metal allowed to rise to the surface, and the underlying solution cannula-transferred under aspirator pressure through a glass wool and Celite-packed sintered glass funnel into a storage flask. The resultant dark-orange solution, 0.81 M in alkenyllithium, was employed directly in the following experiment.¹¹⁹

To a solution of 5.35 g (20.0 mmol) of amide **46** in 150 mL of THF at -78 °C was added 62 mL (50 mmol) of the freshly prepared 0.81 M 2-lithiopropene solution over an 11-min period, maintaining the temperature of the reaction below -65 °C. The light-orange solution was stirred for 40 min at -78 °C, and the reaction was quenched by rapid cannula transfer into 300 mL of a vigorously stirred 2:1 mixture of saturated aqueous NH₄Cl and THF at 0 °C. After 20 min, the two-phase mixture was partitioned between 600 mL of brine and 1 L of diethyl ether, the aqueous layer was washed with 3 × 500 mL of ether, and the combined organic extracts were dried (Na₂SO₄) and concentrated. Purification by flash chromatography (8 × 17 cm of silica gel, linear gradient from 20% to 30% EtOAc/hexane) afforded 4.60 g of pure enone **47** as a viscous oil, along with 0.14 g of mixed fractions. Re-chromatography of the impure fractions (1.5 cm × 18 cm of silica gel, 25% EtOAc/hexane) provided an additional 0.11 g of product, bringing the total yield of enone **47** to 4.71 g (95%): [α]_D²⁴₅₄₆ -10° (c 1.71); IR (thin film) 3470 (br), 3030, 2925, 2860, 1670, 1630, 1495, 1454, 1372, 1120, 1060, 985, 735, 697 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.37–7.26 (m, 5 H, ArH), 6.00 (s, 1 H, one of =CH₂), 5.82 (d, 1 H, *J* = 1.4 Hz, one of =CH₂), 4.51 (s, 2 H, ArCH₂O), 4.05 (apparent quintet, 1 H, *J* = 5.6 Hz, C₇-H), 3.50–3.38 (m, 3 H, C₆-H and ArCH₂OCH₂), 2.91 (d, 1 H, *J* = 4.1 Hz, OH), 1.86 (s, 3 H, C₄-CH₃), 1.17 (d, 3 H, *J* = 7.1 Hz, C₆-CH₃); ¹³C (75.5 MHz, CDCl₃) δ 205.9, 143.9, 137.9, 128.4, 127.7, 125.2, 73.4, 71.6, 71.2, 41.6, 17.6, 13.0; TLC *R*_f = 0.25 (30% EtOAc/hexane). Anal. Calcd for C₁₅H₂₀O₃: C, 72.55; H, 8.12. Found: C, 72.38; H, 8.20.

[2*R*,3*S*,4*R*]-3-Methyl-5-methylene-1-(phenylmethoxy)hexane-2,4-diol (**48**). To a solution of hydroxy enone **47** in 200 mL of 3:1 THF/methanol at -78 °C was added 2.13 g (21.3 mmol) of methoxydiethylborane¹¹⁰ over a 2-min period, producing a voluminous white precipitate. After the white slurry was stirred for 15 min, 805 mg (21.3 mmol) of sodium borohydride was introduced over 1 min. Controlled H₂ evolution was immediately evident, and the slurry dissipated within 10 min, producing a clear, effervescent solution. The reaction was stirred for 4 h at -70 °C, quenched with 30 mL of a 1 N aqueous acetic acid, and warmed to ambient temperature. After stirring for an additional 20 min, the mixture was diluted with 500 mL of saturated aqueous NaHCO₃ and was extracted with 3 × 500 mL of EtOAc. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated to afford a milky oil. This material was azeotroped with 6 × 300 mL of methanol, dissolved in 200 mL of methanol and 20 mL of 0.05 N pH 7 phosphate buffer at 0 °C, and treated with 20 mL of 30% aqueous hydrogen peroxide over 10 min. After 1 h, the mixture was concentrated to ca. 30 mL, azeotroped with 2 × 200 mL of methanol, diluted with 400 mL of saturated aqueous NaHCO₃, and extracted with 3 × 300 mL of EtOAc. The combined organic extracts were washed with brine, dried Na₂SO₄, filtered, and concentrated. Capillary GC analysis (DB-5, 50 m, 6 psi, 180 °C isothermal) of the unpurified product indicated a diastereomer ratio >500:1 in favor of the desired syn diol **48** (*t*_R(syn) = 9.58 min; *t*_R(anti) = 9.80 min). Purification by flash chromatography (8 cm × 17 cm of silica gel, 2.5% 2-propanol/CH₂Cl₂) yielded 4.57 g (99%) of diol **48**: [α]_D²⁴₅₄₆ +8.5° (c 1.00, CH₂Cl₂); IR (thin film) 3400 (br), 3090, 3073, 3030, 2975, 2915,

2865, 1651, 1496, 1454, 1360, 1130, 1100, 1027, 980, 900, 735, 695 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.40–7.26 (m, 5 H, ArH), 5.05 (s, 1 H, one of =CH₂), 4.93 (q, 1 H, *J* = 1.4 Hz, one of =CH₂), 4.60 (d, 1 H, *J* = 11.9 Hz, one of ArCH₂O), 4.53 (d, 1 H, *J* = 11.9 Hz, one of ArCH₂O), 4.27 (br s, 1 H, C₅-H), 4.08 (highly structured m, 1 H, C₇-H), 3.59–3.44 (m, 2 H, ArCH₂OCH₂), 2.92 (d, 1 H, *J* = 2.2 Hz, C₇-OH), 2.82 (d, 1 H, *J* = 2.2 Hz, C₅-OH), 1.88–1.77 (highly structured m, 1 H, C₆-H), 1.67 (d, 3 H, *J* = 0.6 Hz, C₄-CH₃), 0.80 (d, 3 H, *J* = 7.2 Hz, C₆-CH₃); ¹³C (CDCl₃, 75.5 MHz) δ 145.4, 138.0, 128.4, 127.7, 110.6, 78.1, 74.2, 73.4, 72.8, 36.7, 25.3, 19.4, 5.6; TLC *R*_f = 0.27 (3% isopropyl alcohol/CH₂Cl₂). Anal. Calcd for C₁₅H₂₂O₃: C, 71.97; H, 8.86. Found: C, 71.84; H, 8.84.

[4*S*,5*S*,6*R*]-2,2-Bis(1,1-dimethylethyl)-5-methyl-4-(1-methyl-ethenyl)-6-[(phenylmethoxy)methyl]-1,3-dioxa-2-silacyclohexane (**49**). Diol **48** (12.0 g, 47.9 mmol) was azeotropically dried by addition and evaporation of two 10 mL-portions of toluene and was then dissolved in 30 mL of CH₂Cl₂. The solution was charged with 16.7 mL (15.4 g, 143 mmol) of 2,6-lutidine and 20.2 mL (27.4 g, 62.3 mmol) of di-*tert*-butylsilyl triflate, and was heated to 65 °C employing an oil bath.⁵² After 9 h, the solution was diluted with 400 mL of CH₂Cl₂ and was successively extracted with 300 mL of saturated aqueous NaHCO₃, 2 × 300 mL of 0.3 N aqueous NaHSO₄, 300 mL of water, and 300 mL of brine. The organic layer was dried (Na₂SO₄), filtered, and concentrated. Purification of the resulting yellow oil by flash chromatography (10 cm × 25 cm of silica gel, linear gradient from 0.5% to 3.5% EtOAc/hexane) afforded 18.2 g (97%) of silylene **49** as an oil: [α]_D²⁴₅₄₆ +33.5° (c 1.07, CH₂Cl₂); IR (thin film) 3030, 2975, 2940, 2860, 1650, 1478, 1455, 1390, 1365, 1207, 1147, 1112, 1030, 901, 845, 826, 735, 698, 650 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.39–7.27 (m, 5 H, ArH), 5.20 (br s, 1 H, one of =CH₂), 4.94 (apparent qn, 1 H, *J* = 1.5 Hz, one of =CH₂), 4.69 (br s, 1 H, C₅-H), 4.64 (d, 1 H, *J* = 12.1 Hz, one of ArCH₂O), 4.58 (d, 1 H, *J* = 12.1 Hz, one of ArCH₂O), 4.60–4.56 (highly structured m (obscured), 1 H, C₇-H), 3.60 (dd, 1 H, *J* = 7.3 and 9.6 Hz, one of ArCH₂OCH₂), 2.03 (highly structured m, 1 H, C₆-H), 1.12 (s, 9 H, one of Si(*t*-Bu)₂), 1.08 (s, 9 H, one of Si(*t*-Bu)₂), 0.81 (d, 3 H, *J* = 7.1 Hz, C₆-CH₃); ¹³C (CDCl₃, 75.5 MHz) δ 144.7, 138.5, 128.4, 127.7, 127.6, 110.2, 79.6, 75.8, 73.5, 72.6, 35.2, 28.7, 27.7, 23.5, 20.7, 19.3, 4.74; TLC *R*_f = 0.49 (10% EtOAc/hexane). Anal. Calcd for C₂₃H₃₈O₃Si: C, 70.72; H, 9.80. Found: C, 70.77; H, 9.91.

[2*R*,3*S*,4*R*,5*R*]-2,4-Dimethyl-2-hydroxy-3,5-[bis(1,1-dimethylethyl)-silylene]dioxy-6-(phenylmethoxy)-1,2-hexanediol (**50**). To a solution of 293 mg (0.750 mmol) of olefin **49** in 6.5 mL of acetone and 0.9 mL of deionized water was added 117 mg (0.863 mmol) of *N*-methylmorpholine N-oxide monohydrate to afford a clear solution. A solution of 150 μL (0.15 M in water, 0.0225 mmol) of osmium tetroxide was then introduced, yielding an orange-yellow solution. The reaction mixture was quenched after 2 h by introducing 12 mL of saturated aqueous sodium bisulfite and stirring with vigor for 10 min. The biphasic mixture was then diluted with 40 mL of water and extracted with 2 × 70 mL of CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄), filtered, concentrated, and purified by flash chromatography (2.0 × 18 cm of silica gel, 25% EtOAc/hexane), providing 303 mg (95%) of two diastereomeric diols (>60:1 ratio of diols in favor of **50**). Data for major diastereomer **50**: [α]_D²³₅₄₆ -4.8° (c 1.45, CH₂Cl₂); IR (thin film) 3445 (br), 3015, 2970, 2940, 2860, 1478, 1455, 1390, 1365, 1210, 1100, 1005, 877, 846, 825, 738, 695, 647 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.31–7.20 (m, 5 H, ArH), 4.54 (d, 1 H, *J* = 12.1 Hz, one of OCH₂Ar), 4.48 (d, 1 H, *J* = 12.1 Hz, one of OCH₂Ar), 4.40 (ddd, 1 H, *J* = 6.0, 7.3, and 8.2 Hz, ArCH₂OCH₂CH), 4.21 (d, 1 H, *J* = 2.0 Hz, C(OH)(CH₃)CHO), 3.73 (d, 1 H, *J* = 11.0 Hz, one of CH₂OH), 3.48 (dd, 1 H, *J* = 9.6 and 6.0 Hz, one of ArCH₂OCH₂), 3.40 (d, 1 H, *J* = 11.0 Hz, one CH₂OH), 3.38 (dd, 1 H, *J* = 9.6 and 7.2 Hz, one of ArCH₂OCH₂), 3.00–2.55 (br s, 2 H, CH₂OH and C(CH₃)(OH)), 1.99–1.93 (highly structured multiplet, 1 H, CHCH₃), 1.18 (s, 3 H, C(CH₃)(OH)), 1.05 (s, 9 H, one of Si(*t*-Bu)), 0.99 (s, 9 H, one of Si(*t*-Bu)), 0.98 (d, 3 H, *J* = 7.1 Hz, CHCH₃); ¹³C NMR (75.5 MHz, CDCl₃) δ 138.8, 128.3, 127.6, 82.5, 77.2, 74.8, 73.4, 71.9, 67.6, 34.9, 28.7, 23.5, 22.2, 20.6, 6.4; TLC *R*_f = 0.13 (20% EtOAc/hexane). Anal. Calcd for C₂₃H₄₀O₅Si: C, 65.05; H, 9.49. Found: C, 64.92; H, 9.49.

[2*R*,3*S*,4*S*]-2,4-O-[Bis(1,1-dimethylethyl)silylene]-3-methyl-5-methylene-1,2,4-hexanetriol (**51**). A flame-dried 2-L, three-necked, round-bottomed flask was fitted with a mechanical stirrer, 24/40 cold finger, nitrogen inlet/bubbler outlet, septum, and digital temperature probe. The apparatus was flushed with nitrogen, the vessel was cooled to -78 °C, and the cold finger was loaded with dry ice/acetone. Approximately 900 mL of anhydrous ammonia was condensed into the flask, and 1.59 g (39.7 mmol) of freshly filed and cut calcium shavings was added in one portion, rapidly affording a dark blue slurry. After 5 min at -70 °C, the slurry was warmed to reflux (-36 °C) for 15 min and was then recooled to -65 °C. A solution of 7.95 g (20.4 mmol) of benzyl

(119) The procedure detailed above is a modification of the literature procedure reported by Parker (ref 104).

ether **49** in 150 mL of THF was then added by cannula over a 6-min period while maintaining the reaction temperature below -63 °C. The blue slurry was gradually warmed to -45 °C over a 15-min period, and after additional 9 min at -45 °C, the reaction was quenched by the addition of ca. 20 g of solid NH₄Cl. The mixture was evaporated to dryness by employing a warm water bath to drive off the ammonia and THF and the NH₄Cl-impregnated solid thus obtained was slurried into a 2-L separatory funnel via 800 mL of CH₂Cl₂. The basic solution was acidified to pH 7 by addition of 1.1 L of aqueous 1 N NaHSO₄, and the two phases were separated. The aqueous layer was washed with 300 mL of CH₂Cl₂, and the combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated. Purification by flash chromatography (10 cm × 26 cm of silica gel, 11% EtOAc/hexane) provided 4.1 g of pure alcohol **51**, followed by ca. 1 g of mixed fractions. The mixed fractions were rechromatographed (6 cm × 25 cm of silica gel, 11% EtOAc/hexane), and the combined purified material was concentrated from CH₂Cl₂. On evacuating at 0.2 mm overnight, 4.90 g (80%) of alcohol **51** was obtained as a low melting, crystalline solid: mp 41.1–43.2 °C; [α]²²_{D46} +18.5° (c 1.30); IR (thin film with trace CH₂Cl₂) 3420 (br), 3975, 3940, 3900, 3860, 1653, 1477, 1391, 1365, 1140, 1114, 1078, 1010, 939, 903, 848, 828, 650 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 5.16 (br s, 1 H, one of =CH₂), 4.91 (br s, 1 H, one of =CH₂), 4.65 (br s, 1 H, C₅-H), 4.42 (ddd, 1 H, J = 2.5, 3.7, and 8.1 Hz, C₇-H), 3.50 (dd, 1 H, J = 4.6 and 7.7 Hz, one of CH₂OH), 2.30 (d, 1 H, J = 7.7 Hz, OH), 1.83 (m, 1 H, C₆-H), 1.63 (s, 3 H, C₄-CH₃), 1.08 (s, 9 H, one of Si(i-Bu)₂), 1.05 (s, 9 H, one of Si(i-Bu)₂), 0.79 (d, 3 H, J = 7.2 Hz, C₆-CH₃); ¹³C (CDCl₃, 75.5 MHz) δ 144.1, 110.5, 79.5, 77.9, 65.8, 35.5, 28.7, 27.7, 23.5, 20.8, 19.2, 5.42; TLC R_f = 0.53 (30% EtOAc/hexane). Anal. Calcd for C₁₆H₃₂O₃Si: C, 63.95; H, 10.73. Found: C, 64.04; H, 10.94.

[**2R,3S,4S**]-2,4-[[Bis(1,1-dimethylethyl)silylene]dioxy]-3-methyl-5-methylene-1-hexanal (**52**). To a solution of 1.13 mL (1.64 g, 12.9 mmol) of oxalyl chloride in 80 mL of CH₂Cl₂ at -78 °C was added 1.99 mL (2.01 g, 25.8 mmol) of dimethyl sulfoxide dropwise over a 1-min period (gas evolution). After 5 min, a solution of 1.94 g (6.45 mmol) of alcohol **51** in 8 mL of CH₂Cl₂ was slowly added by cannula while maintaining the reaction temperature below -71 °C. The white slurry was stirred for an additional 15 min at -78 °C, and 7.19 mL (5.22 g, 51.6 mmol) of triethylamine was added over a 2-min period, affording a clear solution. The reaction was stirred for 3 min at -78 °C before being gradually warmed to -23 °C over 5 min. The resulting triethylamine hydrochloride laden mixture was held at -22 °C for 3 min and was then quenched with 30 mL of 0.05 M aqueous pH 7 phosphate buffer with simultaneous removal of the cooling bath. After stirring for 5 min at ambient temperature, the two-phase mixture was partitioned between 500 mL of 25% CH₂Cl₂/hexane and 200 mL of water, and the aqueous layer was extracted with 100 mL of CH₂Cl₂. The combined organic extracts were washed with 300 mL of 0.1 N aqueous NaHSO₄, 300 mL of water, and 300 mL of brine and were subsequently dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (5 cm × 16 cm of silica gel, 10% EtOAc/hexane) of the residue gave 1.87 g (97%) of aldehyde **52** as a clear oil: IR (thin film) 2975, 2940, 2900, 2865, 2805, 2710 (w), 1740, 1655, 1478, 1445, 1390, 1365, 1140, 1118, 1012, 904, 860, 842, 827, 650 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 9.71 (s, 1 H, aldehydic H), 5.19 (br s, 1 H, one of =CH₂), 4.95 (br s, 1 H, one of =CH₂), 4.71 (broad s, 1 H, C₅-H), 4.64 (d, 1 H, J = 2.4 Hz, C₇-H), 2.28 (m, 1 H, C₆-H), 1.66 (s, 3 H, J = 7.0 Hz, C₆-CH₃); TLC R_f = 0.43 (10% EtOAc/hexane).

[**4R,5S**]-3-[1-Oxo-2-[(4-methoxyphenyl)methoxy]ethyl]-4-methyl-5-phenyl-2-oxazolidinone (**53**). To a clear, rapidly mechanically stirred -78 °C solution of 39.2 g (200 mmol) of [4-(methoxybenzyl)oxy]acetic acid in 1.2 L of diethyl ether was added 29.3 mL (21.3 g, 210 mmol) of triethylamine, followed by 24.6 mL (24.1 g, 200 mmol) of pivaloyl chloride. Triethylamine hydrochloride immediately began to precipitate, and after 5 min the cooling bath was removed. The slurry was warmed to 0 °C over 30 min and was held at 0 °C for an additional 1 h. Meanwhile, a separate solution of 35.4 g (200 mmol) of [**4R,5S**]-4-methyl-5-phenyl-2-oxazolidinone in 260 mL of THF was prepared. After the oxazolidinone solution was cooled to -78 °C, 76.0 mL (200 mmol) of n-butyllithium (2.63 M in hexane) was added by syringe over 10 min, resulting in a pale orange-red solution which was stirred for 10 min at -78 °C. The flask containing the mixed anhydride was in turn cooled to -78 °C, and the lithiated oxazolidinone was transferred by cannula to the slurry. After the resultant slurry was stirred for 45 min at -70 °C, the reaction mixture was warmed to 0 °C over approximately 20 min and was held at that temperature for an additional 6 h before being quenched with 1.0 L of water with simultaneous warming to room temperature. The mixture was extracted with 2 × 1.0 L of EtOAc, and the combined organic extracts were washed with 1 L of 1 N aqueous NaHSO₄, 1 L of saturated aqueous NaHCO₃, and 0.8 L of brine and were

dried (Na₂SO₄). After filtration and concentration, the resulting solid was recrystallized from 700 mL of absolute ethanol, providing 62.5 g (88%) of imide **53** as white prisms: mp 128–129 °C; [α]²²_{D46} +9.2° (c 4.00, CH₂Cl₂); IR (thin film) 3060, 2990, 2840, 1785, 1720, 1620, 1590, 1515, 1370, 1350, 1250, 1220, 1200, 1150, 1120, 1035, 960, 895, 820 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.44–7.26 (m, 7 H, ArH), 6.87 (d, 2 H, J = 7.6 Hz, two of anisyl ArH), 5.71 (d, 1 H, J = 7.4 Hz, OCHAr), 4.74 (dq, J = 6.6 and 7.4 Hz, 1 H, NCHCH₃), 4.68 (d, 2 H, J = 3.2 Hz, CH₂C=O), 4.61 (s, 2 H, ArCH₂O), 3.79 (s, 3 H, OCH₃), 0.91 (d, J = 6.6 Hz, 3 H, CH₃CHN); ¹³C NMR (75.5 MHz, CDCl₃) δ 169.9, 159.4, 152.8, 133.0, 129.7, 129.3, 128.8, 128.6, 125.6, 113.8, 79.9, 73.1, 69.3, 55.2, 44.4, 14.4; TLC R_f = 0.09 (10% EtOAc/hexane). Anal. Calcd for C₂₀H₂₁NO₅: C, 67.59; H, 5.96. Found: C, 67.47; H, 6.04.

[**3(2R,3S,4R,5S,4R,5S)-3-[1-Oxo-2-[(4-methoxyphenyl)methoxy]-3,4,6-trihydroxy-4,6-O-[bis(1,1-dimethylethyl)silylene]-7-methyleneoctyl]-4-methyl-5-phenyl-2-oxazolidinone**] (**54**). To a solution of 11.66 g (32.81 mmol) of imide **53** in 1.2 L of anhydrous toluene at -70 °C was added 4.57 mL (3.32 g, 32.8 mmol) of triethylamine, followed by 7.18 mL (7.87 g, 28.7 mmol) of di-n-butylboron triflate.¹⁰⁸ The resulting slurry was warmed to -60 °C, momentarily affording a clear solution. Within 15 min, however, a flocculant precipitate (presumably triethylammonium triflate) appeared. After a total of 1 h at -60 °C, the reaction mixture was warmed to -50 °C, stirred for an additional 90 min, and recooled to -60 °C. A solution of 2.45 g (8.21 mmol) of aldehyde **52** in 11 mL of anhydrous toluene was then introduced over a 2-min period by cannula, and after 30 min, the slurry was warmed to -50 °C and stirred for 5 h. The reaction was quenched by addition of 33 mL of 0.05 N aqueous pH 7 phosphate buffer in 5 mL of methanol, and after the resulting mixture was warmed to -10 °C, ca. 700 mL of THF was added to produce a nearly homogeneous solution. A solution of 33 mL of 30% aqueous hydrogen peroxide in 65 mL of THF was then introduced over a 15-min period (caution: initial reaction is highly exothermic), and the mixture thus obtained was stirred for 40 min at 0 °C, concentrated to a volume of 150 mL (ca. 40 mm, rotary evaporator bath temperature not exceeding 25 °C), diluted with 400 mL of 5% aqueous NaHCO₃, and extracted with 3 × 400 mL of CH₂Cl₂. The combined organic extracts were washed with 400 mL of brine, dried (Na₂SO₄), and concentrated to provide an oil. The residual oil was dissolved in 100 mL of ether and then concentrated. This process was repeated three times, ultimately affording an oily white solid. Trituration of this mixture with five 10-mL portions of ether provided 8.21 g (94% recovery) of starting imide **53** as a white solid. The trituration washes were then concentrated, and the residual oil was purified by flash chromatography (10 cm × 26 cm of silica gel, linear gradient from 18% to 20% EtOAc/hexane) to yield 4.20 g (78%) of aldol adduct **54** as a viscous oil: [α]²²_{D46} = -8.9° (c 3.76, CH₂Cl₂); IR (thin film) 3480, 3100, 2987, 2970, 2865, 1785, 1721, 1653, 1617, 1590, 1515, 1480, 1370, 1305, 1200, 1120, 1010, 900, 850, 827, 770, 740, 701, 648 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.43–7.26 (m, 7 H, PhH and two of PMBH), 6.88 (d, 2 H, J = 8.7 Hz, two of PMBH), 5.63 (d, 1 H, J = 6.0 Hz, PhCH), 5.27 (d, 1 H, J = 3.1 Hz, C₆-H), 5.15 (br s, 1 H, one of =CH₂), 4.90 (apparent t, 1 H, J = 1.3 Hz, one of =CH₂), 4.75 (d, 1 H, J = 10.7 Hz, one of ArCH₂O), 4.70 (m, 1 H, NCHCH₃), 4.63 (br s, 1 H, C₅-H), 4.53 (dd, 1 H, J = 2.3 and 9.1 Hz, C₇-H), 4.45 (d, 1 H, J = 10.7 Hz, one of ArCH₂O), 4.04 (ddd, 1 H, J = 9.5 Hz, OH), 2.10 (m, 1 H, C₆-H), 1.62 (s, 3 H, C₄-CH₃), 1.12 (s, 9 H, one of Si(i-Bu)₂), 1.08 (s, 9 H, one of Si(i-Bu)₂), 0.93 (d, 3 H, J = 6.6 Hz, NCHCH₃), 0.85 (d, 3 H, J = 7.2 Hz, C₆-CH₃); ¹³C (CDCl₃, 75.5 MHz) δ 169.4, 159.6, 152.7, 144.6, 133.1, 130.0, 129.7, 128.8, 128.7, 125.6, 113.9, 110.4, 79.8, 79.6, 75.9, 72.9, 72.8, 55.6, 55.2, 34.5, 28.4, 28.0, 23.6, 20.7, 19.2, 14.2, 4.88; TLC R_f = 0.17 (20% EtOAc/hexane). Anal. Calcd for C₃₆H₅₁NO₅: C, 66.13; H, 7.86. Found: C, 66.27; H, 7.91.

[**2R,3S,4R,5S,6S]-2-[(4-Methoxyphenyl)methoxy]-3,4,6-trihydroxy-N,5-dimethyl-4,6-O-[bis(1,1-dimethylethyl)silylene]-7-methylene-N-methoxyoctanamide**] (**55**). To a suspension of 2.77 g (28.4 mmol) of N,O-dimethylhydroxylamine hydrochloride in 8 mL of anhydrous THF at 0 °C was added 14.2 mL (28.4 mmol) of 2.0 M trimethylaluminum in toluene over a 5-min period (caution: vigorous gas evolution). After the addition was complete, the cooling bath was removed, and the solution was stirred for 15 min at room temperature. The aluminum amide solution was cooled to -10 °C, and a solution of 3.10 g (4.74 mmol) of aldol adduct **54** in 6 mL of anhydrous THF was slowly added by cannula while maintaining the internal temperature below -3 °C. During the course of the addition, controlled gas evolution was noted and the reaction mixture became cloudy and developed a pale-orange color. The reaction mixture was warmed to 0 °C over a 10-min period, whereupon it cleared to provide a light-orange solution. After 2.25 h, this solution was transferred by cannula into a rapidly stirred mixture of 75 mL of CH₂Cl₂ and 75 mL of 0.1 N aqueous NaHSO₄ at 0 °C, and the resulting two-phase mixture was stirred at 0 °C for 15 min. After diluting with 200

mL of CH_2Cl_2 and 200 mL of water, the layers were separated, and the aqueous layer was extracted with 2×100 mL of CH_2Cl_2 . The combined organic extracts were washed with 200 mL of brine, dried (Na_2SO_4), filtered, and concentrated. The resulting oil was purified by flash chromatography (7 cm \times 25 cm of silica gel, 30% EtOAc/hexane for 3 L, then 60% EtOAc/hexane for 1.5 L), affording 2.42 g (95%) of amide **55** as a viscous oil, followed by 0.80 g (96% recovery) of oxazolidinone auxiliary. Data for amide **55**: $[\alpha]^{23}_{546} +19.2^\circ$ (*c* 3.83, CH_2Cl_2); IR (CH_2Cl_2) 3440 (br), 3100, 3960, 3860, 1660 (br), 1613, 1588, 1515, 1480, 1387, 1365, 1303, 1250, 1175, 1105, 935, 900, 850, 820, 645 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.32 (d, 2 H, *J* = 8.7 Hz, two of *ArH*), 6.86 (d, 2 H, *J* = 8.7 Hz, two of *ArH*), 5.14 (br s, 1 H, one of $=\text{CH}_2$), 4.89 (apparent t, 1 H, *J* = 1.3 Hz, one of $=\text{CH}_2$), 4.69 (d, 1 H, *J* = 11.2 Hz, one of ArCH_2O), 4.67 (br s, 1 H, $\text{C}_6\text{-H}$), 4.59 (br s, 1 H, $\text{C}_5\text{-H}$), 4.54 (d, 1 H, *J* = 11.2 Hz, one of ArCH_2O), 4.29 (dd, *J* = 2.4 and 9.2 Hz, $\text{C}_7\text{-H}$), 3.95 (ddd, 1 H, *J* = 9.3, 9.3, and 2.4 Hz, $\text{C}_8\text{-H}$), 3.80 (br d, 1 H, *J* = 9.2 Hz, OH), 3.78 (s, 3 H, ArOCH_3), 3.62 (s, 3 H, NOCH_3), 3.18 (s, 3 H, NCH_3), 2.18 (m, 1 H, $\text{C}_6\text{-H}$), 1.62 (s, 3 H, $\text{C}_4\text{-CH}_3$), 1.02 (s, 18 H, $\text{Si}(t\text{-Bu})_2$), 0.85 (d, 3 H, *J* = 7.1 Hz, $\text{C}_6\text{-CH}_3$); ^{13}C NMR (CDCl_3 , 300 MHz) δ 171.5, 159.6, 144.7, 130.0, 129.7, 113.9, 110.0, 79.8, 73.5, 72.2, 71.3, 61.4, 55.2, 34.3 (br), 28.4, 27.9, 23.5, 20.7, 19.2, 4.86; TLC R_f = 0.18 (30% EtOAc/hexane). Anal. Calcd for $\text{C}_{28}\text{H}_{47}\text{NO}_7\text{Si}$: C, 62.54; H, 8.81. Found: C, 62.37; H, 8.78.

[*S,S,3S,4R,5S,6S*]-2-[(4-Methoxyphenyl)methoxy]-3,4,6-trihydroxy-N,5-dimethyl-4,6-O-[bis(1,1-dimethylethyl)silylene]-7-methylene-N-methyoctanamide (**57**). To a solution of 5.51 g (13.0 mmol) of Dess-Martin periodinane⁵⁰ in 40 mL of CH_2Cl_2 was added 1.05 mL (1.03 g, 13.0 mmol) of freshly distilled pyridine. To the resulting clear solution was added a solution containing 3.04 g (5.65 mmol) of β -hydroxy amide **55** in 4 mL of CH_2Cl_2 via a cannula. After 50 min at ambient temperature, TLC monitoring indicated complete and clean transformation to a higher R_f spot (R_f = 0.53 in 40% EtOAc/hexane).

The clear solution was immediately diluted with 40 mL of THF and was cooled to -50 °C. Lithium tri-*sec*-butylborohydride (62 mmol, 62 mL of a 1.0 M solution in THF) was then introduced over a 15-min period, and the reaction mixture was warmed to -24 °C (gas evolution). After 45 min, the yellow slurry was quenched with 30 mL of saturated aqueous NH_4Cl while simultaneously warming to ambient temperature and stirring with vigor. After an additional 15 min of stirring, the mixture was partitioned between 800 mL of CH_2Cl_2 and 400 mL of 0.15 N NaHSO_4 . The aqueous layer was washed with an additional 100 mL of CH_2Cl_2 , and the combined organic extracts were washed successively with 400 mL of water and 400 mL of brine. Drying (Na_2SO_4), filtration, concentration, and flash chromatography of the resulting residue (10 \times 24 cm of silica gel, linear gradient of 35–50% EtOAc/hexane) provided 6.20 g (95%) of the desired product **57**: $[\alpha]^{23}_{546} +69.6^\circ$ (*c* 0.55, CH_2Cl_2); IR (CH_2Cl_2) 3600–3300, 2940, 2760, 1680, 1615, 1515, 1490, 1390, 1305, 1170, 1140, 1060, 1010, 935, 900, 855, 825, 730, 650 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.23 (d, 2 H, *J* = 8.9 Hz, two of *ArH*), 6.84 (d, 2 H, *J* = 8.9 Hz, two of *ArH*), 5.12 (br s, 1 H, one of $=\text{CH}_2$), 4.88 (br s, 1 H, one of $=\text{CH}_2$), 4.79 (d, 1 H, *J* = 12.0 Hz, one of ArCH_2O), 4.67 (br s, 1 H, $\text{C}_9\text{-H}$), 4.57 (br s, 1 H, $\text{C}_5\text{-H}$), 4.47 (dd, *J* = 7.6 and 2.0 Hz, $\text{C}_7\text{-H}$), 4.32 (d, 1 H, *J* = 12.1 Hz, one of ArCH_2O), 4.24 (d, 1 H, *J* = 2.5 Hz, $\text{C}_9\text{-H}$), 3.96 (dd, 1 H, *J* = 7.5 and 2.6 Hz, $\text{C}_8\text{-H}$), 3.79 (s, 3 H, ArOCH_3), 3.57 (s, 3 H, NOCH_3), 3.28 (s, 3 H, NCH_3), 21.69–1.58 (m, 1 H, $\text{C}_6\text{-H}$), 1.52 (s, 3 H, $\text{C}_4\text{-CH}_3$), 1.08 (s, 9 H, one of $\text{Si}(t\text{-Bu})_2$), 1.03 (s, 9 H, one of $\text{Si}(t\text{-Bu})_2$), 0.75 (d, 3 H, *J* = 7.1 Hz, $\text{C}_6\text{-CH}_3$); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 169.5, 159.6, 145.0, 130.0, 110.5, 79.4, 74.2, 72.4, 71.1, 61.0, 55.2, 34.9, 28.6, 27.7, 23.4, 19.2, 5.43; TLC R_f = 0.09 (40% EtOAc/hexane). Anal. Calcd for $\text{C}_{28}\text{H}_{47}\text{NO}_7\text{Si}$: C, 62.54; H, 8.81. Found: C, 62.32; H, 8.94.

[*2R,3R,4S*]-2-[(4-Methoxyphenyl)methoxy]-4-methoxyhept-6-en-3-ol (**61**). To a solution of 7.40 g (46.2 mmol) of diol **59** in 50 mL of *N,N*-dimethylformamide was added 0.25 g (1.1 mmol) of anhydrous camphorsulfonic acid (CSA), and the reaction mixture was stirred for 4.5 h. The resulting solution was diluted with 200 mL of 10:1 hexane/ CH_2Cl_2 and was extracted successively with 3 \times 120 mL of water and 2 \times 100 mL of brine. Drying (Na_2SO_4), filtration, concentration, and flash chromatography (10 \times 28 cm of silica gel, linear gradient of 6–10% EtOAc/hexane) afforded 12.5 g (97%) of **60** as a mixture of acetal anomers.

A solution of 12.5 g (45.0 mmol) of acetal(s) **60** in 250 mL of CH_2Cl_2 was cooled to -78 °C and treated with 22.5 mL (1.0 M in toluene, 225 mmol) of diisobutylaluminum hydride over a 3-min period. After 5 min, the reaction mixture was warmed to -10 °C over a 50-min period and was quenched by cautious addition of 20 mL of methanol. After the solution was warmed to 0 °C, 800 mL of saturated aqueous NH_4Cl and 300 mL of CH_2Cl_2 were introduced and the biphasic mixture was stirred with vigor at room temperature for 12 h. The mixture was then filtered through a large pad of Celite with CH_2Cl_2 and water washings, and the

filtrate was diluted with 400 mL of brine and separated. After the aqueous layer was washed with 200 mL of CH_2Cl_2 , the combined organic extracts were dried (Na_2SO_4), filtered, concentrated, and chromatographed (10 \times 28 cm of silica gel, linear gradient of 20–25% EtOAc/hexane), providing 9.00 g (72%) of the desired reductive cleavage product **61** followed by 1.13 g (9%) of the minor regioisomer (8.0:1 ratio by isolation). Data for **61**: $[\alpha]^{23}_{546} -13.7^\circ$ (*c* 1.65); IR (thin film) 3620–3230 (OH), 3080, 2980, 2940, 2840, 1645, 1615, 1590, 1515, 1465, 1455, 1380, 1305, 1250, 1175, 1090, 1035, 915, 825 cm^{-1} ; ^1H NMR (CDCl_3 , 250 MHz) δ 7.26 (d, 2 H, *J* = 8.6 Hz, two of *ArH*), 6.87 (d, 2 H, *J* = 8.6 Hz, two of *ArH*), 6.00–5.80 (m, 1 H, $\text{CH}=\text{CH}_2$), 5.15–5.05 (m, 2 H, $\text{CH}=\text{CH}_2$), 4.53 (d, 1 H, *J* = 11.3 Hz, one of ArCH_2), 4.38 (d, 1 H, *J* = 11.2 Hz, one of ArCH_2), 3.81–3.78 (m + s, 4 H, ArOCH_3 and CHOH), 3.66 (apparent qn, 1 H, *J* = 6.0 Hz, $\text{CH}_3\text{CHOCH}_2\text{Ar}$), 3.39–3.33 (m + s, 4 H, CHOCH_3), 2.41–2.22 (m, 2 H, $\text{CH}_2\text{CH}=\text{CH}_2$), 2.17 (d, 1 H, *J* = 2.2 Hz, OH), 1.24 (d, 3 H, *J* = 6.2 Hz, $\text{CH}_3\text{CHOCH}_2\text{Ar}$); ^{13}C NMR (CDCl_3 , 62.9 MHz) δ 159.2, 134.9, 130.5, 129.2, 116.7, 113.8, 80.5, 74.7, 72.9, 70.2, 57.1, 55.3, 33.5, 14.5; TLC R_f = 0.24 (30% EtOAc/hexane, R_f (minor) = 0.19). Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{O}_4$: C, 68.55; H, 8.63. Found: C, 68.46; H, 8.75.

[*IR,1(1R),2S*]-[1-[1-(4-Methoxyphenyl)methoxyethyl]-2-methoxy-4-penten-1-yl]oxy]-1,1,1-triethylsilane (**62**). To a 0 °C solution of 9.00 g (32.1 mmol) of alcohol **61** in 90 mL of CH_2Cl_2 was added 10.3 mL (7.47 g, 73.8 mmol) of triethylamine, followed by 9.40 mL (11.0 g, 41.7 mmol) of triethylsilyl trifluoromethanesulfonate. After 1 h at 0 °C, the solution was diluted with 300 mL of 10:1 hexane/ CH_2Cl_2 and washed with 400 mL of 0.15 N aqueous NaHSO_4 . The aqueous layer was extracted with 100 mL of CH_2Cl_2 and the combined organic extracts were washed with 300 mL of brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (10 \times 22 cm of silica gel, linear gradient of 2–3.5% EtOAc/hexane) afforded 12.0 g (95%) of triethylsilyl ether **62** as a clear oil: $[\alpha]^{23}_{546} -21.0^\circ$ (*c* 2.00, CH_2Cl_2), IR (thin film) 3080, 2960, 2940, 2920, 2880, 2840, 1640, 1615, 1590, 1520, 1465, 1305, 1250, 1175, 1155, 1100, 1040, 1010, 910, 825, 795, 740, 730 cm^{-1} ; ^1H NMR (CDCl_3 , 250 MHz) δ 7.24 (d, 2 H, *J* = 8.7 Hz, two of *ArH*), 6.87 (d, 2 H, *J* = 8.7 Hz, two of *ArH*), 6.00–5.80 (m, 1 H, $\text{CH}=\text{CH}_2$), 5.11–5.01 (m, 2 H, $\text{CH}=\text{CH}_2$), 4.51 (d, 1 H, *J* = 11.3 Hz, one of ArCH_2), 4.38 (d, 1 H, *J* = 11.2 Hz, one of ArCH_2), 3.81 (s, 3 H, ArOCH_3), 3.76 (dd, 1 H, *J* = 5.5 and 4.3 Hz, CHOSi), 3.53 (apparent qn, 1 H, *J* = 6.2 Hz, $\text{CH}_3\text{CHOCH}_2\text{Ar}$), 3.34 (s, 3 H, CHOCH_3), 2.30 (m, 2 H, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.21 (d, 3 H, *J* = 6.2 Hz, $\text{CH}_3\text{CHOCH}_2\text{Ar}$), 0.96 (t, 9 H, *J* = 8.2 Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.64 (q, 6 H, *J* = 8.2 Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$); ^{13}C NMR (CDCl_3 , 62.9 MHz) δ 136.5, 131.4, 129.7, 116.6, 114.2, 82.7, 78.0, 75.9, 70.9, 58.2, 34.9, 15.9, 7.5, 5.8; TLC R_f = 0.24 (5% EtOAc/hexane). Anal. Calcd for $\text{C}_{22}\text{H}_{38}\text{O}_4$: C, 66.96; H, 9.71. Found: C, 66.99; H, 9.78.

[*3S,4R,5R*]-3-Methoxy-4-[(triethylsilyl)oxy]-5-[(4-methoxyphenyl)methoxy]hexanal (**63**). Ozone was passed through a cooled (-78 °C) solution of 1.61 g (4.08 mmol) of olefin **62** in 20 mL of 3:1 CH_2Cl_2 /methanol containing 5 drops of pyridine and ca. 3 mg of Sudan III indicator dye until the orange-red solution turned yellow. The reaction was immediately purged of excess ozone employing a stream of nitrogen for 5 min at -78 °C, 8 mL (7 g, 100 mmol) of dimethyl sulfide was added, and the solution was allowed to warm to room temperature. After 6.5 h at 23 °C, the reaction mixture was concentrated, diluted with 200 mL of 1:1 hexane/diethyl ether, and extracted with 100 mL of brine. Drying (Na_2SO_4), filtration, concentration, and flash chromatography (6 \times 18 cm of silica gel, 8% EtOAc/hexane) gave 1.27 g (78%) of aldehyde **63** as a clear oil. This material was submitted without hesitation to DDQ deprotection conditions (subsequent experimental) to effect lactol formation. Data for **63**: IR (thin film) 2960, 2910, 2880, 2840, 2730, 1730, 1615, 1590, 1518, 1465, 1415, 1385, 1325, 1305, 1250, 1210, 1175, 1090, 1040, 1010, 820, 805, 740, 725 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 9.74 (dd, 1 H, *J* = 2.7 and 1.7 Hz, CH_2CHO), 7.23 (d, 2 H, *J* = 8.7 Hz, two of *ArH*), 6.86 (d, 2 H, *J* = 8.7 Hz, two of *ArH*), 4.53 (d, 1 H, *J* = 11.3 Hz, one of ArCH_2), 4.33 (d, 1 H, *J* = 11.4 Hz, one of ArCH_2), 3.80 (s, 3 H, ArOCH_3), 3.76 (dd, 1 H, *J* = 6.0 and 3.3 Hz, CHOSi), 3.37 (dq, 1 H, *J* = 6.1 and 6.6 Hz, $\text{CH}_3\text{CHOCH}_2\text{Ar}$), 3.34 (s, 3 H, CHOCH_3), 2.56 (ddd, 1 H, *J* = 17.0, 8.0, and 2.7 Hz, one of CH_2CHO), 2.39 (ddd, 1 H, *J* = 17.0, 3.8, 1.7 Hz, one of CH_2CHO), 1.21 (d, 3 H, *J* = 6.1 Hz, $\text{CH}_3\text{CHOCH}_2\text{Ar}$), 0.94 (t, 9 H, *J* = 7.7 Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.62 (q, 6 H, *J* = 7.7 Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$); TLC R_f = 0.21 (10% EtOAc/hexane).

2,6-Dideoxy-3-O-methyl-4-O-(triethylsilyl)-D-ribo-hexopyranose (64**).** A solution of 1.25 g (3.15 mmol) of aldehyde **63** in 30 mL of CH_2Cl_2 was treated with 1.5 mL of deionized water, and the biphasic mixture was cooled to 7 °C with vigorous stirring. Solid 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 1.00 g, 4.41 mmol) was then introduced in one portion, immediately affording a black slurry with orange water droplets. After stirring for 40 min at 7–10 °C, the reaction mixture was

diluted with 200 mL of 3:1 hexane/CH₂Cl₂ and was extracted with 100 mL of 5% aqueous NaHCO₃. The aqueous layer was washed with 50 mL of CH₂Cl₂, and the combined aqueous extracts were washed with 200 mL of brine, dried (Na₂SO₄), filtered, and concentrated. Purification by flash chromatography (5 × 20 cm of silica gel, 20–30% EtOAc/hexane) gave 825 mg (95%) of **64** as a 2.7:1 mixture of anomers (¹³C analysis) favoring the equatorial anomer: [α]_D²³ +73.4° (c 1.74, CH₂Cl₂), IR (CH₂Cl₂) 3580 (OH), 3500–3280 (OH), 3060, 2960, 2880, 1455, 1415, 1240, 1130, 1095, 1010, 895, 880, 830, 805 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 5.22–5.02 (m, 1 H, anomeric H), 4.14–4.05 (m, 0.3 H, CHCH₃ (minor)), 3.94 (d, 0.7 H, J = 3.6 Hz, OH (major)), 3.89 (m, 0.7 H, CHCH₃ (major)), 3.62 (m, 0.3 H, CHOCH₃ (minor)), 3.52 (s, 0.9 H, OCH₃ (minor)), 3.50 (m, 0.7 H, CHOCH₃ (major)), 3.41 (s, 2.1 H, OCH₃ (major)), 3.34 (dd, 0.7 H, J = 9.4 and 2.8 Hz, CHOSi), 2.24 (ddd, 0.7 H, J = 13.8, 3.6, and 2.1 Hz, C_{2eq}-H (major)), 2.19 (ddd, 0.3 H, J = 14.4, 3.7, and 1.2 Hz, C_{2ax}-H (minor)), 1.73 (ddd, 0.3 H, J = 14.4, 3.7, and 2.5 Hz, C_{2ax}-H (minor)), 1.49 (ddd, 0.7 H, J = 13.8, 9.7, and 2.4 Hz, C_{2ax}-H (major)), 1.23 (d, 0.9 H, J = 6.3 Hz, CHCH₃ (minor)), 1.21 (d, 2.1 H, J = 6.3 Hz, CHCH₃ (major)), 0.94 (m, 9 H, Si(CH₂CH₃)₃), 0.62 (m, 6 H, Si(CH₂CH₃)₃); ¹³C NMR (CDCl₃, 75.5 MHz) δ 92.0, 91.9 (minor), 78.0, 75.0 (minor), 74.9, 70.1, 63.9, 59.1 (minor), 57.6, 35.9, 33.6 (minor), 18.3, 18.2 (minor), 6.7, 5.0; TLC R_f = 0.13 (20% EtOAc/hexane). Anal. Calcd for C₁₃H₂₈O₄Si: C, 56.48; H, 10.21. Found: C, 56.45; H, 10.26.

2,6-Dideoxy-3-O-methyl-4-O-(triethylsilyl)-β-D-ribo-hexopyranose Acetate (65a). A solution of 7.00 g (25.3 mmol) of azeotropically dried (2 × 10 mL of toluene) lactol **64** in 110 mL of CH₂Cl₂ was sequentially treated with 18 mL (18 g, 228 mmol) of pyridine and 14.3 mL (15.5 g, 152 mmol) of acetic anhydride at ambient temperature, and the resulting solution was stirred for 12 h. After diluting with 300 mL of 3:1 hexane/CH₂Cl₂, the reaction mixture was extracted with 3 × 200 mL of 0.15 N aqueous NaHSO₄ and 1 × 200 mL of brine, and the organic layer was dried (Na₂SO₄), filtered, and concentrated. Rapid flash chromatography (10 × 26 cm of silica gel, linear gradient of 10–20% EtOAc/hexane) provided 7.80 g (97%) of **65a** exclusively as the equatorial acetate. This low-melting, decomposition-prone solid was used without hesitation in glycosidations. Data for **65a**: IR (thin film) 2980, 2880, 1755, 1460, 1365, 1230, 1190, 1160, 1130, 1100, 1055, 1010, 895, 830, 790, 775 cm⁻¹; ¹H NMR (benzene-d₆, 300 MHz) δ 6.36 (dd, 1 H, J = 9.6 and 2.3 Hz, C₁-H), 4.25–4.16 (m, 1 H, C₅-H), 3.35–3.19 (m, 2 H, C₃-H and C₄-H), 3.18 (s, 3 H, OCH₃), 2.06 (ddd, J = 13.2, 4.1, and 2.4 Hz, C_{2eq}-H), 1.66 (s, 3 H, CH₃C=O), 1.56 (ddd, 1 H, J = 13.2, 9.6, and 3.5 Hz, C_{2ax}-H), 1.27 (d, 3 H, J = 6.3 Hz, CHCH₃), 0.93 (t, 9 H, J = 7.9 Hz, Si(CH₂CH₃)₃), 0.51 (q, 6 H, J = 7.9 Hz, Si(CH₂CH₃)₃); TLC R_f = 0.31 (20% EtOAc/hexane).

4,6-O-[Bis(1,1-dimethylethyl)silylene]-5,7,8-trideoxy-3-O-[2,6-di-deoxy-3-O-methyl-4-O-(triethylsilyl)-β-D-ribo-hexopyranosyl]-N-methoxy-2-O-[(4-methoxyphenyl)methyl]-N,5,7-trimethyl-D-glycero-L-ido-oct-7-enamide (66b). A solution of 3.10 g (9.73 mmol) of acetyl glycoside **65a** and 2.80 g (5.21 mmol) of alcohol **57** in 100 mL of toluene was cooled to -8 °C (ice/acetone bath) and treated with 93 mg (0.27 mmol) of trityl perchlorate,¹¹³ affording a yellow slurry. The reaction mixture was gradually warmed to -5 °C over a 30-min period and was then held at this temperature for 55 min. Stirring was terminated, allowing the trityl perchlorate to settle, and the reaction was quenched by rapid cannula transfer into a rapid stirred biphasic mixture consisting of 100 mL of 1:1 hexane/CH₂Cl₂ and 100 mL of 5% aqueous NaHCO₃ (20 mL toluene wash). After 10 min, the mixture was diluted with 100 mL of 2:1 hexane/CH₂Cl₂ and was separated. The aqueous layer was extracted with 50 mL of CH₂Cl₂, and the combined organic extracts were washed with 100 mL of brine, dried (Na₂SO₄), filtered, and concentrated to afford a clear oil. Flash chromatography (8 × 34 cm of silica gel, linear gradient of 25–30% EtOAc/hexane for equatorial anomer, then 40% EtOAc/hexane for axial anomer) provided 2.61 g (63%) of the desired β anomer, followed by 0.78 g of somewhat impure α anomer, and 0.39 g of recovered starting alcohol (13%). Trityl perchlorate mediated equilibration of the α anomer (see following experimental) provided an additional 0.29 g (7%) of desired anomer. The overall yield of the desired equatorial anomer was 2.90 g (70%, 78% based on recovered alcohol). Data for **66b**: [α]_D²³ +66.9° (c 0.88, CH₂Cl₂); IR (thin film) 3060, 2940, 2880, 1685, 1620, 1590, 1520, 1470, 1415, 1390, 1365, 1305, 1250, 1140, 1110, 1010, 940, 880, 860, 840, 825, 740, 730, 650 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.22 (d, 2 H, J = 8.9 Hz, two of ArH), 6.80 (d, 2 H, J = 8.9 Hz, two of ArH), 5.12 (br s, 1 H, one of =CH₂), 5.09 (br s, 1 H, C₅-H), 4.88 (apparent t, 1 H, J = 1.3 Hz, one of =CH₂), 4.78 (d, 1 H, J = 11.5 Hz, one of ArCH₂O), 4.55 (d, 1 H, J = 9.4 Hz, anomeric H), 4.53 (d, 1 H, J = 7.9 Hz, C₇-H), 4.29 (d, 1 H, J = 11.5 Hz, one of CH₂Ar), 4.21 (d, 1 H, J = 2.2 Hz, C₉-H), 4.08–4.02 (m, 1 H, C₈-H), 3.73–3.68 (m, 1 H, C₅-H), 3.57 (s, 3 H, N-OCH₃), 3.49–3.47 (m, 1 H, C₃-H), 3.40 (s, 3 H, C₃-H), 3.26 (dd, 1 H, J = 9.4 and 3.0 Hz,

C₄-H), 3.23 (s, 3 H, NCH₃), 2.28 (ddd, 1 H, J = 13.9, 3.4, and 1.9 Hz, C₂-H_{ax}), 1.68 (ddd, 1 H, J = 13.9, 10.7, and 2.2 Hz, C₂-H_{ax}), 1.65–1.60 (dq, 1 H, J = 2.3 and 7.1 Hz, C₆-H), 1.51 (s, 3 H, CH₂=C(CH₃)), 1.14 (d, 3 H, J = 6.8 Hz, C₅-CH₃), 1.09 (s, 9 H, one of SiC(CH₃)₃), 0.99 (s, 9 H, one of SiC(CH₃)₃), 0.95 (t, 9 H, J = 8.4 Hz, Si(CH₂CH₃)₃), 0.77 (d, 3 H, J = 7.1 Hz, C₆-CH₃), 0.63 (q, 6 H, J = 8.4 Hz, Si(CH₂CH₃)₃); ¹³C NMR (CDCl₃, 75.5 MHz) δ 169.7, 159.4, 145.4, 130.1, 113.8, 110.3, 98.0, 79.6, 78.9, 78.7, 78.4, 76.9, 75.9, 72.0, 70.0, 61.0, 57.0, 55.3, 34.3, 34.2, 33.9, 28.8, 28.7, 27.7, 23.4, 20.7, 19.4, 18.7, 6.9, 6.8, 5.5, 5.1, 4.9; TLC R_f = 0.43 (40% EtOAc/hexane). Anal. Calcd for C₄₁H₇₃O₁₀Si₂N: C, 56.48; H, 61.75; N, 9.23. Found: C, 61.76; H, 9.21.

Selected data for axial anomer **66a**: IR (thin film) 3060, 2960, 2880, 1680, 1516, 1590, 1510, 1480, 1390, 1300, 1250, 940, 890, 825, 730 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.29 (d, 2 H, J = 8.6 Hz, two of ArH), 6.82 (d, 2 H, J = 8.6 Hz, two of ArH), 5.14 (br s, 1 H, one of =CH₂), 4.87 (br s, 1 H, one of =CH₂), 4.78 (br d, 1 H, J = 4.2 Hz, anomeric H), 4.65 (d, 2 H, J = 11.6 Hz, one of CH₃Ar), 4.64 (s, 1 H, C₅-H), 4.60 (d, 1 H, J = 2.4 Hz, C₉-H), 4.55 (dd, 1 H, J = 9.4 and 1.9 Hz, C₈-H), 4.39 (d, 1 H, J = 11.5 Hz, one of CH₂Ar), 4.04 (dd, 1 H, J = 9.4 and 2.2 Hz, C₇-H), 4.04–3.98 (m, 1 H, C₅-H), 3.78 (s, 3 H, NOCH₃), 3.60 (s, 3 H, C₃-OCH₃), 3.42–3.32 (m, 2 H, C₃-H and C₄-H), 3.32 (s, 3 H, C₃-OCH₃), 3.16 (s, 3 H, NCH₃), 2.08 (ddd, 1 H, J = 14.3, 4.2, and 1.7 Hz, C₂-H_{ax}), 1.66–1.63 (m, 1 H, C₆-H), 1.64 (s, 3 H, C₄-CH₃), 1.62 (ddd, 1 H, J = 14.3, 4.8, and 3.2 Hz, C₂-H_{ax}), 1.11 (d, 3 H, J = 6.5 Hz, C₅-CH₃), 1.09 (s, 9 H, SiC(CH₃)₃), 1.02 (s, 9 H, SiC(CH₃)₃), 0.96 (t, 9 H, J = 8.4 Hz, Si(CH₂CH₃)₃), 0.86 (d, 3 H, J = 7.0 Hz, C₆-CH₃), 0.58 (q, 6 H, J = 8.4 Hz, Si(CH₂CH₃)₃); TLC R_f = 0.38 (40% EtOAc/hexane). Anal. Calcd for C₄₁H₇₃O₁₀Si₂N: C, 61.75; H, 9.23. Fund: C, 61.86; H, 9.09.

Equilibration of 66a to 66b. A solution of 0.78 g (approximately 0.77 mmol based on ¹H NMR integration of impure material) of **66a** in 10 mL of toluene was cooled to -8 °C and treated with 17.6 mg (0.051 mmol) of trityl perchlorate.¹¹³ The yellow slurry was warmed to -5 °C over a 20-min period and held at that temperature for an additional 30 min. Stirring was stopped and the clear supernatant was transferred by cannula into 60 mL of rapidly stirred, 0 °C 1:1 CH₂Cl₂/5% aqueous NaHCO₃. After separation of the phases, the organic layer was washed with 50 mL of brine, dried (Na₂SO₄), filtered, concentrated, and chromatographed (5 × 18 cm of silica gel, linear gradient of 30–40% EtOAc/hexane) to provide 0.29 g (47%) of equatorial anomer **66b**, identical in all respects with authentic material prepared by trityl perchlorate mediated glycosidation of acetoxy glycoside **65a** with alcohol **57** (see previous experimental). The total yield of desired anomer after resubmission of α anomer to equilibrating conditions was 2.10 g (70%, 78% based on recovered alcohol).

5,7-O-[Bis(1,1-dimethylethyl)silylene]-1,6,8,9-tetra-deoxy-4-O-[2,6-dideoxy-3-O-methyl-4-O-(triethylsilyl)-β-D-ribo-hexopyranosyl]-3-O-[(4-methoxyphenyl)methyl]-6,8-dimethyl-D-glycero-L-ido-non-8-en-2-ulose (67). A cooled (-78 °C) solution of 2.10 g (2.64 mmol) of amide **66b** in 40 mL of THF was treated with 4.9 mL of methyl lithium (1.5 M in THF, 7.39 mmol, lithium bromide complex) over a 2-min period, and the resulting clear solution was stirred for 40 min at -78 °C. The reaction was quenched by cannula transfer into a precooled (0 °C) and rapidly stirred mixture of 20 mL of saturated aqueous NH₄Cl and 20 mL of 3:1 hexane/CH₂Cl₂, and the vigorously stirred biphasic mixture was allowed to warm to room temperature. After further dilution with 50 mL of 3:1 hexane/CH₂Cl₂ and 50 mL of brine, the two layers were separated, the aqueous layer was washed with 30 mL of CH₂Cl₂, and the combined organic extracts were washed with 150 mL of brine, dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (5 × 22 cm of silica gel, linear gradient of 1–2% EtOAc/CH₂Cl₂) gave 1.89 g (95%) of methyl ketone **67** as a viscous oil: [α]_D²⁴ +45.5° (c 1.63, CH₂Cl₂); IR (thin film) 2970, 2860, 1723, 1615, 1515, 1480, 1460, 1365, 1250, 1120, 1010, 900, 880, 825, 740, 725, 650 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 7.24 (d, 2 H, J = 9.0 Hz, two of ArH), 6.86 (d, 2 H, J = 9.0 Hz, two of ArH), 5.10 (br s, 1 H, one of =CH₂), 4.97 (dd, 1 H, J = 8.8 and 1.8 Hz, anomeric H), 4.87 (br s, 1 H, one of =CH₂), 4.65 (d, 1 H, J = 11.6 Hz, one of ArCH₂O), 4.61 (dd, 1 H, J = 6.7 and 1.9 Hz, C₇-H), 4.51 (br s, 1 H, C₅-H), 4.25 (d, 1 H, J = 11.6 Hz, one of CH₂Ar), 3.93 (dd, 1 H, J = 6.6 and 3.7 Hz, C₈-H), 3.84–3.73 (m, 5 H, C₉-H, C₅-H, and ArOCH₃), 3.50–3.48 (m, 1 H, C₃-H), 3.38 (s, 3 H, C₃-OCH₃), 3.29 (dd, 1 H, J = 9.4 and 2.9 Hz, C₄-H), 2.30 (s, 3 H, CH₃C=O), 2.14 (ddd, 1 H, J = 13.6, 3.5, and 2.0 Hz, C₂-H_{ax}), 1.67–1.59 (m, 1 H, C₆-H), 1.48 (s, 3 H, CH₂=C(CH₃)), 1.39 (ddd, 1 H, J = 13.6, 8.8, and 1.8 Hz, C₂-H_{ax}), 1.18 (d, 3 H, J = 7.2 Hz, C₅-CH₃), 1.08 (s, 9 H, one of SiC(CH₃)₃), 1.04 (s, 9 H, one of SiC(CH₃)₃), 0.96 (t, 9 H, J = 7.6 Hz, Si(CH₂CH₃)₃), 0.86 (d, 3 H, J = 7.1 Hz, C₆-CH₃), 0.62 (q, 6 H, J = 7.6 Hz, Si(CH₂CH₃)₃); ¹³C NMR (CDCl₃, 62.5 MHz) δ 210.0, 158.6, 144.4, 129.4, 114.0, 110.5, 98.0, 83.6, 79.9, 79.5, 78.2, 75.2, 72.9, 70.6, 57.6, 55.3, 35.4, 34.4, 28.7, 28.1, 27.9, 23.6, 20.9, 19.2, 18.5, 6.7, 6.0, 5.1;

TLC R_f = 0.23 (1% EtOAc/CH₂Cl₂). Anal. Calcd for C₄₀H₇₀O₉Si₂: C, 63.96; H, 9.39. Found: C, 63.91; H, 9.25.

5,7-O-[Bis(1,1-dimethylethyl)silylene]-1,6,8,9-tetra(deoxy-4-O-[2,6-dideoxy-3-O-methyl-4-O-(triethylsilyl)- β -D-*ribo*-hexopyranosyl]-6,8-dimethyl-D-glycero-L-ido-non-8-en-2-ulose (68). To a solution of 1.20 g (1.60 mmol) of 4-methoxybenzyl ether 67 in 33 mL of CH₂Cl₂ was added 1.65 mL of deionized water. The resulting biphasic solution was cooled to 10 °C with vigorous stirring and 544 mg (2.40 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was introduced in one portion, immediately providing a black mixture interspersed with orange water droplets. The reaction mixture was warmed to ambient temperature and stirred for an additional 2.5 h, eventually producing a red-orange slurry (DDQ hydroquinone precipitate) which was then diluted with 80 mL of CH₂Cl₂ and extracted with 100 mL of saturated aqueous NaHCO₃. The aqueous layer was back-extracted with 2 × 50 mL of CH₂Cl₂, and the combined organic extracts were dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (6 × 18 cm of silica gel, linear gradient of 1–1.5% EtOAc/CH₂Cl₂) afforded 532 mg (86%) of hydroxy ketone 68 as a clear oil: $[\alpha]^{24}_{D46}$ +7.7° (c 2.75, CH₂Cl₂); IR (thin film) 3600–3300, 3060, 2940, 2890, 1715, 1655, 1480, 1395, 1360, 1270, 1195, 1140, 1100, 1090, 1010, 940, 905, 880, 855, 830, 740, 710, 650 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 5.17 (br s, 1 H, one of =CH₂), 5.11 (dd, 1 H, J = 9.6 and 2.0 Hz, anomeric H), 4.91 (br s, 1 H, one of =CH₂), 4.65 (br s, 1 H, C₅-H), 4.56 (dd, 1 H, J = 5.8 and 2.4 Hz, C₇-H), 4.28 (d, 1 H, J = 7.6 Hz, OH), 4.19 (dd, 1 H, J = 5.8 and 3.0 Hz, C₈-H), 4.03 (dd, 1 H, J = 7.4 and 3.0 Hz, C₅-H), 3.90–3.84 (m, 1 H, C₅-H), 3.50 (apparent t, 1 H, J = 3.0 Hz, C₃-H), 3.41 (s, 3 H, C₃-OCH₃), 3.32 (dd, 1 H, J = 9.3 and 2.8 Hz, C₄-H), 2.30 (s, 3 H, CH₃C=O), 2.15 (ddd, 1 H, J = 13.8, 3.4, and 2.2 Hz, C₂-H_{eq}), 1.90–1.84 (m, 1 H, C₆-H), 1.62 (s, 3 H, CH₂=C(CH₃)), 1.52 (ddd, 1 H, J = 13.8, 9.6, and 2.3 Hz, C₂-H_{ax}), 1.22 (d, 3 H, J = 6.3 Hz, C₅-CH₃), 1.06 (s, 9 H, one of SiC(CH₃)₃), 1.04 (s, 9 H, one of SiC(CH₃)₃), 0.96 (t, 9 H, J = 8.0 Hz, Si(CH₂CH₃)₃), 0.94 (d, 3 H, J = 7.1 Hz, C₆-CH₃), 0.63 (q, 6 H, J = 8.0 Hz, Si(CH₂CH₃)₃); ¹³C NMR (CDCl₃, 125.77 MHz) δ 203.8, 144.2, 110.5, 94.5, 79.7, 79.6, 78.0, 75.7, 75.0, 74.4, 70.2, 57.9, 36.1, 35.1, 28.4, 27.9, 27.2, 23.5, 20.8, 19.2, 18.2, 6.8, 5.8, 4.9; TLC R_f = 0.27 (20% EtOAc/hexane). Anal. Calcd for C₃₂H₆₂O₈Si₂: C, 60.91; H, 9.90. Found: C, 61.03; H, 9.78.

[4R-[4*c*(1*R,2*R**,3*R**,5*a*,6*a*)]-[1-[2,2-Bis(1,1-dimethylethyl)-5-methyl-6-(1-methylethyl)-1,3-dioxa-2-silacyclohex-4-yl]-2,3-dihydro-3-methyl-7-(phenylthio)heptyl] 2,6-Dideoxy-3-O-methyl-4-O-(triethylsilyl)- β -D-*ribo*-hexopyranoside (69).** To a stirred mixture of 243 mg (10.0 mmol) of magnesium chips in 10 mL of anhydrous THF was added a crystal of iodine, producing a light-brown slurry. A solution of 2.70 g (11.0 mmol) of 4-bromobutyl phenylsulfide in 5 mL of anhydrous THF was then introduced dropwise by cannula over a 4-min period. The light-brown color discharged approximately 1 min into the addition, and a gradual exotherm to 40 °C was noted. During the next 1 h, the reaction mixture was periodically warmed to 40 °C by using a heat gun, and essentially all of the magnesium was consumed. After recooling the reaction to ambient temperature, the clear solution was diluted with 17 mL of anhydrous THF, and the Grignard solution thus obtained, 0.31 M in organomagnesium, was employed directly in the next reaction.^{79,106}

Hydroxy ketone 68 (743 mg, 1.18 mmol) was azeotropically dried with two 5 mL portions of anhydrous toluene, and was dissolved in 5.5 mL of anhydrous THF. The resulting clear solution was cooled to –50 °C, and 12.3 mL (3.97 mmol) of freshly prepared Grignard reagent was introduced dropwise over a 4-min period while maintaining the reaction temperature below –35 °C. After 20 min at –40 °C, the reaction was warmed to –25 °C over a 5-min period and left to stir for 14.5 h. The reaction was quenched by addition of 20 mL of saturated aqueous NH₄Cl and was warmed to room temperature. The mixture was partitioned between 100 mL of CH₂Cl₂ and 80 mL of saturated aqueous NH₄Cl, the aqueous layer was extracted with two 60-mL portions of CH₂Cl₂, and the combined organic extracts were dried (Na₂SO₄), filtered, and concentrated. Purification of the residual oil by flash chromatography (7 cm × 24 cm of silica gel, linear gradient of 10–14% EtOAc/hexane) afforded 855 mg (91%) of diol 69, a clear oil, as a single diastereomer: $[\alpha]^{23}_{D46}$ +20.0° (c 2.38, CH₂Cl₂); IR (thin film) 3600–32502, 3060, 2930, 2860, 1655, 1590, 1480, 1440, 1390, 1365, 1315, 1240, 1170, 1000, 940, 900, 870, 825, 735, 650 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.32–7.10 (m, 5 H, ArH), 5.30 (dd, 1 H, J = 9.2 and 1.7 Hz, anomeric H), 5.18 (br s, 1 H, one of =CH₂), 4.93 (br s, 1 H, one of =CH₂), 4.72 (dd, 1 H, J = 8.7 and 2.0 Hz, C₇-H), 4.70 (br s, 1 H, C₅-H), 4.13 (d, 1 H, J = 8.3 Hz, C₈-H), 4.00–3.94 (m, 1 H, C₅-H), 3.81 (1 H, J = 11.2 Hz, C₉-H), 3.51–3.50 (m, 1 H, C₃-H), 3.50 (s, 1 H, OH), 3.40 (s, 3 H, C₃-OCH₃), 3.34 (dd, 1 H, J = 9.3 and 2.7 Hz, C₄-H), 3.23 (d, 1 H, J = 11.2 Hz, OH), 2.93 (t, 2 H, J = 7.3 Hz, C₁₄-H), 2.27 (d, 1 H, J = 13.5 Hz, C₂-H_{eq}), 2.01–1.95 (m, 1 H, C₆-H), 1.70–1.45 (m, 7 H, C₁₁–C₁₃CH₂ and C₂-H_{ax}), 1.62 (s, 3 H, C₄-CH₃), 1.25 (d, 3 H, J = 6.3 Hz, C₅-CH₃), 1.22

(s, 3 H, C₁₀-CH₃), 1.12 (s, 9 H, SiC(CH₃)₃), 1.07 (s, 9 H, SiC(CH₃)₃), 0.97 (t, 9 H, J = 7.9 Hz, Si(CH₂CH₃)₃), 0.83 (d, 3 H, J = 7.1 Hz, C₆-CH₃), 0.63 (q, 6 H, J = 7.9 Hz, Si(CH₂CH₃)₃), 0.83 (d, 3 H, J = 7.1 Hz, C₆-CH₃), 0.63 (q, 6 H, J = 7.9 Hz, Si(CH₂CH₃)₃); ¹³C NMR (CDCl₃, 125.77 MHz) δ 144.2, 136.9, 128.9, 128.8, 125.6, 110.7, 94.4, 79.4, 79.3, 78.1, 75.5, 74.9, 72.2, 70.5, 58.1, 38.4, 35.5, 34.5, 33.5, 29.8, 28.5, 27.8, 23.4, 23.3, 22.9, 20.8, 19.4, 18.2, 6.8, 5.4, 4.9; TLC R_f = 0.05 (10% EtOAc/hexane). Anal. Calcd for C₄₂H₇₆O₈SSi₂: C, 63.27; H, 9.61. Found: C, 63.17; H, 9.67.

[4*R*-[4*c*(1*R,2*R**,3*R**,5*a*,6*a*)]-[1-[2,2-Bis(1,1-dimethylethyl)-5-methyl-6-(1-methylethyl)-1,3-dioxa-2-silacyclohex-4-yl]-2,3-bis[(triethylsilyloxy)-3-methyl-7-(phenylthio)heptyl] 2,6-Dideoxy-3-O-methyl-4-O-(triethylsilyl)- β -D-*ribo*-hexopyranoside (70).** To a cooled (–50 °C) solution of 483 mg (0.606 mmol) of diol 69 in 2.0 mL of THF was added 833 μ L (1.33 mmol) of *n*-butyllithium (1.60 M in hexane) dropwise over a 3 min-period, maintaining the internal temperature of the reaction below –40 °C. After 3 min, 0.926 mL (1.08 g, 4.08 mmol) of triethylsilyl trifluoromethanesulfonate (TESOTf) was introduced, and the clear solution was warmed to –10 °C over a 10-min period. After an additional 1.6 h at –10 °C, the reaction mixture was quenched by cannula transfer into a rapidly stirred and cooled (0 °C) biphasic mixture of 30 mL of saturated aqueous NH₄Cl and 50 mL of CH₂Cl₂. The phases were sep'd., the aq. phase was washed with 20 mL of CH₂Cl₂, and the combined organic extracts were washed with 40 mL of brine, dried (Na₂SO₄), filtered, and concentrated. Purification by flash chromatography (5 × 23 cm of silica gel, linear gradient of 1–4% EtOAc/hexane) gave 562 mg (90%) of the fully silylated material 70, followed by 51 mg (8%) of partially silylated material. Resubmission of the latter to an analogous silylation procedure (1.1 equiv of *n*-BuLi/1.1 equiv of TESOTf) afforded an addnl. 40 mg of product (overall yield of 97%). Data for 70: $[\alpha]^{23}_{D46}$ +20.2° (c 4.64, CH₂Cl₂); IR (thin film) 3060, 2960, 2880, 1655, 1590, 1460, 1420, 1365, 1265, 1240, 1170, 1100, 1010, 935, 900, 880, 850, 830, 740, 690, 650 cm⁻¹; ¹H NMR (benzene-d₆, 500 MHz) δ 7.33 (d, 2 H, J = 7.8 Hz, ArH), 7.09 (t, 2 H, J = 7.8 Hz, ArH), 6.92 (t, 1 H, J = 7.8 Hz, ArH), 5.55 (br s, 1 H, one of =CH₂), 5.17 (dd, 1 H, J = 9.2 and 1.4 Hz, anomeric H), 5.04 (br s, 1 H, one of =CH₂), 4.85 (br s, 1 H, C₅-H), 4.50 (s, 1 H, C₇-H), 4.46 (d, 1 H, J = 6.1 Hz, C₉-H), 4.00 (d, 1 H, J = 6.1 Hz, C₈-H), 4.00–3.94 (m, 1 H, C₅-H), 3.33–3.28 (partially obscured m, 2 H, C₃-H and C₄-H), 3.31 (s, 3 H, C₃-OCH₃), 2.93–2.87 (m, 1 H, one of C₁₄-CH₂), 2.80–2.73 (m, 1 H, one of C₁₄-CH₂), 2.32 (d, 1 H, J = 10.4 Hz, C₂-H_{eq}), 2.18–2.13 (m, 1 H, C₆-H), 1.96–1.89 (m, 1 H), 1.71–1.62 (m, 5 H, C₁₁–C₁₃CH₂), 1.68 (s, 3 H, C₄-CH₃), 1.61 (partially obscured ddd, 1 H, C₂-H_{ax}), 1.56 (d, 3 H, J = 7.1 Hz, C₆-CH₃), 1.38 (s, 3 H, C₁₀-CH₃), 1.37 (s, 9 H, SiC(CH₃)₃), 1.30 (d, 3 H, J = 6.3 Hz, C₅-CH₃), 1.25 (s, 9 H, SiC(CH₃)₃), 1.17 (t, 9 H, Si(CH₂CH₃)₃), 1.04–0.91 (m, 18 H, Si(CH₂CH₃)₃), 0.73–0.52 (m, 18 H, Si(CH₂CH₃)₃); ¹³C NMR (benzene-d₆, 75.5 MHz) δ 144.7, 129.2, 129.1, 125.6, 110.8, 95.8, 86.2, 81.6, 80.9, 79.2, 78.9, 76.4, 72.3, 67.8, 58.3, 37.6, 36.9, 36.3, 33.8, 30.5, 29.1, 28.4, 27.4, 24.5, 23.9, 19.3, 18.9, 7.6, 7.5, 7.4, 7.1, 6.9, 5.8, 5.4; TLC R_f = 0.49 (5% EtOAc/hexane). Anal. Calcd for C₅₄H₁₀₄O₈SSi₄: C, 63.23; H, 10.22. Found: C, 63.09; H, 10.27.

3,5-O-[Bis(1,1-dimethylethyl)silylene]-4,9,10,11,12-pentadeoxy-6-O-[2,6-dideoxy-3-O-methyl-4-O-(triethylsilyl)- β -D-*ribo*-hexopyranosyl]-4-methyl-2,8-di-C-methyl-12-(phenylsulfonyl)-7,8-bis-O-(triethylsilyl)-D-xylo-L-gulo-dodecitol (71). To a solution of 490 mg (0.478 mmol) of sulfide olefin 70 and 453 mg (3.35 mmol) of *N*-methylmorpholine *N*-oxide monohydrate in 25 mL of 5:5:1 THF/acetone/water was added 569 μ L (0.15 M in water, 0.085 mmol) of osmium tetroxide, affording a pale-yellow solution. Thin-layer chromatographic analysis of the reaction indicated rapid formation of the sulfone olefin, followed by relatively slow bis-hydroxylation of this intermediate. After 22 h, the solution was diluted with 20 mL of CH₂Cl₂ and was quenched by addition of 20 mL of saturated aqueous sodium bisulfite. After vigorously stirring the biphasic mixture for 10 min, the mixture was partitioned between 50 mL of water and 50 mL of CH₂Cl₂, the aqueous layer was washed with 30 mL of CH₂Cl₂, and the combined organic extracts were dried (Na₂SO₄), filtered, and concentrated. Purification of the resulting oil by flash chromatography (3 × 16 cm of silica gel, linear gradient of 15–20% EtOAc/hexane) provided 503 mg (96%) of the desired diol sulfone 71: $[\alpha]^{23}_{D46}$ –3.5° (c 0.80, CH₂Cl₂); IR (thin film) 3600–3300, 3060, 2960, 2880, 1740, 1465, 1365, 1330, 1310, 1240, 1090, 1050, 1000, 900, 880, 820, 735, 690, 645 cm⁻¹; ¹H NMR (benzene-d₆, 500 MHz) δ 7.88 (d, 2 H, J = 8.0 Hz, ArH), 7.07–7.00 (m, 3 H, ArH), 5.10 (br d, 1 H, J = 11.4 Hz, anomeric H), 4.42 (d, 1 H, J = 1.6 Hz, C₅-H), 4.37 (d, 1 H, J = 5.8 Hz, C₈-H), 4.33 (s, 1 H, C₉-H), 3.89 (d, 1 H, J = 5.9 Hz, C₇-H), 3.88–3.84 (m, 1 H, C₅-H), 3.79 (d, 1 H, J = 9.9 Hz, one of CH₂OH), 3.45 (dd, 1 H, J = 10.0 and 6.5 Hz, one of CH₂OH), 3.35–3.27 (m, 2 H, C₃-H and C₄-H), 3.30 (s, 3 H, C₃-OCH₃), 3.01–2.94 (m, 1 H, one of C₁₄-CH₂), 2.89–2.83 (m, 1 H, one of C₁₄-CH₂), 2.70 (s, 1 H, C₄-OH), 2.28 (ddd, 1 H, J = 11.9, 3.2 and 1.3 Hz, C₂-H_{eq}), 2.26–2.20 (m, 1 H,

$C_6\text{-}H$, 2.05 (br s, 1 H, CH_2OH), 1.84–1.71 (m, 2 H), 1.68 (d, 3 H, J = 7.0 Hz, $\text{C}_6\text{-CH}_3$), 1.65–1.48 (m, 5 H, including $\text{C}_2\text{-H}_{\text{ax}}$), 1.33 (d, 3 H, J = 6.3 Hz, $\text{C}_5\text{-CH}_3$), 1.31 (s, 3 H, $\text{C}_{10}\text{-CH}_3$ or $\text{C}_4\text{-CH}_3$), 1.29 (s, 3 H, $\text{C}_{10}\text{-CH}_3$ or $\text{C}_4\text{-CH}$), 1.27 (s, 9 H, one of $\text{SiC}(\text{CH}_3)_3$), 1.12 (t, 9 H, J = 8.0 Hz, one of $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 1.02–0.86 (m, 18 H, two of $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.65–0.53 (m, 18 H, $\text{Si}(\text{CH}_2\text{CH}_3)_3$); ^{13}C NMR (benzene- d_6 , 125.77 MHz) δ 140.6, 132.9, 128.4, 127.9, 95.8, 83.5, 82.6, 80.9, 78.9, 78.8, 76.3, 74.8, 72.0, 69.9, 68.1, 58.4, 56.1, 39.3, 36.9, 36.2, 29.0, 28.4, 26.9, 24.3, 23.9, 22.5, 21.4, 18.9, 8.6, 7.6, 7.5, 7.3, 7.1, 5.8, 5.3; TLC R_f = 0.18 (20% EtOAc/hexane). Anal. Calcd for $\text{C}_{54}\text{H}_{106}\text{O}_{12}\text{SSi}_4$: C, 59.40; H, 9.79. Found: C, 59.50; H, 9.86.

3,5-O-[Bis(1,1-dimethylethyl)silylene]-4,9,10,11,12-pentadeoxy-6-O-[2,6-dideoxy-3-O-methyl-4-O-(triethylsilyl)- β -D-ribo-hexopyranosyl]-4-methyl-2,8-di-C-methyl-12-(phenylsulfonyl)-2,7,8-tris-O-(triethylsilyl)-D-xylo-L-gulo-dodecanal (73). To a solution of 90 μL (1.03 mmol) of oxalyl chloride in 4 mL of CH_2Cl_2 at -78°C was added 110 μL (1.55 mmol) of dimethyl sulfoxide dropwise over a 1-min period (gas evolution). After 5 min, a solution of 225 mg (0.206 mmol) of alcohol 71 in 1.0 mL of CH_2Cl_2 was slowly added by cannula while maintaining the reaction temperature below -70°C . The white slurry was stirred for an additional 30 min at -78°C , and 0.57 mL (4.1 mmol) of triethylamine was added over a 1-min period, affording a clear solution. The reaction was stirred for 10 min at -78°C before gradually warming to -30°C over 8 min. The resulting triethylamine hydrochloride laden mixture was held at -30°C for 10 min and was then quenched with 10 mL of 0.05 M aqueous pH 7 phosphate buffer with simultaneous removal of the cooling bath. After stirring for 5 min at ambient temperature, the two-phase mixture was partitioned between 30 mL of 15% CH_2Cl_2 /hexane and 20 mL of water, and the aqueous layer was extracted with 20 mL of CH_2Cl_2 . The combined organic extracts were successively washed with 30 mL of 0.1 N aqueous NaHSO_4 , 30 mL of water, and 30 mL of brine and were subsequently dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (2 cm \times 18 cm of silica gel, 10–15% EtOAc/hexane) of the residue gave 195 mg (87%) of aldehyde 72 as a clear oil (TLC R_f = 0.18 in 10% EtOAc/hexane). This highly oxidation-prone aldehyde was silylated without hesitation.

To a cooled (0°C) solution of 190 mg (0.174 mmol) of alcohol 72 in 1 mL of CH_2Cl_2 was added 51 μL (0.436 mmol) of 2,6-lutidine, followed by 53 μL (0.235 mmol) of triethylsilyl trifluoromethanesulfonate. After 15 min at 0°C , the solution was diluted with 20 mL of 4:1 hexane/ CH_2Cl_2 and washed with 15 mL of 0.15 N aqueous NaHSO_4 . The aqueous layer was extracted with 10 mL of CH_2Cl_2 , and the combined organic extracts were washed with 20 mL of brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (2 \times 20 cm of silica gel, 7% EtOAc/hexane) afforded 200 mg (96%) of triethylsilyl ether 73 as a clear oil: IR (thin film) 3070, 2960, 2890, 1740, 1480, 1460, 1450, 1415, 1320, 1310, 1265, 1240, 1150, 1110, 1090, 1005, 880, 825, 740, 690, 650 cm $^{-1}$; ^1H NMR (benzene- d_6 , 500 MHz) δ 9.87 (s, 1 H, CHO), 7.90 (d, 2 H, J = 7.5 Hz, ArH), 7.08–7.02 (m, 3 H, ArH), 5.05 (d, 1 H, J = 8.9 Hz, anomeric H), 4.48 (d, 1 H, J = 1.8 Hz, $\text{C}_5\text{-H}$), 4.37 (d, 1 H, J = 6.0 Hz, $\text{C}_9\text{-H}$), 4.33 (br s, 1 H, $\text{C}_7\text{-H}$), 3.91 (d, 1 H, J = 6.0 Hz, $\text{C}_8\text{-H}$), 3.86–3.79 (m, 1 H, $\text{C}_5\text{-H}$), 3.32–3.26 (m, 5 H, $\text{C}_3\text{-OCH}_3$, $\text{C}_3\text{-H}$, and $\text{C}_4\text{-H}$), 3.00–2.93 (m, 1 H, one of $\text{C}_{14}\text{-CH}_2$), 2.88–2.81 (m, 1 H, one of $\text{C}_{14}\text{-CH}_2$), 2.26 (d, 1 H, J = 13.8 Hz, $\text{C}_2\text{-H}_{\text{eq}}$), 2.22–2.16 (m, 1 H, $\text{C}_6\text{-H}$), 1.87–1.70 (m, 2 H), 1.64 (d, 3 H, J = 7.4 Hz, $\text{C}_6\text{-CH}_3$), 1.62–1.44 (m, 5 H including $\text{C}_2\text{-H}_{\text{ax}}$), 1.43 (s, 3 H, $\text{C}_{10}\text{-CH}_3$ or $\text{C}_4\text{-CH}_3$), 1.36 (s, 3 H, $\text{C}_{10}\text{-CH}_3$ or $\text{C}_4\text{-CH}_3$), 1.28 (s, 9 H, $\text{SiC}(\text{CH}_3)_3$), 1.24 (s, 9 H, $\text{SiC}(\text{CH}_3)_3$), 1.12 (t, 9 H, J = 7.8 Hz, one of $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 1.04–0.94 (m, 27 H, three of $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.91–0.86 (q, 6 H, J = 8.0 Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.66–0.52 (m, 18 H, $\text{Si}(\text{CH}_2\text{CH}_3)_3$); ^{13}C NMR (benzene- d_6 , 125.77 MHz) δ 212.3, 140.6, 132.9, 129.2, 128.4, 128.3, 127.9, 95.8, 83.4, 83.0, 82.0, 80.8, 78.9, 78.8, 76.2, 72.1, 69.9, 58.3, 56.1, 39.6, 37.0, 36.1, 29.1, 28.3, 27.2, 24.4, 24.1, 24.0, 21.4, 19.4, 18.9, 8.7, 7.6, 7.5, 7.3, 7.2, 7.12, 6.9, 5.7, 5.3; TLC R_f = 0.27 (10% EtOAc/hexane).

5,7-O-[Bis(1,1-dimethylethyl)silylene]-2,3,6,11,12,13,14-heptadecoxy-8-O-[2,6-dideoxy-3-O-methyl-4-O-(triethylsilyl)- β -D-ribo-hexopyranosyl]-6-methyl-4,10-di-C-methyl-14-(phenylsulfonyl)-4,9,10-tris-O-(triethylsilyl)-(2E)-D-xylo-L-gulo-tetradec-2-enic Acid (74). To a solution of diethyl [[(trimethylsilyl)oxy]carbonyl]methanephosphonate¹¹² (0.552 mmol) in 1.3 mL of THF was added (343 μL (0.549 mmol) of n -butyllithium (1.60 M solution in hexane) over 45 s, producing a mild exotherm. The resulting clear solution was stirred for an additional 40 min before a solution of 190 mg (0.158 mmol) of aldehyde 73 in 0.8 mL of THF (0.2 mL wash) was introduced. After 17.5 h at ambient temperature, the clear solution was diluted with 50 mL of EtOAc and was acidified to pH 2 with 0.1 N aqueous NaHSO_4 . The aqueous extract was washed with 30 mL of EtOAc, and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated by rotary evaporation to afford a clear oil. Purification of this material by flash chromatography (2 \times 21 cm of silica gel, linear gradient of 20–38% EtOAc/hexane)

provided 179 mg (91%) of acid 74 as a white foam: $[\alpha]^{23}_{D46}$ −3.9° (c 0.80, CH_2Cl_2); IR (thin film) 3450–2400, 2970, 2880, 1725, 1700, 1658, 1480, 1465, 1450, 1415, 1380, 1310, 1240, 1150, 1090, 1005, 940, 880, 825, 740, 690, 645 cm $^{-1}$; ^1H NMR (benzene- d_6 , 500 MHz) δ 7.90 (dd, 2 H, J = 7.5 and 1.4 Hz, ArH), 7.52 (d, 1 H, J = 16.8 Hz, $\text{C}_3\text{-H}$), 7.10–7.04 (m, 3 H, ArH), 6.18 (d, 1 H, J = 16.8 Hz, $\text{C}_2\text{-H}$), 5.05 (d, 1 H, J = 9.2 Hz, anomeric H), 4.38 (d, 1 H, J = 5.5 Hz, $\text{C}_9\text{-H}$), 4.31 (br s, 1 H, $\text{C}_7\text{-H}$ or $\text{C}_5\text{-H}$), 4.23 (br s, 1 H, $\text{C}_5\text{-H}$ or $\text{C}_7\text{-H}$), 3.91 (d, 1 H, J = 5.4 Hz, $\text{C}_8\text{-H}$), 3.86–3.79 (m, 1 H, $\text{C}_5\text{-H}$), 3.34–3.23 (m, 5 H, $\text{C}_3\text{-OCH}_3$, $\text{C}_3\text{-H}$, and $\text{C}_4\text{-H}$), 3.00–2.93 (m, 1 H, one of $\text{C}_{14}\text{-CH}_2$), 2.90–2.83 (m, 1 H, one of $\text{C}_{14}\text{-CH}_2$), 2.28 (d, 1 H, J = 13.5 Hz, $\text{C}_2\text{-H}_{\text{eq}}$), 2.18–2.13 (m, 1 H, $\text{C}_6\text{-H}$), 1.89–1.70 (m, 2 H), 1.63 (d, 3 H, J = 7.4 Hz, $\text{C}_6\text{-CH}_3$), 1.62–1.40 (m, 5 H including $\text{C}_2\text{-H}_{\text{ax}}$), 1.36 (s, 3 H, $\text{C}_{10}\text{-CH}_3$ or $\text{C}_4\text{-CH}_3$), 1.35 (s, 9 H, $\text{SiC}(\text{CH}_3)_3$), 1.29 (s, 3 H, $\text{C}_{10}\text{-CH}_3$ or $\text{C}_4\text{-CH}_3$), 1.25 (s, 9 H, $\text{SiC}(\text{CH}_3)_3$), 1.13 (t, 9 H, J = 7.9 Hz, one of $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 1.13 (t, 9 H, J = 7.9 Hz, one of $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 1.05 (t, 9 H, J = 7.8 Hz, one of $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 1.00 (t, 9 H, J = 7.9 Hz, one of $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.96 (t, 9 H, J = 7.9 Hz, one of $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.91–0.86 (q, 6 H, J = 8.0 Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.69–0.52 (m, 18 H, $\text{Si}(\text{CH}_2\text{CH}_3)_3$); ^{13}C NMR (125.77 MHz, benzene- d_6) δ 172.4, 155.8, 140.6, 132.9, 129.2, 128.4, 128.3, 127.9, 119.8, 95.8, 84.7, 83.3, 80.9, 78.9, 78.3, 76.2, 72.0, 69.9, 58.3, 56.1, 40.1, 36.8, 29.2, 28.4, 27.1, 24.4, 24.1, 21.5, 18.9, 8.5, 7.6, 7.5, 7.4, 7.3, 7.2, 7.1, 5.8, 5.3; TLC R_f = 0.09 (20% EtOAc/hexane). Anal. Calcd for $\text{C}_{62}\text{H}_{120}\text{O}_{13}\text{SSi}_5$: C, 59.79; H, 9.71. Found: C, 59.93; H, 9.83.

[2S-[2 α -(1R*[1R*[4R*(2E,4S*),5S*,6S*],2S*,3S*,7E,9R*,11-R*]],3a,4a,6a[8R*(S*,9R*)]]-4-[6-[1-[[2,6-Dideoxy-3-O-methyl-4-O-(triethylsilyl)- β -D-ribo-hexopyranosyl]oxy]-9-[2-[8-[2-[(diethyl(1-methylethyl)silyl)oxy]butyl]-4-hydroxy-3,9-dimethyl-1,7-dioxaspiro[5.5]-undec-2-yl]-1-[(4-methoxyphenyl)methoxy]ethyl]-12-[[1,(1-dimethylethyl)dimeethylsilyl]oxy]-3,11-dimethyl-2,3-bis(triethylsilyl)oxy]-7-dodecenyl]-2,2-bis(1,1-dimethylethyl)-5-methyl-1,3-dioxa-2-silacyclohex-4-yl]-4-[(triethylsilyl)oxy]-2-pentenoic Acid (75). To a solution of 218 μL (2.10 mmol) of diethylamine in 3.5 mL of THF at -10°C was added 1.25 mL (2.00 mmol) of n -butyllithium (1.60 M in hexane) over a 45-s period. The resulting colorless solution was warmed to 0°C and stirred for 15 min. Titration of this solution just prior to use (BHT, fluorene)¹⁰⁵ indicated formation of a 0.41 M solution of lithium diethylamide.

In a separate flask, 160 mg (0.128 mmol) of sulfone acid 74 was azeotropically dried by addition and evaporation of 3 \times 2 mL of toluene, dissolved in 1.5 mL of THF, and cooled to -78°C . To the clear sulfone acid solution was introduced 660 μL (0.41 M in THF, 0.270 mmol) of lithium diethylamide dropwise over a 3-min period. A bright yellow color indicative of sulfone anion formation was noted soon after addition of the second equivalent of base was initiated. The canary yellow solution thus obtained was warmed to -55°C and stirred for 1 h before being recooled to -78°C .

In a third flask, 122 mg (0.128 mmol) of aldehyde 37 was azeotropically dried with 2 \times 2 mL of toluene and was dissolved in 0.8 mL of THF. The clear aldehyde solution was then introduced dropwise to the dianion solution by cannula over a 3-min period (0.2 mL THF wash, complete disappearance of yellow dianion color approximately 90% into the addition). After 1.2 h at -78°C , the reaction was quenched by cannula transfer into 50 mL of rapidly stirred, 0°C 1:1 aqueous pH 2 NaHSO_4 /EtOAc, and the mixture was warmed to room temperature. The two layers were separated, the aqueous phase was washed with 20 mL of EtOAc, and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to afford 290 mg of unpurified material. TLC, ^1H NMR, and IR analysis of this material indicated less than 10% of either of the two starting materials was evident: IR (thin film) 3600–2400, 1710, 1700, 1655, 1615, 1520, 1470, 1420, 1380, 1300, 1210, 1110, 1000, 1020, 880, 830, 720 cm $^{-1}$; ^1H NMR (500 MHz, benzene- d_6) δ 7.80 (br d, 2 H, J = 8.6 Hz, sulfone ArH), 7.41 (d, 1 H, J = 15.5 Hz, $\text{C}_3\text{-H}$), 7.39 (m, 2 H, PMB aromatic H), 7.1–6.9 (m, 5 H, ArH), 6.28 (d, 2 H, J = 15.5 Hz, $\text{C}_2\text{-H}$), 5.40–5.30 (m, 1 H), 4.90–3.50 (m, 18 H) 3.50–3.30 (m, 9 H including 2 \times OCH_3), 2.70–2.55 (m, 2 H), 2.35–0.50 (m, 100 H), 0.15–0.12 (m, 6 H, $\text{Si}(\text{CH}_3)_2$); TLC R_f = 0.58–0.67 (40% EtOAc/hexane).

To a flask containing 290 mg (assumed 0.128 mmol) of the unpurified hydroxy sulfones from the previous reaction (azeotropically dried with 3 \times 2 mL of toluene) was added 187 mg (1.54 mmol) of (*N,N*-dimethylamino)pyridine, followed by 1.8 mL of CH_2Cl_2 . Acetic anhydride (120 μL , 1.28 mmol) was then introduced in one portion, affording a yellow solution. After 12 h at ambient temperature, the orange solution was concentrated to an oil employing nitrogen flow, 1 mL of THF and 1 mL of water were introduced, and the mixture was stirred for 20 min. After diluting with 60 mL of EtOAc, the solution was acidified to pH 2.0 with 0.1 N aqueous NaHSO_4 , and the layers were separated. The aqueous extract was washed with 20 mL of EtOAc, and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to afford

300 mg of an acrid oil which was employed without further purification in the subsequent step. Data for acetoxy sulfones: IR (thin film) 2600–2450, 1750, 1760, 1700, 1655, 1620, 1520, 1470, 1420, 1380, 1320, 1300, 1150, 1100, 1020, 880, 830, 730 cm⁻¹; TLC R_f = 0.58–0.66 (40% EtOAc/hexane).

To a solution of 300 mg (assumed 0.128 mmol) of the acetoxy sulfones in 3 mL of methanol and 3 mL of THF at -40 °C was added ca. 200 mg of powdered NaHCO₃, followed by 2.5 g of THF-washed and pulverized 6% sodium amalgam. After 5 min, the slurry was warmed to -30 °C and was held at this temperature for 55 min while stirring with vigor. The reaction was quenched by pipet transfer of the supernatant into a rapidly stirred and cooled (0 °C) mixture consisting of 80 mL of 1:1 EtOAc/pH 2 aqueous NaHSO₄ (EtOAc washes). After further acidifying the aqueous layer to pH 2 with 0.1 N aqueous NaHSO₄, the two layers were separated and the aqueous extract was washed with 20 mL of EtOAc. The combined organic extracts were then dried (Na₂SO₄), filtered, and concentrated, affording an oil. Purification of this residue by flash chromatography (3.5 × 20 cm of silica gel, linear gradient of 18–23% EtOAc/hexane) gave 159 mg (66% for three steps) of the desired hydroxy acid 75 as a white foam: $[\alpha]^{24}_{D_6}$ -18° (c 0.50, CH₂Cl₂); IR (thin film) 3540–2400, 3060, 2960, 2880, 1700, 1655, 1615, 1515, 1465, 1415, 1385, 1365, 1305, 1265, 1250, 1170, 1090, 1010, 975, 880, 840, 825, 740 cm⁻¹; ¹H NMR (500 MHz with COSY-90, benzene-*d*₆) δ 7.53 (d, 2 H, *J* = 15.9 Hz, C₃-*H*), 7.41 (d, 2 H, *J* = 8.4 Hz, two of Ar*H*), 6.88 (d, 2 H, *J* = 8.4 Hz, two of Ar*H*), 6.18 (d, 1 H, *J* = 15.9 Hz, C₂-*H*), 5.63 (dt, 1 H, *J* = 15.3 and 6.0 Hz, C₁₄-*H*), 5.52 (dd, 1 H, *J* = 15.3 and 8.5 Hz, C₁₅-*H*), 5.08 (d, 1 H, *J* = 9.1 Hz, anomeric *H*), 4.65 (d, 1 H, *J* = 11.1 Hz, one of CH₂Ar), 4.63 (d, 1 H, *J* = 11.1 Hz, one of CH₂Ar), 4.48 (d, 1 H, *J* = 5.6 Hz, C₉-*H*), 4.35 (br s, 1 H, C₅-*H*), 4.27 (br s, 1 H, C₇-*H*), 4.26–4.20 (m, 1 H, C₁₉-*H*), 4.08–3.96 (m, 4 H, C₃-*H*, C₈-*H*, C₂₁-*H*, and C₃₂-*H*), 3.85–3.79 (m, 1 H, C₃₀-*H*), 3.73–3.69 (m, 1 H, C₁₇-*H*), 3.63 (dd, 1 H, *J* = 9.6 and 4.4 Hz, one of C₂₄-CH₂), 3.51 (dd, 1 H, *J* = 9.6 and 6.3 Hz, one of C₂₄-CH₂), 3.39 (s, 3 H, one of OCH₃), 3.37 (s, 3 H, one of OCH₃), 3.38–3.29 (m, 2 H, C₃-*H* and C₄-*H*), 2.79–2.71 (m, 1 H, C₁₆-*H*), 2.32 (d, 1 H, *J* = 13.8 Hz, C₂-H_{ax}), 2.30–2.24 (m, 1 H, C₆-*H*), 2.24–2.20 (m, 1 H), 2.15–2.08 (m, 2 H, C₂₂-CH₂), 2.05–1.97 (m, 2 H, including C₂₃-*H*), 1.94–1.86 (m, 3 H, including C₃₁-CH₂), 1.86–1.82 (m, 1 H), 1.82–1.78 (m, 2 H, including C₂₀-*H*), 1.75–1.70 (m, 4 H, including one of C₁₈-CH₂), 1.70–1.63 (m, 2 H), 1.68 (d, 3 H, *J* = 7.1 Hz, C₆-*H*), 1.62–1.55 (m, 2 H, including C₂-H_{ax}), 1.45 (dd, 1 H, *J* = 18.0 and 12.5 Hz, C₂₅-H_{ax}), 1.40 (s, 3 H, C₁₀-CH₃ or C₄-CH₃), 1.38 (s, 9 H, one or Si(i-Bu)), 1.28 (s, 9 H, one of Si(i-Bu)), 1.18–0.90 (m, 67 H), 0.78–0.55 (m, 29 H, Si(CH₂CH₃)₃ and Si(CH₂CH₃)₂), 0.13 (s, 3 H, one of Si(CH₃)₂), 0.12 (s, 3 H, one of Si(CH₃)₂); ¹³C NMR (125.77 MHz, benzene-*d*₆) δ 171.6, 159.6, 155.5, 132.3, 1312.8, 131.5, 129.1, 129.0, 127.9, 119.3, 114.1, 97.7, 95.7, 84.9, 81.6, 81.0, 79.3, 78.8, 78.3, 76.3, 71.8, 70.6, 70.5, 69.7, 69.6, 68.3, 58.4, 54.8, 40.5, 36.3, 36.2, 36.1, 35.3, 34.2, 30.4, 30.0, 29.5, 28.4, 24.2, 21.6, 19.2, 18.5, 17.7, 13.6, 11.5, 9.3, 8.0, 7.8, 7.7, 7.6, 7.4, 7.2, 6.1, 5.4, 4.6, 4.5, 0.4, -5.0, -5.1; TLC R_f = 0.28 (5% EtOAc/hexane). Anal. Calcd for C₁₀₀H₁₉₄O₁₈Si₇: C, 63.85; H, 10.39. Found: C, 64.02; H, 10.26.

[1S-[1R*,4E,6S*,7R*,11S*,12R*,14S*,18E,20R*-(R*),21R*,23R*,25S*[5R*,6R*(S*)],27S*,28S*]-]6-[2-[(Diethyl(1-methylethyl)silyloxy)butyl]-9',9'-bis(1,1-dimethylethyl)-20'-[3-[(1,1-dimethylethyl)dimethylsilyloxy]-2-methylpropyl]-3,4,5,6-tetrahydro-21'-hydroxy-5,6,14',27',28'-pentamethyl-3'-oxo-6',13',14'-tris[(triethylsilyl)oxy]spiro[2H-pyran-2,2S'-[2,8,10,24]tetraoxa[9]silatricyclo[21.3.1.1^{7,11}]octacosa-4',18'-dien-12'-yl] 2,6-Dideoxy-3-O-methyl-4-O-(triethylsilyl)- β -D-ribo-hexopyranoside (76). Hydroxy acid 75 (70.0 mg, 37.2 μ mol) and (*N,N*-dimethylamino)pyridine (DMAP, 13.6 mg, 117 μ mol) were placed in a flask and azeotropically dried with 3 × 3 mL of toluene. The resulting solid was dissolved in 18.5 mL of dry, ethanol-free chloroform¹⁰³ and this hydroxy acid solution was transferred to a 20 mL gas-tight syringe.

A solution of 192 mg (93.0 mmol) of *N,N*-dicyclohexylcarbodiimide (DCC), 100 mg (0.818 mmol) of DMAP, and 142 mg (0.893 mmol) of DMAP-HCl in 106 mL of dry, ethanol-free chloroform was heated to reflux. The hydroxy acid 75 was then added to the refluxing solution over a period of 21 h employing a syringe pump (The needle was inserted through the top of condenser and positioned such that refluxing chloroform continually washed developing droplets of substrate into the reaction vessel). After the addition was complete, the syringe was rinsed with 0.5 mL of chloroform, and this material was delivered to the reaction vessel by syringe pump over 0.6 h. The reaction mixture was cooled to 50 °C and excess DCC was consumed by adding 710 mg (5.8 mmol) of DMAP, 142 μ L (136 mg, 2.25 mmol) of acetic acid, and 1.8 mL of methanol in succession and stirring the resulting clear solution for 2 h. The solution was cooled to ambient temperature, diluted with 200 mL of hexane, and extracted successively with 2 × 150 mL of 0.1 N aqueous NaHSO₄, 150

mL of saturated aqueous NaHCO₃, and 100 mL of brine. The organic layer was then dried (Na₂SO₄), filtered, and concentrated to afford a solid laden with an oil. The majority of the solid was removed by dissolving the oil in 5 mL of 2% *tert*-butyl methyl ether/hexane and filtering through a plug of cotton (2 mL rinse). Concentration of the filtrate and purification of the residual oil (3.5 × 23 cm of silica gel, linear gradient of 1.8–2.0% *tert*-butyl methyl ether/hexane) afforded 13.8 mg of slightly impure macrocycle 76, followed by 53.8 mg of pure material. Preparative thin-layer chromatography of the mixed fractions (200 × 200 × 0.25 mm plate with concentration zone, 3% *tert*-butyl methyl ether/hexane) provided an additional 10.0 mg of pure 76 (combined yield = 63.8 mg, 92%). Data for macrocycle 76: $[\alpha]^{24}_{D_6}$ -5.8° (c 0.78, CH₂Cl₂); IR (thin film) 2960, 2880, 1720, 1650, 1615, 1590, 1515, 1460, 1415, 1385, 1375, 1305, 1265, 1245, 1215, 1165, 1100, 1005, 970, 875, 830, 810, 775, 730 cm⁻¹; ¹H NMR (500 MHz with COSY-90, benzene-*d*₆) δ 7.39 (d, 2 H, *J* = 8.4 Hz, two of Ar*H*), 7.18 (d, 2 H, *J* = 15.4 Hz, C₃-*H*), 6.93 (d, 2 H, *J* = 8.4 Hz, two of Ar*H*), 6.34 (d, 1 H, *J* = 15.4 Hz, C₂-*H*), 5.80 (dt, 1 H, *J* = 11.8 and 4.8 Hz, C₂₁-*H*), 5.60 (ddd, 1 H, *J* = 15.4, 9.0, and 4.5 Hz, C₁₄-*H*), 5.48 (br dd, 1 H, *J* = 15.6 and 8.0 Hz, C₁₅-*H*), 5.16 (d, 1 H, *J* = 9.1 Hz, anomeric *H*), 4.73 (d, 1 H, *J* = 12.3 Hz, one of CH₂Ar), 4.50 (d, 1 H, *J* = 12.3 Hz, one of CH₂Ar), 4.38–4.34 (m, 2 H, C₅-*H* and C₉-*H*), 4.26–4.22 (m, 1 H, C₁₉-*H*), 4.10 (br s, 1 H, C₇-*H*), 4.08–4.00 (m, 2 H, C₃-*H* and C₃₂-*H*), 3.96–3.90 (m, 1 H, C₈-*H*), 3.87–3.81 (m, 1 H, C₃₀-*H*), 3.72 (br d, 1 H, *J* = 6.0 Hz, one of C₂₄-CH₂), 3.62–3.57 (m, 1 H, C₁₇-*H*), 3.46 (dd, 1 H, *J* = 9.4 and 6.0 Hz, one of C₂₄-CH₂), 3.37 (s, 3 H, one of OCH₃), 3.33 (s, 3 H, one of OCH₃), 3.38–3.30 (m, 2 H, C₃-*H* and C₄-*H*), 2.61–2.55 (m, 1 H, C₁₆-*H*), 2.49–2.44 (m, 1 H, C₂₀-*H*), 2.37 (br d, 1 H, *J* = 13.5 Hz, C₂-H_{ax}), 2.28–2.21 (m, 1 H), 2.18–2.10 (m, 2 H, C₆-*H* and one of C₁₈-CH₂), 2.09–2.06 (m, 3 H, C₁₃-CH₂ and one of C₁₈-CH₂), 1.95–1.83 (m, 3 H), 1.80–1.70 (m, 4 H, including C₂-H_{ax}), 1.68–1.55 (m, 5 H), 1.51 (s, 3 H, C₁₀-CH₃ or C₄-CH₃), 1.48 (d, 3 H, *J* = 6.3 Hz, C₅-CH₃), 1.45–1.40 (m, 2 H, C₂₂-CH₂), 1.41 (s, 9 H, one of Si(i-Bu)), 1.31 (s, 9 H, one of Si(i-Bu)), 1.24–1.22 (obscured m, 1 H, C₂₅-H_{ax}), 1.22–0.91 (m, 68 H), 0.85–0.55 (m, 29 H), 0.17 (s, 3 H, one of Si(CH₃)₂), 0.16 (s, 3 H, one of Si(CH₃)₂); ¹³C NMR (125.77 MHz, benzene-*d*₆) δ 175.7, 158.9, 153.2, 133.0, 129.2, 128.1, 127.9, 114.1, 97.7, 95.7, 85.0, 80.1, 79.2, 78.8, 78.5, 76.3, 71.8, 70.6, 70.5, 69.7, 69.6, 68.3, 58.4, 54.8, 40.5, 36.3, 36.2, 36.1, 35.3, 34.2, 30.4, 30.0, 29.5, 28.4, 24.2, 21.6, 19.2, 18.5, 17.7, 13.6, 11.5, 9.3, 8.0, 7.8, 7.7, 7.6, 7.4, 7.2, 6.1, 5.4, 4.6, 4.5, 0.4, -5.0, -5.1; TLC R_f = 0.28 (5% EtOAc/hexane). Anal. Calcd for C₁₀₀H₁₉₂O₁₇Si₇: C, 64.46; H, 10.39. Found: C, 64.46; H, 10.30.

[1S-[1R*,4E,6S*,7R*,11S*,12R*,14S*,18E,20R*-(R*),21R*,23R*,25S*[5R*,6R*(S*)],27S*,28S*]-]6-[2-[(Diethyl(1-methylethyl)silyloxy)butyl]-9',9'-bis(1,1-dimethylethyl)-20'-[3-[(1,1-dimethylethyl)dimethylsilyloxy]-2-methylpropyl]-3,4,5,6-tetrahydro-21'-hydroxy-5,6,14',27',28'-pentamethyl-3'-oxo-6',13',14'-tris[(triethylsilyl)oxy]spiro[2H-pyran-2,2S'-[2,8,10,24]tetraoxa[9]silatricyclo[21.3.1.1^{7,11}]octacosa-4',18'-dien-12'-yl] 2,6-Dideoxy-3-O-methyl-4-O-(triethylsilyl)- β -D-ribo-hexopyranoside (77). A solution of 39.1 mg (21.0 μ mol) of 4-methoxybenzyl ether 76 in 3.0 mL of CH₂Cl₂ was treated with 0.17 mL of deionized water and vigorous stirring was initiated. Solid 2,3-dichloro-5,6-cyano-1,4-benzoquinone (DDQ, 8.6 mg, 37.8 μ mol) was then introduced in one portion, immediately affording a reddish slurry intermingled with clear water droplets. After stirring for 35 min at ambient temperature, the reaction mixture was quenched by the introduction of 3 mL of saturated aqueous NaHCO₃, 15 mL of water was added, and the mixture was extracted with 2 × 25 mL of 4:1 hexane/CH₂Cl₂. The combined organic extracts were washed with 30 mL of brine, dried (Na₂SO₄), filtered, and concentrated to provide a clear oil. Flash chromatography of this material (2 × 24 cm of silica gel, linear gradient of 1.5–2.0% EtOAc/hexane) gave 36.0 mg (98%) of the desired alcohol 77: $[\alpha]^{24}_{D_6}$ -21.5° (c 1.55, CH₂Cl₂); IR (thin film) 3620–3380 (w), 3040, 2960, 2880, 1740, 1715, 1655 (w), 1645 (w), 1460, 1415, 1385, 1360, 1265, 1215, 1160, 1105, 1005, 905, 895, 875, 835, 825, 810, 790 cm⁻¹; ¹H NMR (500 MHz with COSY-90, benzene-*d*₆) δ 7.10 (d, 2 H, *J* = 15.7 Hz, C₃-*H*), 6.46 (d, 1 H, *J* = 15.7 Hz, C₂-*H*), 5.86 (apparent dt, 1 H, *J* = 8.8 and 6.2 Hz, C₂₁-*H*), 5.54 (ddd, 1 H, *J* = 15.7, 7.7, and 4.7 Hz, C₁₄-*H*), 5.25 (dd, 1 H, *J* = 15.7 and 10.0 Hz, C₁₅-*H*), 5.16 (d, 1 H, *J* = 9.1 Hz, anomeric *H*), 4.36 (br s, 1 H, C₅-*H*), 4.31 (d, 1 H, *J* = 8.0 Hz, C₃₂-*H* or C₁₉-*H*), 4.25 (d, 1 H, *J* = 5.6 Hz, C₈-*H* or C₉-*H*), 4.17 (br s, 1 H, C₇-*H*), 4.13–4.09 (m, 1 H, C₁₉-*H* or C₃₂-*H*), 4.06–3.99 (m, 2 H, C₅-*H* and either C₈-*H* or C₉-*H*), 3.93–3.88 (m, 1 H, C₃₀-*H*), 3.83–3.78 (m, 1 H, C₁₇-*H*), 3.64 (dd, 1 H, *J* = 9.6 and 5.5 Hz, one of C₂₄-CH₂), 3.34 (s, 3 H, OCH₃), 3.33–3.28 (m, 2 H, C₃-*H* and C₄-*H*), 2.59–2.53 (m, 1 H, C₂₀-*H*), 2.40–2.33 (m, 2 H, C₂-H_{ax} and C₁₆-*H*), 2.30–2.07 (m, 5 H, including C₆-*H*), 2.04 (dd, 1 H, *J* = 14.0 and 6.8 Hz, C₂₅-H_{ax}), 1.97–1.90 (m, 3 H), 1.83 (apparent t, 1 H, *J* = 14.0 Hz, C₂₅-H_{ax}), 1.80–1.53 (m, 10 H, including C₆-CH₃ and C₂-H_{ax}), 1.48 (s, 3 H, C₄-CH₃ or C₁₀-CH₃),

1.45–1.43 (m, 12 H, one of CHCH_3 and one of $\text{Si}(t\text{-Bu})$), 1.40–1.37 (m, 2 H), 1.33 (s, 9 H, one $\text{Si}(t\text{-Bu})$), 1.26–0.92 (m, 78 H), 0.85–0.54 (m, 29 H, $\text{Si}(\text{CH}_2\text{CH}_3)_3$ and $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 0.17 (s, 3 H, one of $\text{Si}(\text{CH}_3)_2$), 0.15 (s, 3 H, one of $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (125.77 MHz, benzene- d_6) δ 164.8, 152.4, 134.0, 132.7, 120.9, 97.7, 96.5, 83.5, 82.5, 79.7, 78.8, 78.7, 76.2, 73.8, 72.6, 71.1, 70.6, 69.9, 69.3, 67.4, 65.4, 58.4, 49.7, 40.2, 38.0, 36.5, 36.1, 35.7, 35.2, 33.9, 30.7, 30.3, 30.1, 29.5, 29.3, 28.5, 28.4, 27.0, 26.2, 25.1, 24.2, 21.6, 19.5, 19.0, 18.6, 17.8, 17.78, 13.7, 11.3, 9.8, 8.2, 8.0, 7.7, 7.62, 7.58, 7.53, 7.51, 7.3, 7.2, 6.0, 5.8, 5.4, 4.7, 4.6, –5.09, –5.13; TLC R_f = 0.26 (5% EtOAc/hexane). Anal. Calcd for $\text{C}_{92}\text{H}_{182}\text{O}_{16}\text{Si}_7$: C, 63.39; H, 10.64. Found: C, 63.45; H, 10.65.

[1*S* - [1*R* *, 4*E*, 6*S* *, 7*R* *, 12*S* *, 14*S* *, 18*E*, 20*R* * - (*R* *), 23*R* *, 25*S**[5*R* *, 6*R**(*S**)], 27*S* *, 28*S* *]-6-[2-[[Diethyl(1-methyl-ethyl)silyl]oxy]butyl]-9',9'-bis-(1,1-dimethylethyl)-20'-[3-[(1,1-dimethylethyl)dimethylsilyl]oxy]-2'-methylpropyl]-3,4,5,6-tetrahydro-5,6',14',27',28'-pentamethyl-3',21'-dioxo-6',13',14'-tris[(triethylsilyl)oxy]spiro[2*H*-pyran-2,25'-[2*S*, 10,24]tetraoxa[9]silatricyclo[21.3.1.1^{7,11}]octacosa-4',18'-dien-12'-yl] 2,6-Dideoxy-3-*O*-methyl-4-*O*-(triethylsilyl)- β -D-ribo-hexopyranoside (78). Preparation of pyridine-buffered Dess–Martin periodinane⁵⁰ stock solution: 64.8 mg (0.153 mmol) of the Dess–Martin periodinane was added to an argon-purged flask (glove bag transfer). The solid was dissolved in 2.7 mL of CH_2Cl_2 , and 80 μL (78 mg, 0.70 mmol) of pyridine was added, producing a clear solution. This stock solution was employed in oxidations within 10 min.

To a solution of 33.3 mg (19.1 μmol) of alcohol 77 was added 2.7 mL (8.0 equiv) of freshly prepared periodinane stock solution in one portion. After 0.75 h, the clear solution was diluted with 3 mL of diethyl ether and was quenched by introducing 3 mL of 1:1 saturated aqueous NaHCO_3 /sodium bisulfite and stirring the resulting mixture for 5 min. Upon further dilution with 20 mL of ether, the mixture was washed with 2 \times 10 mL of saturated aqueous NaHCO_3 and 1 \times 10 mL of brine, and the organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting oily residue was purified by flash chromatography (1.8 \times 17 cm of silica gel, 2% EtOAc/hexane) to provide 31.5 mg (95%) of the desired ketone 78: $[\alpha]^{22}_{D,546}$ 29.4° (c 1.22, CH_2Cl_2); IR (thin film) 3060, 2950, 2880, 1725, 1718, 1650, 1465, 1415, 1390, 1365, 1310, 1265, 1240, 1220, 1165, 1100, 1005, 945, 910, 880, 835, 815, 775, 630 cm^{-1} ; ^1H NMR (500 MHz with COSY-90, benzene- d_6) δ 7.05 (d, 2 H, J = 15.5 Hz, $\text{C}_3\text{-H}$), 6.43 (d, 1 H, J = 15.5 Hz, $\text{C}_2\text{-H}$), 6.02–5.97 (m, 1 H, $\text{C}_{21}\text{-H}$), 5.63–5.57 (m, 1 H, $\text{C}_{14}\text{-H}$), 5.37 (dd, 1 H, J = 14.8 and 8.8 Hz, $\text{C}_{15}\text{-H}$), 5.11 (d, 1 H, J = 9.1 Hz, anomeric H), 4.68–4.65 (m, 1 H, $\text{C}_{19}\text{-H}$), 4.37 (br s, 1 H, $\text{C}_5\text{-H}$), 4.32 (d, 1 H, J = 7.5 Hz, $\text{C}_9\text{-H}$), 4.11 (br s, 1 H, $\text{C}_7\text{-H}$), 4.03 (d, 1 H, J = 7.5 Hz, $\text{C}_8\text{-H}$), 4.03–3.90 (m, 3 H, $\text{C}_{24}\text{-CH}_2$ and $\text{C}_5\text{-H}$), 3.38–3.35 (dd, 1 H, J = 10.5 and 5.5 Hz, $\text{C}_4\text{-H}$), 3.32 (s, 3 H, OCH_3), 3.32–3.28 (m, 1 H, $\text{C}_3\text{-H}$), 3.15 (dd, 1 H, J = 10.2 and 8.8 Hz, $\text{C}_{16}\text{-H}$), 2.99 (dd, 1 H, J = 17.5 and 10.2 Hz, one of $\text{C}_{18}\text{-CH}_2$), 2.76–2.68 (m, 2 H, $\text{C}_{20}\text{-H}$ and one of $\text{C}_{18}\text{-CH}_2$), 2.32 (d, 1 H, J = 13.0 Hz, $\text{C}_2\text{-H}_{\text{eq}}$), 2.312–2.22 (m, 1 H, one of CHCH_3), 2.14–2.06 (m, 1 H, one of CHCH_3), 2.05–2.00 (m, 1 H, $\text{C}_6\text{-H}$), 1.95–1.88 (m, 5 H), 1.85–1.80 (m, 3 H, including $\text{C}_{25}\text{-H}_{\text{ax}}$), 1.73 (d, 3 H, J = 6.4 Hz, $\text{C}_6\text{-CH}_3$), 1.72–1.53 (m, 7 H, including $\text{C}_{27}\text{-H}_{\text{ax}}$), 1.48 (s, 3 H, $\text{C}_4\text{-CH}_3$ of $\text{C}_{10}\text{-CH}_3$), 1.43 (s, 3 H, $\text{C}_4\text{-CH}_3$ or $\text{C}_{10}\text{-CH}_3$), 1.41 (s, 9 H, one of $\text{Si}(t\text{-Bu})_2$), 1.33 (d, 3 H, J = 6.1 Hz, $\text{C}_5\text{-CH}_3$), 1.28 (s, 9 H, one of $\text{Si}(t\text{-Bu})_2$), 1.23–0.92 (m, 76 H, including $\text{C}_{20}\text{-CH}_3$), 0.82–0.53 (m, 29 H, $\text{Si}(\text{CH}_2\text{CH}_3)_3$ and $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 0.11 (s, 3 H, one of $\text{Si}(\text{CH}_3)_2$), 0.08 (s, 3 H, one of $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (125.77 MHz, benzene- d_6) δ 206.2, 164.2, 151.1, 135.2, 129.0, 120.9, 97.7, 95.8, 84.3, 81.8, 79.3, 79.1, 78.6, 78.1, 76.0, 73.1, 72.8, 70.1, 69.8, 69.2, 67.9, 67.0, 58.6, 57.1, 41.2, 40.3, 38.7, 36.4, 36.2, 35.9, 35.8, 33.9, 32.9, 31.7, 31.4, 31.0, 30.1, 29.6, 28.5, 27.2, 26.8, 26.2, 24.5, 24.2, 22.5, 21.6, 19.5, 19.5, 18.5, 17.8, 16.7, 13.7, 11.4, 9.4, 8.14, 8.07, 8.0, 7.7, 7.61, 7.56, 7.53, 7.2, 6.5, 6.0, 5.8, 5.3, 4.6, –5.2, –5.3; TLC R_f = 0.20 (3% EtOAc/hexane). Anal. Calcd for $\text{C}_{92}\text{H}_{182}\text{O}_{16}\text{Si}_7$: C, 63.47; H, 10.54. Found: C, 63.49; H, 10.67.

Cytovaricin (1). To a 2-mL glass shell vial containing 22.5 mg (12.9 μmol) of ketone 78 was added 350 μL of freshly prepared, buffered pyridinium hydrofluoride (stock solution prepared from 10 mL of THF, 5.7 mL of pyridine, and 2.1 g of Fluka pyridinium hydrofluoride). Two additional portions of the stock solution were introduced after 25 h (100 μL) and 36 h (300 μL). After a total reaction time of 56 h, the milky

white reaction mixture was diluted with 30 mL of CH_2Cl_2 and was successively extracted with 3 \times 15 mL of saturated aqueous copper sulfate, 15 mL of saturated aqueous NaHCO_3 , and 15 mL of brine. The organic layer was then dried (Na_2SO_4), filtered, and concentrated to afford a white solid. Purification of this material by preparative thin-layer chromatography (material divided into two equal portions and applied to two 200 \times 200 \times 0.25 mm preparative silica gel plates (concentration zone) and elution with 4.5% methanol/dichloromethane) and repeated concentration from acetonitrile provided 8.6 mg (74%) of cytovaricin as a white powder. Recrystallization of a 2.0 mg sample of synthetic cytovaricin was accomplished by dissolution in 0.4 mL of acetonitrile without heating. Subsequent cooling to 0 °C over a 12-h period produced crystalline cytovaricin (1.9 mg) as clear orthorhombic crystals:¹²⁰ mp 207–208 °C (natural 207–208 °C); $[\alpha]^{22}_{D,546}$ –12°, $[\alpha]^{23}_{D,546}$ +48° (c 0.50, CH_3CN) (natural $[\alpha]^{23}_{D,546}$ –11°; $[\alpha]^{23}_{D,546}$ +50° (c 0.50, CH_3CN)); IR (KBr pellet) 3650, 3100, 2980, 2940, 1720, 1650, 1390, 1320, 1270, 1230, 1165, 1090, 1075, 1000, 870 cm^{-1} ; ^1H NMR (CD_3CN , 500 MHz with COSY-90) δ 7.00 (dd, 1 H, J = 15.4 and 1.4 Hz, $\text{C}_3\text{-H}$), 5.99 (d, 1 H, J = 15.4 Hz, $\text{C}_2\text{-H}$), 5.34–5.27 (m, 2 H, $\text{C}_{14}\text{-H}$ and $\text{C}_{15}\text{-H}$), 5.23 (s, 1 H, $\text{C}_7\text{-OH}$), 5.18–5.13 (highly structured m, 1 H, $\text{C}_{21}\text{-H}$), 5.12 (s, 1 H, $\text{C}_5\text{-OH}$), 4.95 (s, 1 H, $\text{C}_{17}\text{-OH}$), 4.83 (dd, 1 H, J = 9.7 and 1.7 Hz, $\text{C}_1\text{-H}$), 4.19 (dt, 1 H, J = 11.4 and 2.8 Hz, $\text{C}_{19}\text{-H}$), 4.00 (br d, 1 H, J = 11.1 Hz, $\text{C}_{30}\text{-H}$), 3.83 (t, 1 H, H = 9.0 Hz, $\text{C}_{24}\text{-H}_{\text{eq}}$), 3.83–3.80 (m, 1 H, $\text{C}_8\text{-H}$), 3.78 (s, 1 H, $\text{C}_5\text{-H}$), 3.75–3.67 (m, 1 H, $\text{C}_{32}\text{-H}$), 3.69 (dq, 1 H, J = 9.7 and 6.2 Hz, $\text{C}_5\text{-H}$), 3.57–3.55 (m, 1 H, $\text{C}_3\text{-OCH}_3$), 3.28 (d, 1 H, J = 3.0 Hz, $\text{C}_{32}\text{-OH}$), 3.25 (s, 1 H, $\text{C}_4\text{-OH}$), 3.14 (ddd, 1 H, J = 9.6, 9.5, and 3.3 Hz, $\text{C}_4\text{-H}$), 2.97 (d, 1 H, J = 10.6 Hz, $\text{C}_9\text{-H}$), 2.83 (d, 1 H, J = 9.5 Hz, $\text{C}_4\text{-H}$), 2.75 (d, 1 H, J = 10.8 Hz, $\text{C}_9\text{-OH}$), 2.48 (s, 1 H, $\text{C}_{10}\text{-OH}$), 2.38 (br d, 1 H, J = 9.8 Hz, $\text{C}_{16}\text{-H}$), 2.34 (ddd, 1 H, J = 14.0, 3.4, and 2.2 Hz, $\text{C}_2\text{-H}_{\text{eq}}$), 2.15–2.03 (m, 3 H, $\text{C}_{13}\text{-CH}_2$ and $\text{C}_{20}\text{-H}$), 1.90–1.80 (m, 2 H), 1.78–1.65 (m, 4 H, $\text{C}_{25}\text{-CH}_2$, $\text{C}_{23}\text{-H}$, and one of $\text{C}_{18}\text{-CH}_2$), 1.65–1.59 (m, 3 H, including $\text{C}_6\text{-H}$), 1.58–1.45 (m, 6 H), 1.45–1.35 (m, 4 H including $\text{C}_{27}\text{-H}_{\text{ax}}$), 1.34–1.28 (m, 1 H), 1.27 (s, 3 H, $\text{C}_{10}\text{-CH}_3$), 1.23–1.18 (partially obscured m, 1 H), 1.20 (d, 3 H, J = 6.2 Hz, $\text{C}_5\text{-CH}_3$), 1.02 (s, 3 H, $\text{C}_4\text{-CH}_3$), 0.93 (t, 3 H, J = 7.4 Hz, $\text{C}_{34}\text{-CH}_3$), 0.91 (d, 3 H, J = 7.0 Hz, $\text{C}_{29}\text{-CH}_3$), 0.85 (d, 3 H, J = 6.9 Hz, $\text{C}_6\text{-CH}_3$), 0.78 (d, 3 H, J = 6.6 Hz, $\text{C}_{23}\text{-CH}_3$), 0.73 (d, 3 H, J = 6.9 Hz, $\text{C}_{20}\text{-CH}_3$); ^{13}C NMR (CD_3CN , 75.5 MHz) δ 165.7, 134.2, 132.7, 119.5, 100.5, 99.1, 97.8, 83.8, 79.6, 78.3, 77.8, 76.1, 75.7, 74.7, 73.4, 72.0, 69.3, 68.5, 67.3, 66.7, 57.6, 51.4, 42.3, 40.6, 38.2, 36.4, 35.9, 35.2, 34.7, 34.3, 33.9, 31.5, 31.2, 31.3, 29.6, 28.6, 27.5, 22.7, 18.4, 17.2, 11.4, 10.6, 6.9, 6.0, 1.9, 0.9, 0.8; TLC R_f = 0.20 (4% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$). Exact Mass Calcd for $\text{C}_{47}\text{H}_{80}\text{O}_{16}\text{Na}$ ($\text{M}^+ + \text{Na}$): 923.5344. Found: 923.5349. Anal. Calcd for $\text{C}_{47}\text{H}_{80}\text{O}_{16}$: C, 62.64; H, 8.95. Found: C, 62.51; H, 8.83.

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Supplementary Material Available: The experimental procedures and associated discussion of the synthesis of 8-*epi*-cytovaricin as well as the crystal data for triol 56 (26 pages). Ordering information is given on any current masthead page.

(120) All data for the natural product reported here were obtained by using natural cytovaricin kindly provided by Professor K. Isono. All literature data (ref 2) for natural cytovaricin were in accord with the data reported above (IR, melting point). Rotation data for the natural product and synthetic material were reexamined in acetonitrile instead of dichloromethane because of the potential for dienol ether formation (2) in the presence of chlorinated solvents.