for HPLC use and were spectral grade for spectroscopy. Rotations were measured on a Perkin-Elmer 141 polarimeter.

Two-Dimensional NMR Procedures. Standard pulse sequences[16] were used for the homo COSY (ref 16b, Figure 37), and the hetero (ref 16b, Figure 35) experiments.

Isolation Procedures. The fresh *S. mycofijiensis* from Vanuatu (1.7 kg wet weight) was preserved and returned to University of California, Santa Cruz, for workup consisting of soaking (≈48 h, room temperature) in methanol (twice) and finally dichloromethane, and three separate dark viscous oils (respectively 1.96 g, 2.06 g, 2.50 g) were obtained. These oils were examined by ^{13}C NMR spectroscopy, which revealed a mixture of latrunculin A, mycothiazole, and other unidentified secondary metabolites (but no dendrolasin) in the first oil, while lipids and steroids were the major components of the other two oils. A portion of the first methanol extract crude oil (1.08 g) was then successively partitioned between equal volumes of aqueous MeOH (percent adjusted to produce a biphase solution) and a solvent series of hexanes (360 mg), CCl_4 (550 mg), and CH_2Cl_2 (170 mg). Analysis by ^{13}C NMR spectroscopy showed that mycothiazole and latrunculin A were major components of the CCl_4 partition fraction. This was then chromatographed (normal-phase flash column chromatography) with ethyl acetate–hexanes in a ratio of 5:95 with successive increases in ethyl acetate until pure ethyl acetate was attained. The fractions that displayed sharp, low-field signals in the ^{1}H NMR spectra were combined and further purified via preparative normal-phase HPLC (10 μm silica gel column; solvent = ethyl acetate–hexanes, 30:70) to yield (percents based on the crude oil used in the partition): mycothiazole (**1**) (68.7 mg, 6.3%, of shorter retention time) and latrunculin A (130.0 mg, 12.0%).

Mycothiazole (1): viscous oil $[\alpha]^{20}_{D}$ −3.8° (*c* 2.9, $CHCl_3$); IR (neat) 3600–3200, 2910, 1720, 1530, 1450, 1390, 1270, 1025 cm^{-1}; UV λ_{max} 235 (5270), 290 (1780); NMR data in Table I; HREIMS, *m/z*, in Schemes I and II and 220.1154 ($C_{13}H_{18}NS$), 192.0853 ($C_{11}H_{14}NS$), 166.0698 ($C_9H_{12}NS$), 140.0561 ($C_7H_{10}NS$).

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Registry No. 1, 114582-75-1.

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(16) For reviews see: (a) Shoolery, J. N. *J. Nat. Prod.* **1984**, *47*, 226. (b) Benn, R.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 350.

Total Synthesis of Zincophorin

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Contribution from the Department of Chemistry, Yale University,
New Haven, Connecticut 06511. *Received December 9, 1987*

Abstract: The total synthesis of the title compound, which is a zinc-binding antibiotic, is described. The synthesis starts with aldehyde **4** and Grignard reagent **6**. The key steps are (i) the cyclocondensation of aldehyde **10** with diene **11** under the influence of magnesium bromide, (ii) the cyclocondensation of aldehyde **24** with diene **33** under the influence of $BF_3 \cdot OEt_2$, (iii) the carbon Ferrier reaction of glycal acetate **37** with (*E*)-crotyltrimethylsilane, and (iv) the reductive merger of aldehyde **2a** with sulfone **3**.

Many naturally occurring polyoxygenated ionophores have useful antiinfectious properties.[1] The primary mode of action seems to reside in the capacity of the ionophore to form lipophilic complexes with cations, thus affecting proton–cation exchange processes across biological membranes.[2] To date, the ionophoric antibiotics that have received the greatest attention are those with complex monovalent alkaline cations such as Li^+, Na^+, and K^+ or divalent alkaline earth cations such as Ca^{2+} and Mg^{2+}.

In this context a report in 1984 by an ICI group, describing the isolation of a zinc-sequestering antibiotic was of considerable interest.[3] This compound, zincophorin, was isolated from a strain of *Streptomyces griseus*. Apparently the same compound, previously called griseochellin, had been isolated from cultures of a modified strain of the same microorganism by Radics.[4] The constitution of griseochellin, though not its stereochemistry, was ascertained from extensive NMR measurements. The three-dimensional structure of zincophorin, also referred to as M144255, was determined to be structure **1** (including absolute configuration) by crystallographic measurements of its zinc–magnesium salt.[3]

Zincophorin exhibits strong in vitro activity against Gram-positive bacteria, as well as against *Clostridium coelchii*. A recent report, via the patent literature, registered the claim that griseochellin methyl ester exhibits a strong inhibitory action against influenza WSN/virus with sharply reduced host cell toxicity relative to the corresponding acid.[5]

In light of its novel structure and its profile of biological activity, zincophorin (griseochellin) provides an interesting context for chemical exploration, including total synthesis. It was not unnatural for our research group to undertake for itself the goal of a total synthesis of zincophorin. The most serious issues involved in such a venture would center around the introduction of the required configurations at the various oxygenated stereogenic centers. Our group had been involved with this type of objective, arising from its explorations into the Lewis acid induced aldehyde–siloxy diene cyclocondensation reaction and into the chemistry of pyranoid systems arising from such reactions.[6,7]

A plausible retrosynthetic disconnection point for a total synthesis of **1** would be the 16–17 double bond. In the forward sense, this double bond might be fashioned by reductive elimination of a β-hydroxy sulfone equivalent produced by the condensation of the anion of sulfone **3** with aldehyde **2** (P = unspecified blocking

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(1) *Polyether Antibiotics*; Westley, J. W., Ed.; Marcel Dekker: New York, 1982; Vol. 1 and 2.

(2) Dobler, M. *Ionophores and Their Structures*; Wiley: New York, 1981.

(3) Brooks, H. A.; Poyser, J. P.; Gardner, D.; King, T. *J. Antibiot.* **1984**, *37*, 1501.

(4) (a) Radics, L. *J. Chem. Soc., Chem. Commun.* **1984**, 599. (b) Grafe, U.; Schade, W.; Roth, M.; Radics, L.; Incze, M.; Ujszaszy, K. *J. Antibiot.* **1984**, *37*, 836.

(5) Grafe, U. Ger. (East) DD 231,793.

(6) Danishefsky, S. J. *Aldrichimica Acta* **1986**, *19*, 59.

(7) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15.

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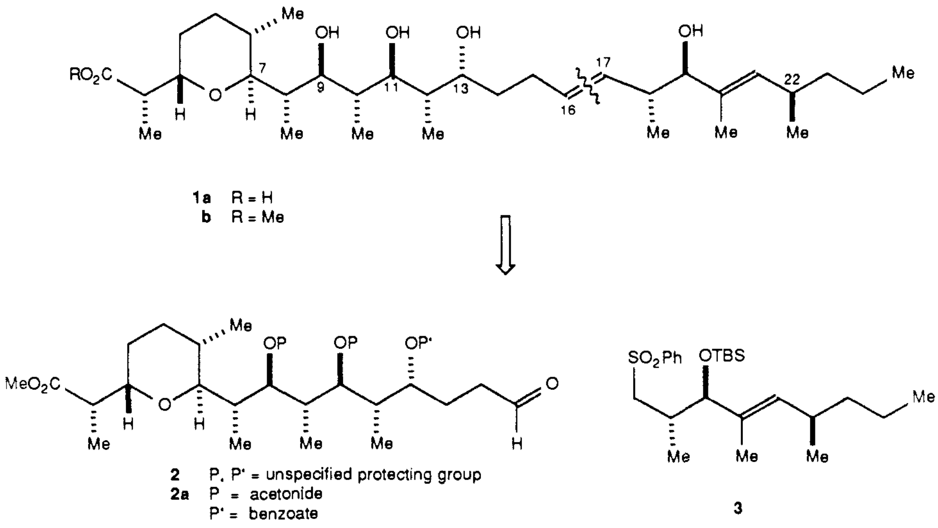
Scheme I

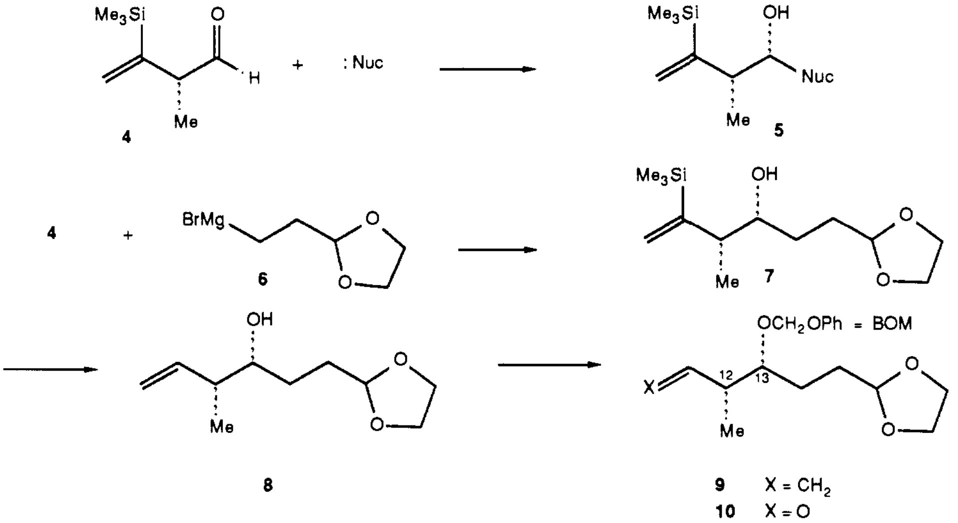


1a R = H
b R = Me

2 P, P' = unspecified protecting group
2a P = acetonide
P' = benzoate

3

Scheme II



4 **5** **6** **7** **8**

9 X = CH$_2$
10 X = O

groups). Elsewhere we have described the synthesis of sulfone **3** of the absolute stereochemistry (as shown) that is required for zincophorin.[8] This route made recourse to an appropriate valeryloxazolidone auxiliary for introduction of the C$_{22}$-methyl group.[9] It also employed a propionate-derived silylketene acetal, which was equipped with an *N*-methylephedrine auxiliary[10] in order to install (after a Mukaiyama-like reaction)[11] the anti-C$_{18}$–C$_{19}$ stereochemistry[12] in the required absolute sense. Thus, the stereoselectivity in the synthesis of **3** arose from margins of control, which were provided by external reagents.[13]

In this paper we describe and document the total synthesis of zincophorin. For this purpose we set as a major goal system the aldehyde **2a**, with the specific oxygen-protective arrangements indicated. This compound was in fact synthesized and coupled to compound **3**, affording, after suitable manipulations, zincophorin itself[14] (Scheme I).

The need to obtain aldehyde **2a** in essentially enantiomerically homogeneous form in the absolute sense shown was well recognized at the outset. It was through the coupling of segments of appropriately matched dissymmetry that we hoped to establish connectivity between the various chiral sectors of zincophorin. The system we chose as our starting material was the known *S* aldehyde **4**, prepared according to the protocols of Sato,[15] by using the asymmetric epoxidation of (*E*)-crotyl alcohol, as provided by the very powerful Sharpless technology.[16,17]

This aldehyde was selected because of the unusually high facial selectivity that is manifested in its reactions with a broad range of nucleophiles.[18] In every case thus far examined, the sense of the selectivity was that predicted by the Cram[19] or Felkin formulations[20] of the problem. Thus, reactions of **4** with a general

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[8] Zelle, R. E.; DeNinno, M. P.; Selnick, H. G.; Danishefsky, S. J. *J. Org. Chem.* **1986**, *51*, 5032.

[9] (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (b) Evans, D. A.; Mathre, D. J.; Scott, W. L. *J. Org. Chem.* **1985**, *50*, 1830.

[10] Gennari, C.; Bernardi, A.; Columbo, L.; Scolastico, C. *J. Am. Chem. Soc.* **1985**, *107*, 5812.

[11] Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011; *J. Am. Chem. Soc.* **1974**, *96*, 7503.

[12] Throughout this paper we employ descriptor terminology used by Masamune to describe the course of aldol constructions. Syn and anti refer to a structural presentation in which the relevant stereogenic centers are in the extended (zig-zag) conformation. Care should be taken with the consistency of the convention. Thus, in compound **12**, the relationship of C$_7$ and C$_8$ is termed as syn since this would be the case if C$_6$–C$_9$ were arranged in the extended conformation. See: Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557.

[13] Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

[14] Danishefsky, S. J.; Selnick, H. G.; DeNinno, M. P.; Zelle, R. E. *J. Am. Chem. Soc.* **1987**, *109*, 1572.

[15] Sato, F.; Kobayashi, Y.; Kitano, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1329

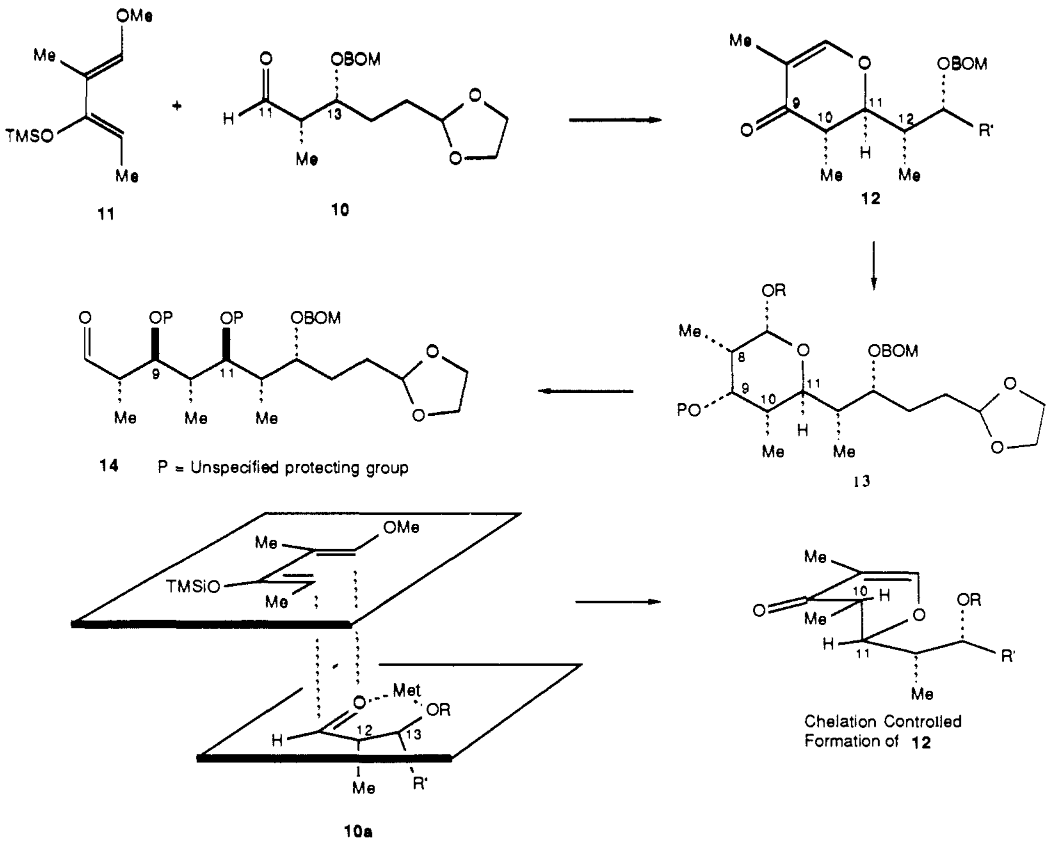
[16] (a) Sharpless, K. B.; Finn, M. G. In *Asymmetric Synthesis*; Morrison, J., Ed.; Academic: Orlando, FL, 1985, Vol. 5, pp 247–308. (b) Rossiter, B. E. *Ibid.* pp 193–246.

[17] Hill, J. G.; Sharpless, K. B. In *Organic Synthesis*; Saucy, G., Ed.; Wiley: New York, 1984, Vol. 63, pp 66–78.

[18] Sato, F.; Kusakabe, M.; Kobayashi, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1130.

[19] Cram, D. J.; Abd. Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Cram, D. J.; Kopecky, K. R. *Ibid.* **1959**, *81*, 2748.

Scheme III



carbon-centered nucleophile, Nu, affords the syn Me–OH product type, **5**. In the case at hand, the nucleophile selected was the Grignard reagent **6**.[21] The product, carbinol **7**, was obtained in 90% yield. No other product was identified.

Treatment of **7** with sodium hydride-HMPA resulted in a carbon to oxygen migration of the trimethylsilyl group.[22] Aqueous workup resulted in a 74% yield of **8**. The hydroxyl group was converted to its (benzyl)methyl ether, **9**, in 90% yield through the usual protocols. Ozonolysis of **9** afforded the aldehyde **10**. We thus had in hand a substrate for our first projected cyclocondensation reaction.

Aldehyde **10** contains the C_{12}–C_{13} syn Me–OH relationship in the absolute sense required for target system **1**.[12] We now envisioned the possibility of employing diene **11** for reaction with this aldehyde. In this phase of endeavor, the goal was that of fashioning a pyran matrix upon which could be introduced the stereochemistry and functionality required to accommodate carbons 8–11. This could be achieved if the ultimate pyran had the configurational arrangement implied in structure **13**. Disassembly of **13** could be envisioned to lead, eventually, to aldehyde type **14** (P = unspecified protecting groups).

We first focus on the C_{12}, C_{11}, and C_{10} relationships in generalized intermediates **13** and **14**. It is quickly recognized that both the C_{11}–C_{10} and the C_{10}–C_9 relationships are anti.[12] This analysis identifies dihydropyrone **12** as a promising intermediate in which these two relationships are encoded. It was assumed that with carbons 11 and 10 properly arranged, the stereochemistry at carbons 8 and 9 could be managed en route to specific versions of generalized subgoals **13** and **14**.

Given the $C_{11}O$–$C_{10}Me$ anti relationship in **12**, the diastereofacial outcome required to reach compound **12** from the reaction of aldehyde **10** with diene **11** is opposite to that contemplated in the most rudimentary form of the Cram–Felkin correlations.[19,20] The requirement for a trans relationship between carbons 10 and 11 (zincophorin numbering) within the dihydropyrone corresponds in principle to an exo alignment of the two reactants in the cyclocondensation reactions.

It was hoped that this connectivity could be achieved by taking advantage of the relationship of the OBOM group at C_{13} with the aldehyde at C_{11} in aldehyde **10**. This juxtaposition could be exploited to produce ligation of the cationic portion of the Lewis acid catalyst, thus favoring a cyclic conformer implied in **10a**. Since the C_{12} methyl group and side chain projecting from C_{13} are both α, it could be anticipated that the nucleophilic diene would attack in a β sense. In this fashion the anti relationship between C_{11} and C_{12} would be established. Such chelation control was well contemplated in the framework of the Cram–Felkin arguments and more recent work.[23] Moreover, previous results from our laboratory had shown that in a chelation-controlled geometry such as implied in **10a**, with the catalyst per force syn to the carbon chain of the aldehyde, an exo topography leading to a trans substitution pattern in the dihydropyrone (cf. C_{10} and C_{11}) would be expected[24] (Scheme III).

An important test of the availability of this thinking was now at hand. In the event, anhydrous magnesium bromide was employed as the catalyst with a view toward its ligatability. The reaction was carried out in methylene chloride at –65 to 0 °C over 5 h. An 80% yield of dihydropyrone was obtained. The major compound, ca. 7:1 ratio, was assigned to be structure **12**. The minor compound, not shown here, was not fully characterized. While the trans C_{10}–C_{11} arrangement was definable by NMR analysis, the assignment of the C_{11}–C_{12} relationship was provisional and was based solely on the mechanistic rationale and precedents discussed above.[24,25]

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(20) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Ahn, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61. (c) Ahn, N. T. *Top. Curr. Chem.* **1980**, *88*, 146.

(21) Roush, R. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269.

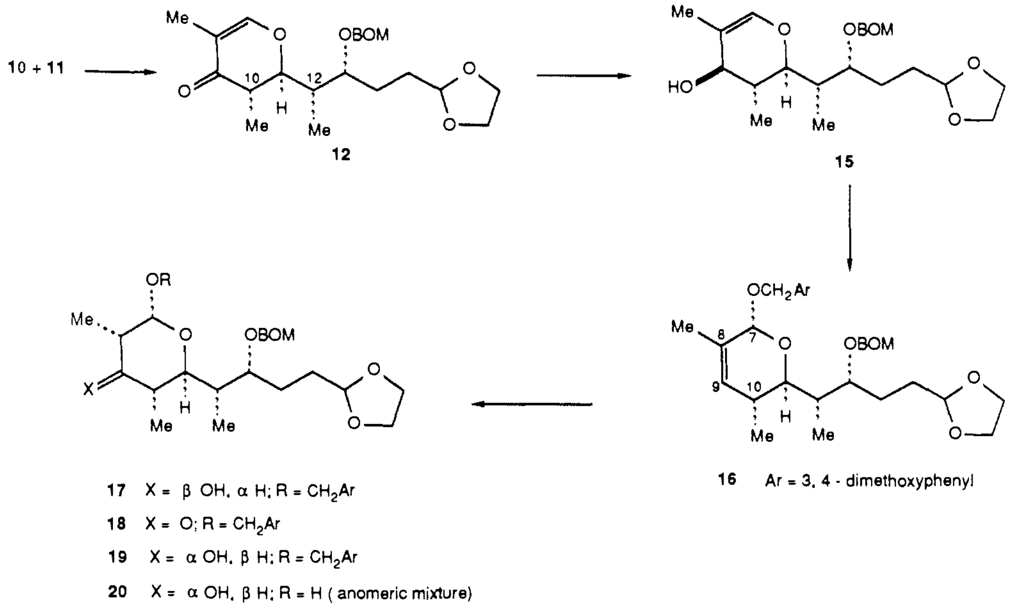
(22) Sato, F.; Tanaka, Y.; Sato, M. *J. Chem. Soc., Chem. Commun.* **1983**, 165.

(23) (a) Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(24) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1256.

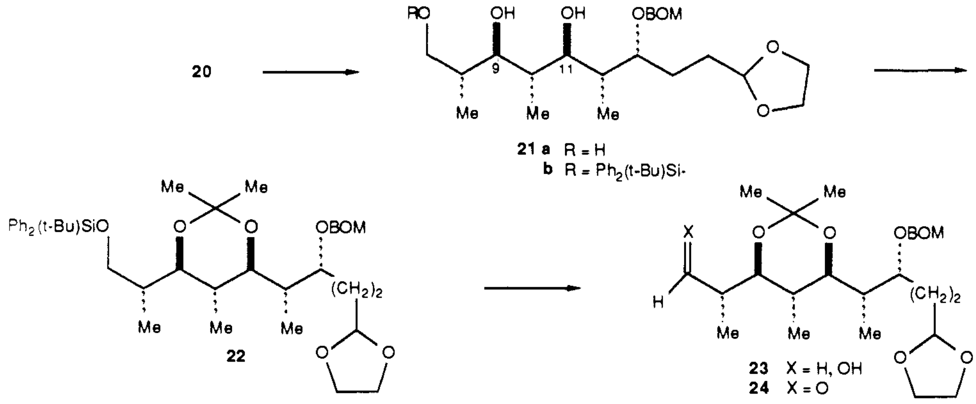
(25) Danishefsky, S. J.; Maring, C. *J. Am. Chem. Soc.* **1985**, *107*, 1269.

Scheme IV



17 X = β OH, α H; R = CH_2Ar
18 X = O; R = CH_2Ar
19 X = α OH, β H; R = CH_2Ar
20 X = α OH, β H; R = H (anomeric mixture)

Scheme V



The next stage of the synthesis involved the installation of the suitable functionality and configurations at carbons 8 and 9 and preparations for dismantling of the first pyranoid matrix. Toward these goals, reduction of the keto group of **12** was achieved by reaction with sodium borohydride in the presence of cerium(III) chloride. The branched glycal **15** was subjected to a Ferrier-type rearrangement[26] through the use of 3,4-dimethoxybenzyl alcohol as the nucleophile. Compound **16** was obtained in 70% yield. The particular alcohol nucleophile was selected with a view toward simplifying the eventual exposure of the free anomeric center at C_7. As can be anticipated from the analysis thus far (see structures **13** and **14**), C_7 is destined to emerge as an aldehyde center and then to participate in another cyclocondensation reaction (vide infra).

On the basis of precedents from our activities directed toward rifamycin,[27] we could anticipate that the synergism of the α substituents at carbons 7 and 10 flanking the trisubstituted C_7–C_8 double bond would direct hydroborating agents to the β-face of the pyran ring. In practice, reaction of **16** with BH_3·DMS followed by oxidation with alkaline hydrogen peroxide afforded a 67% yield of alcohol **17** (Scheme IV). It is seen that in this compound the required stereochemistry at C_8 has been established. However, the configuration of the C_9 hydroxyl group does not correspond with that which is needed (see structures **12** and **13**). Of course, this noncongruence could be easily corrected. Indeed, in practice, Swern-type oxidation of **17** afforded (84%) ketone **18**, which upon reduction with L-Selectride (Aldrich) gave rise (88%) to the axial alcohol **19**. It was a simple matter to liberate the anomeric hydroxyl group at C_7 through reaction of **19** with DDQ.[28] Hemiacetal **20** was in hand.

The relationship of the spectroscopically definable chiral pyranoid domain (carbons 8–11) to the side-chain stereochemistry (see carbons 12 and 13) was still not rigorously known. In the absence of crystallographic verification or linkage with a substance of unambiguous stereostructure, it would be difficult to substantiate these propositions in the case at hand. Thus, further advances toward the final synthetic target would also advance the prospects for structural corroboration.

As discussed above, the pyranoid segment of zincophorin would be assembled via a cyclocondensation reaction. In furtherance of this construct it would be necessary to unveil from the anomeric center of compound **20** the aldehyde center required for the next cyclocondensation reaction. Needless to say, proper anticipatory measures were necessary to protect the oxygen functions at carbons 9 and 11 through this and subsequent processes. A reductive ring-opening strategy was pursued.

Reaction of hemiacetal **20** with lithium borohydride afforded the C_7, C_9, C_{11} triol. It proved to be a simple matter to selectively silylate the primary alcohol at C_7 with $Ph_2(t\text{-}Bu)SiCl$.[29] The C_9 and C_{11} alcohol functions of the resultant diol **21** were engaged as a cyclic acetonide (cf. **22**) via reaction with 2,2-dimethoxypropane in the presence of pyridinium *p*-toluenesulfonate. Cleavage of the silyl group led to the C_9 alcohol **23**, from which

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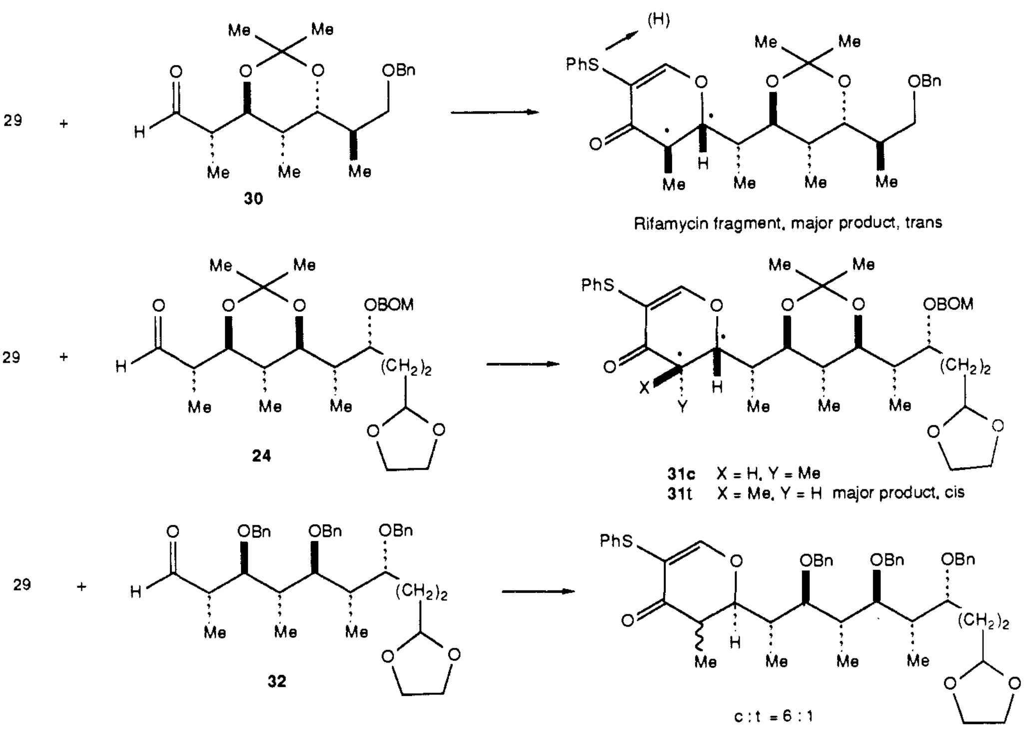
(26) (a) Luche, J. L.; Gamal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848. (b) Ferrier, R. *J. Chem. Soc.* **1964**, 5443.

(27) Danishefsky, S. J.; Myles, D. C.; Harvey, D. F. *J. Am. Chem. Soc.* **1987**, *109*, 862.

(28) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

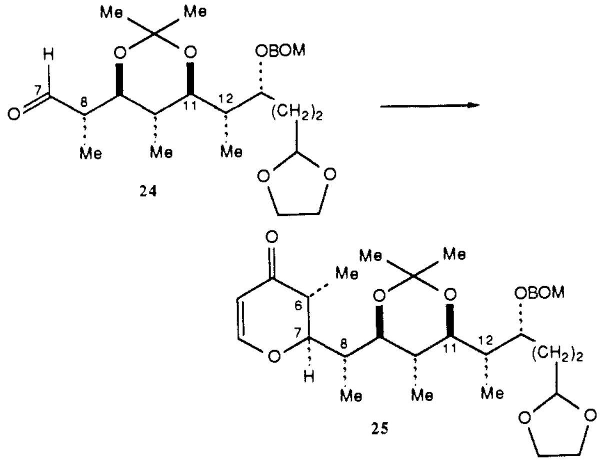
(29) Hanessian, S.; Lavelle, P. *Can. J. Chem.* **1977**, *55*, 562.

Scheme VI



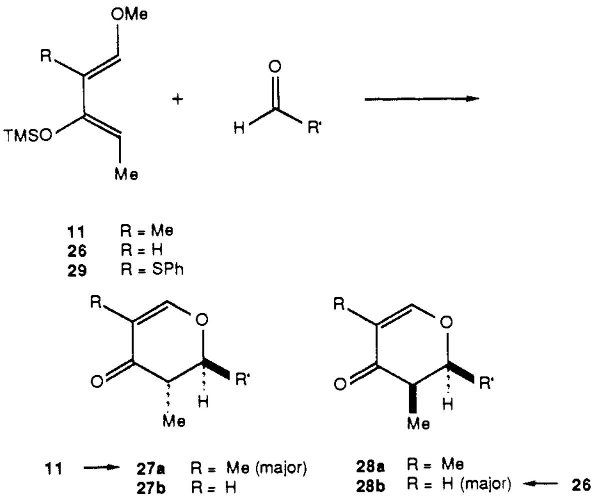
the pivotal aldehyde **24** (ca. 90% from **21**) was obtained by Swern oxidation[30] (Scheme V). This aldehyde would serve as our specific version of the generalized aldehyde **14** type envisioned above.

The next subgoal system was the dihydropyrone **25**. The syn C_7 oxygen-C_8 methyl relationship in **25**[12] renders the system accessible, in principle, by nucleophilic addition to aldehyde **24** in accord with the simplest Cram[19] and Felkin[20] perceptions where chelation control is not operative. Previous work[31,32] had suggested that this syn relationship would be strongly favored through the use of $BF_3{\cdot}OEt_2$ as the catalyst in a cyclocondensation reaction. Remarkably high selectivity in this direction had been noted even with β-alkoxy aldehyde substructures.[33]



(1)

The topographic sense required of the reaction of a suitable diene with aldehyde **24** to reach dihydropyrone **25** must generate a trans relationship between the methyl and side-chain moieties within the ring matrix (see C_6–C_7 relationship). It is well to take note of earlier findings[31-33] relating to this type of problem. The reactions of dimethyl diene **11** with a variety of aldehydes under $BF_3{\cdot}OEt_2$ catalysis had indeed given strong trans–cis topographic selectivity (i.e., **27a** R = Me was substantially favored over **28a** R_a = Me). *Remarkably, however, the C_2 nor diene **26**, with similar aldehydes under identical catalysis, afforded primarily the cis compound **28b** in preference to the trans compound **27b**.*[31] Since in zincophorin the pyran system is unsubstituted at C_4, the use of the readily available dimethyl diene **11** seemed to be unpromising.



(2)

We had previously faced this type of problem in the synthesis of the chiral sector of rifamycin S.[27] In that instance we made recourse to diene **29**. The presence of the thiophenyl group at C_2 of the diene favored (4.5:1) the formation of *trans*-dihydropyrone (vide infra). Subsequently, the sulfur-based constituent was replaced by hydrogen. The specific pre-rifamycin aldehyde that we employed was compound **30**. Given this background, we were surprised to find that cyclocondensation of aldehyde **24** with diene **29** under $BF_3{\cdot}OEt_2$ catalysis followed by cyclization afforded a 2:1 ratio of undesired *cis*-dihydropyrone, **31c**, to the desired **31t**.

Since the most striking difference between **24** and **30** lay in the stereochemistry of the substitution of the dioxolane system, we prepared aldehyde **32**,[34] in which two benzyloxy groups were employed in place of the dioxolane substructure. *Indeed, this*

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(30) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

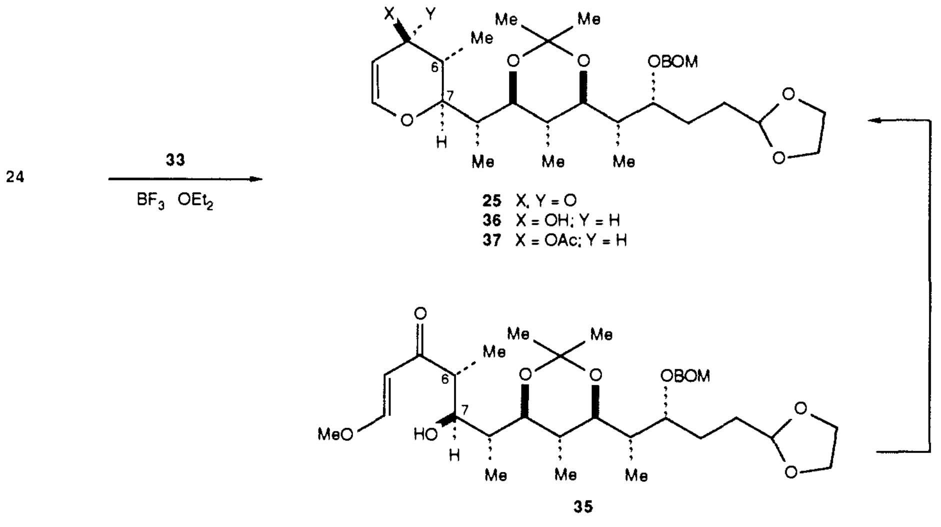
(31) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246.

(32) Myles, D. C. Yale University, unpublished results.

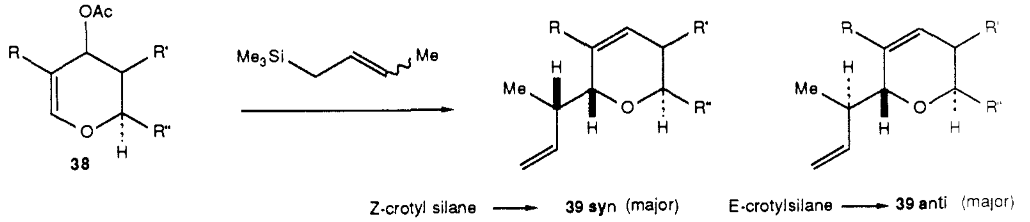
(33) Harvey, D. F. Ph.D. Thesis, Yale University, 1985.

(34) Prepared from **24** by the following sequence: (i) H_2,$Pd(OH)_2$, (ii) Ph(*t*-Bu)SiCl, (iii) BnBr, NaH, (iv) TBAF, (v) Swern.

Scheme VII

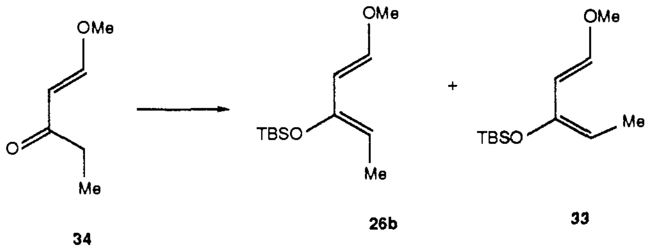


Scheme VIII



structural variation was not without consequence, but in the undesired direction. The ratio of *cis-* to *trans*-dihydropyrone (**31c**:**31t**) derived from **32** was 6:1 (Scheme VI).

While the precise structural features that distinguish **24** from **30** in their sharply contrasting stereochemical performances with respect to diene **29** still remain unclear, a workable though labored solution to the problem at hand was found. This involved the use of the difficultly available diene **33**.[31] This *E* diene is the minor product (relative to **26**) in the enol silylation of the corresponding enone **34**. The required **33** is separated from **26** by exploiting the far greater reactivity of the latter toward cyclocondensation with benzaldehyde,[31] with use of zinc chloride as the Lewis acid catalysts.



Reaction of homogeneous **33** with aldehyde **24** under $BF_3 \cdot OEt_2$ catalysts directly produced small amounts (5–10%) of essentially homogeneous trans-substituted dihydropyrone assumed to have the stereochemistry implied in structure **25**. Also present were two "aldol" products shown as **35** (ca. 60%). The major product is of the C_6–C_7 threo relationship, as shown, since cyclization with PPTS afforded a 43% overall yield of the desired **25**. Thus, through the use of diene **33**, the overall operational selectivity in favor of **25** was ca. 4.5:1. We note that the small component of the reaction, which proceded directly to dihydropyrone rather than via aldol intermediate, gave **25** with much greater selectivity, though in very low yield. Reduction of **25** with sodium borohydride in the presence of cerium(III) chloride afforded glycal **36**, which, upon acetylation, afforded **37** (90% overall yield) (Scheme VII).

At this juncture is was planned to exploit an example of the carbon nucleophile version of the Ferrier rearrangement.[35] The nucleophile envisioned was (*E*)-trimethylcrotylsilane.

This general reaction was discovered in our laboratory and its stereochemical nuances have been examined in some detail.[36] It was found that with glycal acetates of the type **38**, both (*E*)- and (*Z*)-crotylsilanes afford *C*-glycosyl compounds of the type **39**, wherein the nucleophile had attacked in an apparently axial sense. *However, the geometry of the silane does significantly influence the stereogenic center of the butenyl group.* The use of *E* silanes tended to favor the anti[37] isomer **39a**, while the *Z* silane favored the syn[37] product **39s**. In that work it was noted that the preference for anti product, of the type needed for zincophorin, was greatest when R in **38** was not hydrogen.

Thus the failure of diene **29** to produce workable amounts of **31t** (vide supra) was doubly damaging. It obliged us to use the difficultly accessible *Z* diene **33**. Moreover it essentially dictated the use of a version of **38**, R = H, in which anti selectivity of (*E*)-crotylsilane would be eroded relative to the situation where R = SPh.

In the event, reaction of **37** with (*E*)-trimethylcrotylsilane in the presence of $BF_3 \cdot OEt_2$ at −78 °C afforded a 60% yield of a 3.5:1 mixture of closely related products. At the time it was not possible to assign the stereochemistry of these products on the basis of spectral analysis. On the basis of precedents available to us, it was assumed that the major product was the desired anti isomer **40a**.[37] This surmise proved to be correct (vide infra). The major (a series) and minor (s series) were not separated at this stage. Rather, the mixture was carried forward. The terminal vinyl group was selectively attacked with osmium tetroxide, and the resultant diol was cleaved with sodium metaperiodate to afford the **41a**–**41s** mixture of aldehydes (49%) (Scheme IX). Jones oxidation of this mixture followed by methylation with diazomethane afforded

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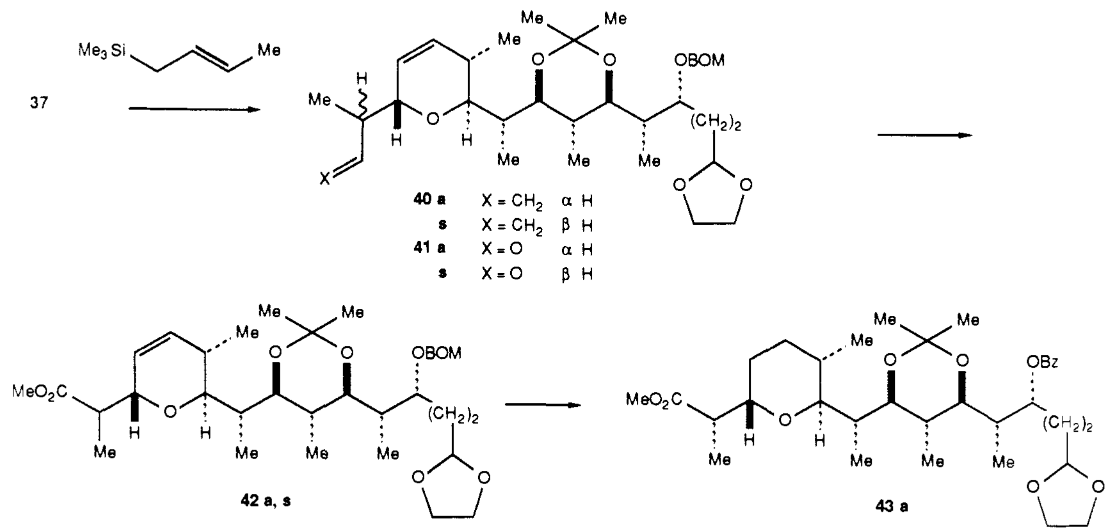
[35] Danishefsky, S. J.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 3803.

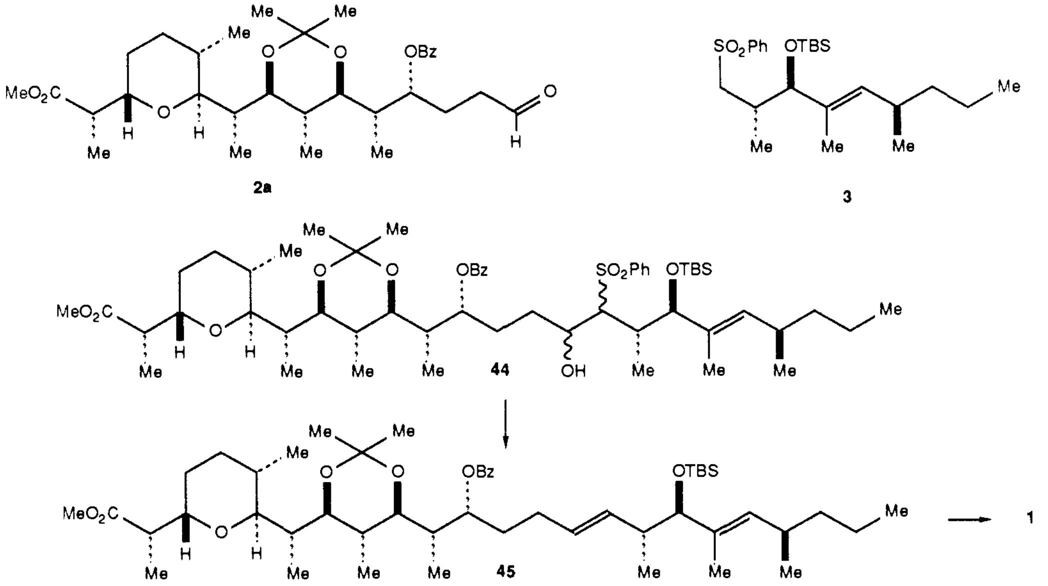
[36] Danishefsky, S. J.; Lartey, P.; DeNinno, S. *J. Am. Chem. Soc.* **1987**, *109*, 2082.

[37] We have introduced the syn and anti expressions to describe the connectivity of the α-branched side substituent with the stereogenic center of the tetrahydropyran ring to which it is bound. This convention is based on a conformer in which the longest carbon chain is placed in the antiperiplanar relationship with the carbon–carbon bond of the pyran. The relationship of the smaller alkyl branch with the ring oxygen in this extended conformer is covered through the syn–anti descriptors.

Scheme IX



Scheme X



(91%) the methyl esters **42a–42s**. Concurrent reduction of the double bond and hydrogenolysis of the (benzyloxy)methyl blocking group was accomplished through the use of hydrogen over Pearlmann's catalyst.[38] Subsequent benzoylation gave the **43a–43s** mixture and afforded homogeneous **43a** after purification by HPLC.

Treatment of the major isomer with *p*-TsOH in aqueous acetone liberated the aldehyde function and afforded homogeneous aldehyde **2a**. *The material thus obtained by total synthesis was identical with material obtained by degradation of zincophorin by the criteria of NMR (490 MHz) and infrared spectroscopy as well as optical rotation (synthetic* **44**, *$[\alpha]_D$ +18.9° (c 0.29, $CHCl_3$); from degradation $[\alpha]_D$ +20.3° (c 2.23, $CHCl_3$)) and chromatogrpahic comparisons.* The assignments of configurations to the major products of the addition of the Grignard reagent **6** to aldehyde **4**, the cyclocondensation of aldehyde **10** with diene **11**, the cyclocondensation of aldehyde **24** with diene **33**, and the carbon Ferrier reaction of **37** with (*E*)-trimethylcrotylsilane, none of which had been proven spectroscopically, had now been corroborated.

As mentioned at the outset, the silyloxy sulfone **3** (P' = OTBS) had been obtained by total synthesis.[8] Its structure and stereochemistry had also been established to be as shown, by correlation with a sample prepared by degradation of zincophorin and subsequent modification. The setting was thus in place for the final assault on the total synthesis of zincophorin itself. Recourse was to be made to a Julia coupling[39] to unite the two components and to fashion the *E*-16–17 double bond.

Some early difficulties were encountered in merging the two components. Attempted coupling of the lithium salt of **3** (presumably generated from its reaction with *n*-butyllithium and aldehyde **44**) led to substantial recovery of starting materials. Subsequently it was found that treatment of the lithiated version of **3** with anhydrous magnesium bromide prior to addition of **2a** afforded an 88% yield of what was assigned to be a diastereomeric mixture of β-hydroxy sulfones.[40] Treatment of the mixture with sodium amalgam sufficed to introduce the 16–17 double bond as an 8:1 mixture of *E–Z* isomers. The blocking groups of the major isomer, **44**, were removed by successive treatment with aqueous HCl–methanol–THF at 50 °C followed by basic hydrolysis (aqueous lithium hydroxide–methanol–THF) (Scheme X). There was thus generated the difficulty characterizable zinc-free, zincophorin free acid **1a**. Esterification of this material with diazomethane afforded zincophorin methyl ester (60% overall) identical with the natural material by spectroscopic (NMR and IR) and chromatographic criteria and corresponding quite closely

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[38] Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1663.

[39] Kocienski, P. J.; Lythgoe, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1400.

[40] Presumably, enolization of **2a** was the major pathway when Li^+ was used as the counterion.

in optical rotation (synthetic **1b** $[\alpha]_D$ +22.4° (*c* 0.84, $CHCl_3$); authentic $[\alpha]_D$ +20.9° (*c* 2.0, $CHCl_3$)).

Summary

The total synthesis of this first documented zinc-sequestering antibiotic was thus achieved. While the synthesis was far from 100% stereospecific, the 13 sp^3 stereogenic centers and two double bonds were each obtained with a minimum selectivity of 3.5:1 in the desired direction. Current activities in our laboratory are directed toward defining the relationship of structure and stereochemistry to zinc binding and to biological activity. Results will be reported in due course.

Experimental Section[41]

(3*R*,4*S*)-(1,3-Dioxolan-2-yl)-4-methyl-5-(trimethylsilyl)-5-hexen-3-ol (7). A solution of aldehyde **4** (12.4 g, 79.5 mmol) in 150 mL of THF at −78 °C was treated with 80 mL of a freshly prepared 1 M solution of the Grignard derived from 2-(2-bromoethyl)-1,3-dioxolane. The reaction was allowed to warm to 0 °C and then poured into 500 mL of water. The aqueous phase was extracted with 3 × 100 mL of methylene chloride, and the combined organics were dried over anhydrous $MgSO_4$ and concentrated at reduced pressure. Chromatography of the residue (50% ether–hexanes) gave 18.45 g (90%) of alcohol **7** as a colorless oil: $[\alpha]_D{}^{25}$ +23.78° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 3480, 2960, 2890, 1410, 1250, 1142 cm^{-1}; NMR ($CDCl_3$) δ 5.68 (d, 1 H, *J* = 2.3 Hz), 5.51 (d, 1 H, *J* = 2.3 Hz), 4.90 (app t, 1 H, *J* = 4.4 Hz), 4.05–3.80 (m, 4 H), 3.63–3.52 (m, 1 H), 2.42 (app q, 1 H, *J* = 6.7 Hz), 2.04 (d, 1 H, *J* = 3.2 Hz), 1.95–1.45 (m, 4 H), 1.06 (d, 3 H, *J* = 6.7 Hz), 0.11 (s, 9 H); MS, *m/e* 258 (M^+, 0.2), 257 (1.1). Anal. Calcd for $C_{13}H_{26}O_3Si$: C, 60.41; H, 10.13. Found: C, 60.56; H, 9.94.

(3*R*,4*R*)-(1,3-Dioxolan-2-yl)-4-methyl-5-hexen-3-ol (8). A solution of **7** (18.45 g, 71.51 mmol) in50 mL of THF was added to a stirring suspension of sodium hydride (2.3 g of 50% dispersion, 48 mmol) in 300 mL of 3:2 HMPA–THF at room temperature. The reaction was stirred at room temperature for 22 h and carefully quenched by the addition of 10 mL of methanol and 1 L of ice water. The aqueous phase was extracted with ether (4 × 200 mL), and the combined organics were dried over anhydrous $MgSO_4$ and concentrated at reduced pressure. Silica gel chromatography (40% ether/hexanes) gave 9.90 g (74%) of olefin **8** as a colorless oil: $[\alpha]^{25}{}_D$ 27.15° (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 3475 (br), 2960, 2880, 1638, 1450, 1415 cm^{-1}; NMR ($CDCl_3$) δ 5.72 (ddd, 1 H, *J* = 16.7, 10.1, 7.0 Hz), 5.09 (dd, 1 H, *J* = 16.1, 1.1 Hz), 5.07 (dd, 1 H, *J* = 10.1, 1.1 Hz), 4.91 (app t, 1 H, *J* = 4.5 Hz), 4.05–3.85 (m, 4 H), 3.55–3.47 (m, 4 H), 2.40–2.21 (m, 1 H), 2.05–1960 (m, 3 H), 1.60–1.40 (m, 1 H), 1.08 (d, 3 H, *J* = 6.5 Hz); MS, *m/e* 186 (M^+, 0.1), 185 (M^+ − 1, 0.8); HRMS calcd for $C_{10}H_{17}O_3$ (M^+ − 1) 185.1178, found 185.1189.

(3*R*,4*R*)-2-[4-Methyl-3-[(phenylmethoxy)methoxy]-5-hexenyl]-1,3-dioxolane (9). A solution of 8.3 g (44.6 mmol) of alcohol **8** in 50 mL of diisopropylamine at room temperature was treated with 8.4 g (5.35 mmol) of freshly distilled benzoyloxymethyl chloride and stirred at room temperature for 16 h. The diisopropylamine was then evaporated at reduced pressure, and the residue was partitioned between 300 mL of water and 100 mL of methylene chloride. The phases were separated, and the aqueous phase was extracted with two additional 100-mL portions of methylene chloride. The combined organics were dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. Silica gel chromatography (35% ether–hexanes) gave 12.42 g (91%) of BOM ether **9** as a colorless oil: $[\alpha]^{25}{}_D$ +27.15° (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 3005, 2960, 2885, 1450, 1140 cm^{-1}; NMR ($CDCl_3$) δ 7.4–7.25 (m, 5 H), 5.96–5.75 (m, 1 H), 5.09 (dd, 1 H, *J* = 17.0, 1.1 Hz), 5.06 (dd, 1 H, *J* = 10.0, 1.1 Hz), 4.82 (AB q, 2 H, *J* = 8.0 Hz, $\Delta\nu_{AB}$ = 7.9 Hz), 4.65 (s, 2 H), 4.03–3.75 (m, 4 H), 3.62–3.52 (m, 1 H), 2.60–2.40 (m, 1 H), 1.98–1.79 (m, 1 H), 1.79–1.50 (m, 3 H), 1.08 (d, 3 H, *J* = 6.5 Hz); MS, *m/e* 305 (M^+ − 1, 0.1). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.92; H, 8.40.

[*R*(*R,*S**)]-α-Methyl-β-[(phenylmethoxy)methoxy]-1,3-dioxolane-2-pentanal (10).** Ozone was bubbled through a cold (−78 °C) solution of 12.5 g (40.8 mmol) of olefin **9** in 480 mL of 2:1 methylene chloride–methanol containing 3.4 g of suspended solid sodium bicarbonate, until a blue color persisted (ca. 20 min). Excess ozone was purged by bubbling nitrogen through the reaction for 2 min. Dimethyl sulfide was then added, and the reaction was allowed to warm slowly to room temperature. Zinc dust was then added (2.67 g, 40.8 mmol), followed by AcOH added portionwise over a 1-h period (10 mL total) until TLC analysis showed only one major product. The mixture was then filtered and poured into 300 mL of saturated aqueous $NaHCO_3$. The phases were separated, and the aqueous phase was extracted with 3 × 100-mL portions of methylene chloride. The combined organics were dried ($MgSO_4$) and concentrated at reduced pressure. Chromatography (1:1 ether–hexanes) gave 10.1 g (80%) of aldehyde **10** as a colorless oil: $[\alpha]^{25}{}_D$ 19.78° (*c* 5.4, $CHCl_3$); IR ($CHCl_3$) 3020, 2960, 2890, 2725, 1725, 1455 cm^{-1}; NMR ($CDCl_3$) δ 9.81 (d, 1 H, *J* = 0.6 Hz), 7.42–7.24 (m, 5 H), 4.89 (app t, 1 H, *J* = 4.3 Hz), 4.80 (AB q, 2 H, *J* = 7.2 Hz, $\Delta\nu_{AB}$ = 8.42 Hz), 4.58 (AB q, 2 H, *J* = 11.8 Hz, $\Delta\nu_{AB}$ = 10.0 Hz), 4.20–4.10 (m, 1 H), 4.01–3.83 (m, 4 H), 2.60 (dq, 1 H, *J* = 6.9, 3.6 Hz), 1.90–1.65 (m, 4 H), 1.14 (d, 3 H, *J* = 6.9 Hz); MS, *m/e* 307 (M^+ − 1, 0.2). HRMS (CI) calcd for $C_{17}H_{25}O_5$ (M^+ + 1) 309.1702, found 309.1697.

[2*S*[2α(1*R,2*S**),3β]]-2-[4-(1,3-Dioxolan-2-yl)-1-methyl-2-[(phenylmethoxy)methoxy]butyl]-2,3-dihydro-3,5-dimethyl-4*H*-pyran-4-one (12).** A solution of 6.49 g (21.0 mmol) of aldehyde **10** and 12.64 g (63.2 mmol) of diene **11** in 250 mL of methylene chloride was cooled to −65 °C and treated with 15.7 mL (31.6 mmol) of a 2.5 M solution of $MgBr_2{\cdot}OEt_2$ in 1:1 ether–benzene. The reaction mixture was allowed to warm slowly to 0 °C over a 5-h period and quenched by pouring into 250 mL of saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with methylene chloride. The combined organics were dried ($MgSO_4$), and the solvent was removed in vacuo. Chromatography on silica gel (50% ether–hexanes) gave 6.8 g (80%) of pyrone **14** as a 7:1 mixture of trans to cis isomers, which proved inseparable by HPLC in three solvent systems. Analytical data for the major isomer: $[\alpha]^{25}{}_D$ −110.39° (*c* 2.5, $CHCl_3$); IR ($CHCl_3$) 3010, 2980, 1660, 1625, 1460, 1385 cm^{-1}; NMR ($CDCl_3$) δ 7.41–7.24 (m, 5 H), 7.08 (br, s, 1 H), 4.76 (app t, 1 H, *J* = 4.5 Hz), 4.82 (s, 2 H), 4.65 (s, 2 H), 4.20 (dd, 1 H, *J* = 10.0, 6.0 Hz), 4.00–3.80 (m, 5 H), 2.65–2.50 (dq, 1 H, *J* = 10.0, 6.5 Hz), 2.15–2.03 (m, 1 H), 1.94–1.52 (m, 4 H), 1.64 (br s, 3 H), 1.23 (d, 3 H, *J* = 6.5 Hz), 0.92 (d, 3 H, *J* = 6.9 Hz); MS, *m/e* 404 (M^+ − 1, 0.1). HRMS (CI) calcd for $C_{23}H_{33}O_3$ (M^+ + 1) 405.2278, found 405.2273.

[2*R*[2α(1*S,2*R**),3β,6β]]-6-[(3,4-Dimethoxyphenyl)methoxy]-2-[4-(1,3-dioxolan-2-yl)-1-methyl-2-[(phenylmethoxy)methoxy]butyl]-3,6-dihydro-3,5-dimethyl-2*H*-pyran (16).** A solution of 6.42 g (15.8 mmol) of pyrone **12** and 7.65 g (20.54 mmol) of $CeCl_3{\cdot}7H_2O$ in 200 mL of 1:1 ethanol–methylene chloride was cooled to −78 °C and treated with a solution of 900 mg (23.8 mmol) of $NaBH_4$ in 10 mL of ethanol. The reaction was allowed to warm slowly to −20 °C and then poured into 300 mL of saturated aqueous $NaHCO_3$. Extraction with CH_2Cl_2 (3 × 100 mL), drying ($MgSO_4$), and concentration gave the crude alcohol **15** as a colorless oil, which was normally used in the next reaction without further purification. The crude alcohol **15** thus obtained was dissolved in 100 mL of benzene and treated with 9.7 g (57.6 mmol) of 3,4-dimethoxybenzyl alcohol and 50 mg of *p*-TsOH at room temperature. After 1 h the reaction was poured into 100 mL of saturated aqueous $NaHCO_3$, and the layers were separated. The aqueous phase was extracted with three additional 50-mL portions of methylene chloride, and the combined phase was extracted with three additional 50-mL portions of methylene chloride, and the combined organics were dried ($MgSO_4$) and concentrated at reduced pressure. The residue was chromatographed on silica gel to give 6.85 g (78%) of Ferrier product **16** as a colorless oil: $[\alpha]^{25}{}_D$ −4.5° (*c* 2.55, $CHCl_3$); IR ($CHCl_3$) 3010, 2975, 2880, 1519, 1465, 1458 cm^{-1}; NMR ($CDCl_3$) δ 7.40–7.27 (m, 5 H), 6.96–6.80 (m, 3 H), 5.39 (br s, 1 H), 4.90 (t, 1 H, *J* = 4.5 Hz), 4.84 (AB q, 2 H, *J* = 7.0 Hz, $\Delta\nu_{AB}$ = 25.3 Hz), 4.75 (br s, 1 H), 4.66 (AB q, 2 H, *J* = 12.0 Hz, $\Delta\nu_{AB}$ = 24.0 Hz), 4.63 (AB q, 2 H, *J* = 11.7 Hz, $\Delta\nu_{AB}$ = 57.5 Hz), 4.00–3.82 (m, 5 H), 3.88 (s 3 H), 3.87 (s, 3 H), 3.51 (dd, 1 H, *J* = 10.0, 3.2 Hz), 2.41 (m, 1 H), 1.98 (m, 1 H), 1.90–1.65 (m, 4 H), 1.67 (br s, 3 H), 1.16 (d, 3 H, *J* = 7.2 Hz), 0.92 (d, 3 H, *J* = 7.0 Hz); MS, *m/e* 389 (0.5) loss of 3,4-dimethoxybenzyl. Anal. Calcd for $C_{32}H_{44}O_8$: C, 69.04; H, 7.96. Found: C, 68.71; H, 8.03.

Analytical data for allylic alcohol 15: $[\alpha]_D$ −71.5° (*c* 2.7); IR ($CHCl_3$) 3601 (br), 2965, 2882, 1666, 1453, 1381, 1162 cm^{-1}; NMR ($CDCl_3$) δ 7.40–7.24 (m, 5 H), 6.16 (br s, 1 H), 4.88 (app t, 1 H, *J* = 4.3 Hz), 4.78 (s, 2 H), 4.64 (AB q, 2 H, *J* = 11.8 Hz, $\Delta\nu_{AB}$ = 18.9 Hz), 4.01–3.83 (m, 6 H), 3.65 (dd, 1 H, *J* = 7.2 Hz), 1.01 (d, 3 H, *J* = 7.1 Hz); MS, *m/e* 406 (M^+, 0.8). HRMS (CI) calcd for $C_{23}H_{35}O_6$ (M^+ + 1) 407.2435, found 407.2463.

[2*R*[2α,3α,4β,5α,6β(1*S,2*R**)]]-2-[(3,4-Dimethoxyphenyl)methoxy]-6-[4-(1,3-dioxolan-2-yl)-1-methyl-2-[(phenylmethoxy)methoxy]butyl]tetrahydro-3,5-dimethyl-2*H*-pyran-4-ol (17).** A solution of olefin **16** (7.8 g, 14 mmol) in 300 mL of THF was cooled to 0 °C and treated with 2.8 mL of 10 M $BH_3{\cdot}DMS$. The reaction mixture was allowed to warm to room temperature over 8 h at which time 50 mL of 1 N NaOH was added followed by 10 mL of 30% H_2O_2. After being stirred at room temperature for 12 h, the reaction was diluted with 500 mL of H_2O and

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[41] High-resolution mass spectra were recorded on a Kratos MS 80RFA instrument by Dan Pentek. The 500-MHz NMR spectra were recorded on a Bruker WM500 spectrometer. For additional general experimental details, see ref 36.

extracted with 4 × 100 mL of CH_2Cl_2. The organics were combined and dried ($MgSO_4$), and the solvent was removed in vacuo. Chromatography of the residue (10% hexanes–ether) gave 5.3 g (67%) of alcohol **17** as a colorless oil: $[\alpha]^{25}_{D}$ −26.9° (*c* 1.27, $CHCl_3$); IR ($CHCl_3$) 3600 (br), 2985, 2940, 2880, 1595, 1517, 1465 cm^{-1}; NMR ($CDCl_3$) δ 7.40–7.24 (m, 5 H), 6.90–6.80 (m, 3 H), 4.89 (t, 1 H, J = 4.5 Hz), 4.67 (AG q, 2 H, J = 11.5 Hz, $\Delta\nu_{AB}$ = 31.3 Hz), 4.48 (AB q, 2 H, J = 12.0 Hz, $\Delta\nu_{AB}$ = 64.1 Hz), 4.00–3.82 (m, 5 H), 3.88 (s, 6 H), 3.50 (dd, 1 H, J = 10.7, 2.3 Hz), 3.30 (br dt, 1 H, J = 10.0, 5.3 Hz, collapsing to an app t, J = 10.0 Hz on addition of D_2O), 2.02–1.50 (m, 7 H), 1.38 (br d, 1 H, J = 5.3 Hz exch), 1.13 (d, 3 H, J = 7.2 Hz), 1.01 (d, 3 H, J = 6.8 Hz), 0.95 (d, 3 H, 6.3 Hz); MS, *m/e* 574 (M^+, 0.4). Anal. Calcd for $C_{32}H_{46}O_9$: C, 66.87; H, 8.06. Found: C, 66.60; H, 8.02.

[2R[2α,3α,5α,6β,(1S*,2R*)]]-2-[(3,4-Dimethoxyphenyl)methoxy]-6-[4-(1,3-dioxolan-2-yl)-1-methyl-2-[(phenylmethoxy)methoxy]butyl]-tetrahydro-3,5-dimethyl-4H-pyran-4-one (18). A cold solution of oxallyl chloride (658 mL, 957 mg, 7.50 mmol) was treated with 1.23 g (15.7 mmol) of DMSO. After the gas evolution had ceased, a solution of 3.61 g (6.28 mmol) of alcohol **17** in 10 mL of CH_2Cl_2 was added slowly. After 15 min the reaction was quenched by the addition of 3.17 g (31.4 mmol) of triethylamine. The mixture was then warmed to 0 °C and poured into 100 mL of pH 7 buffer. The layers were separated, and the aqueous phase was extracted with 3 × 50-mL portions of CH_2Cl_2. After drying ($MgSO_4$) and removal of the solvent, the residue was chromatographed on silica gel (60% ether–hexanes) to give 3.01 g (84%) of pyranone **18** as a colorless oil: $[\alpha]^{25}_{D}$ −28.28° (*c* 1.34, $CHCl_3$); IR ($CHCl_3$) 3015, 2940, 2880, 1718, 1518, 1465, 1454 cm^{-1}; NMR ($CDCl_3$) δ 7.40–7.24 (m, 5 H), 6.85 (br s, 3 H), 4.99 (d, 1 H, J = 4.0 Hz), 4.90 (t, 1 H, J = 4.4 Hz), 4.87 (AB q, 2 H, J = 6.8 Hz, $\Delta\nu_{AB}$ = 22.9 Hz), 4.68 (AB q, 2 H, J = 11.9 Hz, DnAB = 26.25 Hz), 4.49 (AB q, 2 H, J = 12.1 Hz, $\Delta\nu_{AB}$ = 57.1 Hz), 4.03–3.85 (m, 5 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.72 (dd, 1 H, J = 10.5, 2.5 Hz), 2.78–2.55 (m, 2 H), 2.04–1.70 (m, 5 H), 1.18 (d, 3 H, J = 7.1 Hz), 0.99 (d, 3 H, J = 6.9 Hz), 0.97 (d, 3 H, J = 7.0 Hz); MS, *m/e* 572 (M^+, 1.2). HRMS calcd for $C_{22}H_{44}O_9$ 572.2986, found 572.2966.

[2R[2α,3α,4α,5α,6β(1S*,2R*)]]-2-[(3,4-Dimethoxyphenyl)methoxy]-6-[4-(1,3-dioxolan-2-yl)-1-methyl-2-[(phenylmethoxy)methoxy]butyl]tetrahydro-3,5-dimethyl-2H-pyran-4-ol (19). A cold (−78 °C) solution of pyranone **18** (3.01 g, 5.26 mmol) in THF (150 mL) was treated with 6.8 mL of a 1 M solution of lithium tri-*sec*-butyl borohydride (L-Selectride, Aldrich). The reaction mixture was kept at −78 °C for 0.5 h and then warmed to −30 °C. The reaction was quenched by adding 27 mL of 1 N NaOH followed by 12 mL of 30% H_2O_2. After being warmed to 0 °C, the mixture was poured into 500 mL of H_2O, and the aqueous phase was extracted with methylene chloride (4 × 75 mL). The combined organics were dried ($MgSO_4$), and the solvent was evaporated at reduced pressure. Chromatography of the residue (10% hexanes–ether) gave 2.7 g (88%) of alcohol **19** as a colorless oil: $[\alpha]^{25}_{D}$ −21.68° (*c* 5.34, $CHCl_3$); IR $CHCl_3$ 3520 (br), 3015, 2970, 290, 2890, 1518, 1465 cm^{-1}; NMR ($CDCl_3$) δ 7.42–7.24 (m, 5 H), 6.91–6.80 (m, 3 H), 4.92 (t, 1 H, J = 4.2 Hz), 4.81 (AB q, 2 H, J = 7.0 Hz, $\Delta\nu_{AB}$ = 24.5 Hz), 4.71 (d, 1 H, J = 2.9 Hz), 4.66 (AB q, 2 H, J = 12.0 Hz, $\Delta\nu_{AB}$ = 36.76 Hz); 4.61 (AB q, 2 H, J = 11.9 Hz, $\Delta\nu_{AB}$ = 72.3 Hz), 4.0–3.82 (m, 5 H), 3.88 (br s, 6 H), 3.65 (dd, 1 H, J = 11.0, 2.1 Hz), 3.5 (br d, 1 H, J = 10.0 Hz), 3.02 (d, 1 H, J = 10.0 Hz, exch), 2.0–1.6 (m, 7 H), 1.17 (d, 3 H, J = 7.1 Hz), 1.05 (d, 3 H, J = 7.2 Hz), 0.95 (d, 3 H, J = 6.8 Hz); MS, *m/e* 574 (M^+, 0.4). Anal. Calcd for $C_{32}H_{46}O_9$: C, 66.87; H, 8.06. Found: C, 66.50; H, 8.01.

Lactol Triol 21a. A solution of alcohol **19** (2.01 g, 3.05 mmol) in methylene chloride (120 mL) was treated with 3 mL of H_2O and then 874 mg (3.85 mmol) of DDQ. The dark green solution was stirred vigorously at room temperature as the green color faded and the reaction became heterogeneous. After 4.5 h the reaction mixture was poured into H_2O, and the layers were separated. The aqueous phase was extracted with 3 × 50 mL of methylene chloride. The combined organics were dried, and the solvent was removed in vacuo. Chromatography (30% ether–hexanes) gave 1.19 g (80%) of lactol **20** as a ca. 3:2 mixture of anomers, which were not purified further and were used directly in the next reaction. A solution of the lactol **20** (1.49 g, 3.5 mmol) in THF (50 mL) was treated with 99 mg (4.55 mmol) of lithium borohydride at room temperature. After the mixture was stirred for 16 h, excess lithium borohydride was quenched by the addition of 4 mL of methanol and then pouring of the reaction mixture into 100 mL of H_2O. The aqueous phase was extracted with CH_2Cl_2 (4 × 50 mL), and the combined organics were dried ($MgSO_4$) and concentrated at reduced pressure. Chromatography of the residue gave 1.23 g (82%) of triol **21a** as a colorless oil: $[\alpha]^{25}_{D}$ −23.09° (*c* 2.81, $CHCl_3$); IR ($CHCl_3$) 3430 (br), 2980, 2790, 1430, 1220 cm^{-1}; NMR ($CDCl_3$) δ 7.40–7.28 (m, 5 H), 5.3 (d, 1 H, J = 2.3 Hz exch), 4.91–4.80 (m, 3 H), 4.66 (AB q, 2 H, J = 12.1 Hz, $\Delta\nu_{AB}$ = 18.5 Hz), 4.48 (d, 1 H, J = 5.0 Hz, exch), 4.13–4.00 (m, 1 H), 4.00–3.84 (m, 5 H), 3.70–3.50 (m, 4 H), 2.15–1.80 (m, 4 H), 1.74–1.60 (m, 3 H), 1.09 (d, 3 H, J = 7.5 Hz), 1.04 (d, 3 H, J = 7.0 Hz), 0.89 (d, 3 H, J = 6.9 Hz); MS, *m/e* 349 (M^+ − 77, 0.9). Anal. Calcd for $C_{23}H_{38}O_7$: C, 64.76; H, 8.98. Found: C, 64.51; H, 9.12.

***tert*-Butyldiphenylsilyl Ether (21b).** A solution of triol **21a** (1.70 g, 3.99 mmol) in 15 mL of DMF was treated with 380 mg (5.58 mmol) of imidazole and 1.31 g (4.78 mmol) of *tert*-butyldiphenylsilyl chloride. After 2 h the reaction was diluted with ether (50 mL) and washed with H_2O (50 mL). The aqueous phase was extracted with two additional 50-mL portions of ether, and the combined organics were dried ($MgSO_4$) and concentrated at reduced pressure. Chromatography of the residue on silica gel (50% ether–hexanes) gave 2.51 g (95%) of monosilyl ether **21b** as a colorless oil: $[\alpha]^{25}_{D}$ −13.6° (*c* 4.48, $CHCl_3$) δ 7.72–7.63 (m, 4 H), 7.48–7.25 (m, 11 H), 4.87 (t, 1 H, J = 4.3 Hz), 4.78 (AB q, 2 H, J = 6.0 Hz, $\Delta\nu_{AB}$ = 4.0 Hz), 4.60 (AB q, 2 H, J = 8.0 Hz, $\Delta\nu_{AB}$ = 2.0 Hz), 4.43 (d, 1 H, J = 3.0 Hz, exch), 4.12 (d, 1 H, J = 7.5, 4.1, 3.0 Hz), 3.54 (app, br q, 1 H, J = 5.8 Hz, collapses to an app t, J = 5.8 Hz, after D_2O), 2.13–1.50 (m, 7 H), 1.07 (d, 3 H, J = 7.2 Hz), 1.06 (s, 9 H), 0.99 (d, 3 H, J = 6.9 Hz), 0.85 (d, 3 H, J = 6.9 Hz); MS, *m/e* 525 (M^+ − 139). Anal. Calcd for $C_{39}H_{56}O_7Si$: C, 70.44; H, 8.48. Found: C, 70.35; H, 8.20.

Acetonide 22. A solution of 1.11 g (1.66 mmol) of monosilyl ether **21b** in 10 mL of 2,2-dimethoxypropane was treated with 15 mg of camphorsulfonic acid. After 1.5 h the reaction was quenched by the addition of 750 mL of triethylamine. The reaction was then concentrated at reduced pressure, and the residue was chromatographed (50% ether–hexanes) to give 1.17 g (99%) of acetonide **22** as a colorless oil: $[\alpha]^{25}_{D}$ +21.90° (*c* 1.83, $CHCl_3$); IR ($CHCl_3$) 2980, 2930, 2790, 1430, 1380, 1220 cm^{-1}; NMR ($CDCl_3$) δ 7.80–7.65 (m, 4 H), 7.50–7.24 (m, 11 H), 4.85 (t, 1 H, J = 4.3 Hz), 4.78 (AB q, 2 H, J = 6.8 Hz, $\Delta\nu_{AB}$ = 32.1 Hz), 4.61 (AB q, 2 H, J = 11.9 Hz, $\Delta\nu_{AB}$ = 47.3 Hz), 3.99–3.80 (m, 6 H), 3.47 (dd, 1 H, J = 10.1, 6.8 Hz), 3.40–3.29 (m, 2 H), 2.02 (m, 1 H), 1.90–1.50 (m, 6 H), 1.32 (s, 3 H), 1.29 (s, 3 H), 1.05 (s, 9 H), 0.99 (d, 3 H, J = 7.1 Hz), 0.97 (d, 3 H, J = 7.0 Hz), 0.68 (d, 3 H, J = 6.4 Hz); MS, *m/e* 689 (M^+ − 15, 3.1). Anal. Calcd for $C_{42}H_{60}O_7Si$: C, 71.56; H, 8.57. Found: C, 71.44; H, 8.61.

Alcohol Acetonide 23. A solution of the monosilyl ether acetonide **22** (1.17 g, 1.65 mmol) in 10 mL of DMF was treated with 3.4 mL of a 1 N solution of tetra-*n*-butylammonium fluoride in THF at room temperature. After 5 h the reaction was diluted with 20 mL of ether and poured into 30 mL of saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with 3 × 20-mL portions of ether. The combined organics were dried over $MgSO_4$, and the solvent was removed in vacuo. Chromatography of the residue (60% ether–hexanes) gave 775 mg (100%) of alcohol **23** as a colorless oil: $[\alpha]^{25}_{D}$ +25.02° (*c* 2.23, $CHCl_3$); IR ($CHCl_3$) 3540, 2970, 2940, 2880, 1455, 1383, 1258, 1205 cm^{-1}; NMR ($CDCl_3$) δ 7.40–7.24 (m, 5 H), 4.92–4.85 (m, 2 H), 4.73 (d, 1 H, J = 6.5 Hz), 4.65 (AB q, 2 H, J = 11.9 Hz, $\Delta\nu_{AB}$ = 46.9 Hz), 4.00–3.82 (m, 6 H), 3.54–3.48 (m, 2 H), 3.43 (dd, 1 H, J = 10.1, 2.6 Hz), 2.20–1.60 (m, 8 H), 1.35 (s, 6 H), 1.13 (d, 3 H, J = 7.1 Hz), 1.03 (d, 3 H, J = 7.1 Hz), 0.77 (d, 3 H, J = 6.5 Hz); MS *m/e* 451 (M^+ − 15, 8.6). Anal. Calcd for $C_{26}H_{42}O_7$: C, 66.92; H, 9.07. Found: C, 66.80; H, 8.96.

[4S[4α(R*),5β,6α(1R*,2S*)]]-6-[4-(1,3-Dioxolan-2-yl)-1-methyl-2-[(phenylmethoxy)methoxy]butyl]-α,2,2,5-tetramethyl-1,3-dioxane-4-acetaldehyde (24). Alcohol **23** (550 mg, 1.18 mmol) was oxidized by the method of Mancuso and Swern in a manner similar to that already described for the conversion of **17** to **18**. The yield of aldehyde **24** was 504 mg (92%), obtained as a colorless oil: $[\alpha]^{25}_{D}$ +35.64° (*c* 2.73, $CHCl_3$); IR ($CHCl_3$) 2940, 2880, 1728, 1455, 1380, 1252 cm^{-1}; NMR ($CDCl_3$) δ 9.79 (d, 1 H, J = 2.4 Hz), 7.42–7.24 (m, 5 H), 4.93–4.85 (m, 5 H), 4.73 (d, 1 H, J = 6.6 Hz), 4.65 (AB q, 2 H, J = 11.9 Hz, DnAB = 46.9 Hz), 4.00–3.80 (m, 5 H), 3.64 (dd, 1 H, J = 10.4, 2.0 Hz), 3.43 (dd, 1 H, J = 10.3, 2.9 Hz), 2.55 (ddq, 1 H, J = 7.1, 2.4, 2.0 Hz), 2.00–1.70 (m, 6 H), 1.37 (s, 3 H), 1.33 (s, 3 H), 1.19 (d, 3 H, J = 7.0 Hz), 1.02 (d, 3 H, J = 7.1 Hz), 0.80 (d, 3 H, J = 6.5 Hz); MS, *m/e* 449 (M^+ − 15, 2.8); HRMS (EI) calcd for $C_{25}H_{37}O_7$ (M^+ − 15) 449.2540, found 449.2546.

[4R[4α[R*(2R*,3R*)],5β,6α(1S*,2R*)]]-2-[1-[6-[4-(1,3-Dioxolan-2-yl)-1-methyl-2-[(phenylmethoxy)methoxy]butyl]-2,2,5-trimethyl-1,3-dioxan-4-yl]ethyl]-2,3-dihydro-3-methyl-4H-pyran-4-one (25). A cold (−78 °C) solution of aldehyde **24** (96.4 mg, 0.207 mmol) and diene **33** (85 mg, 0.37 mmol) in 2 mL of propionitrile was treated with 45 mL (52.9 mg, 0.37 mmol) of $BF_3{\cdot}OEt_2$. After 3 min, 5 mL of saturated aqueous $NaHCO_3$ was added, and the aqueous phase was extracted with 3 × 5-mL portions of CH_2Cl_2. The combined organics were dried over anhydrous $MgSO_4$ and concentrated at reduced pressure. Chromatography of the residue gave, in order of elution, 6.6 mg (6%) of trans pyrone **25**, 14.3 mg (12%) of erythro aldol **35e**, and 60.1 mg (50%) of threo aldol **35t**.

Trans pyrone 25: $[\alpha]^{25}_{D}$ +47.9° (c 3.42, $CHCl_3$); IR ($CHCl_3$) 2965, 2930, 2880, 1682, 1604, 1455, 1404, 1380 cm^{-1}; NMR ($CDCl_3$) δ 7.40–7.24 (m, 6 H), 5.36 (d, 1 H, J = 5.8 Hz), 4.88 (t, 1 H, J = 4.5 Hz), 4.82 (AB q, 2 H, J = 6.6 Hz, $\Delta\nu_{AB}$ = 37.6 Hz), 4.65 (AB q, 2 H, J = 11.8 Hz, $\Delta\nu_{AB}$ = 46.2 Hz), 4.44 (dd, 1 H, J = 12.8, 2.2 Hz), 4.00–3.80 (m, 6 H), 3.52 (dd, 1 H, J = 8.9, 5.9 Hz), 3.43 (dd, 1 H, J = 9.2, 4.3 Hz), 2.58 (dq, 1 H, J = 12.8, 7.0 Hz), 2.13 (m, 1 H), 1.95 (m, 6 H), 1.35 (s, 3 H), 1.33 (s, 3 H), 1.09 (d, 3 H, J = 7.0 Hz), 1.05 (d, 3 H, J = 7.1 Hz), 0.87 (d, 3 H, J = 6.5 Hz); MS, m/e 545 (M$^+$ − 1, 0.9), 531 (M$^+$ − 15, 26); HRMS calcd for $C_{30}H_{43}O_8$ (M$^+$ − 15) 531.2954, found 531.2952.

Erythro aldol 35e: $[\alpha]^{25}_{D}$ +7.5° (c 1.68, $CHCl_3$); IR ($CHCl_3$) 3520, 2983, 2958, 2879, 1685, 1653, 1620, 1595, 1455, 1380, 1252 cm^{-1}; NMR ($CDCl_3$) δ 7.63 (d, 1 H, J = 12.6 Hz), 7.40–7.24 (m, 5 H), 5.61 (d, 1 H, J = 12.6 Hz), 4.91 (t, 1 H, J = 4.2 Hz), 4.82 (AB q, 2 H, J = 6.9 Hz, $\Delta\nu_{AB}$ = 34.3 Hz), 4.66 (AB q, 2 H, J = 11.9 Hz, $\Delta\nu_{AB}$ = 49.08 Hz), 4.16 (br d, 1 H, J = 10 Hz), 4.00–3.80 (m, 6 H), 3.70 (s, 3 H), 3.48 (dd, 1 H, J = 10.2, 1.7 Hz), 3.43 (dd, 1 H, J = 10.2, 3.0 Hz), 2.76 (dq, 1 H, J = 9.8, 6.9 Hz), 2.05–1.60 (m, 7 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 1.27 (d, 3 H), J = 6.9 Hz), 1.03 (d, 3 H, J = 7.1 Hz), 0.99 (d, 3 H, J = 7.2 Hz), 0.75 (d, 3 H, J = 6.5 Hz).

Threo aldol 35t: $[\alpha]^{25}_{D}$ +13.46° (c 1.85, $CHCl_3$); IR ($CHCl_3$) 3520, 2970, 2938, 2879, 1685, 1660, 1640, 1597, 1452, 1380 cm^{-1}; NMR ($CDCl_3$) δ 7.69 (d, 1 H, J = 12.6 Hz), 7.40–7.24 (m, 5 H), 5.73 (d, 1 H, J = 12.6 Hz), 4.91 (t, 1 H, J = 4.2 Hz), 4.78 (AB q, 2 H, J = 6.7 Hz, $\Delta\nu_{AB}$ = 20.72 Hz), 4.66 (AB q, 2 H, J = 12.0 Hz, $\Delta\nu_{AB}$ = 38.7 Hz), 4.19 (dd, 1 H, J = 9.7, 0.9 Hz), 4.00–3.80 (m, 6 H), 3.71 (s, 3 H), 3.57 (dd, 1 H, J = 10.7, 2.2 Hz), 3.43 (dd, 1 H, J = 10.2, 3.2 Hz), 2.79 (dq, 1 H, J = 9.4, 6.9 Hz), 2.05–1.67 (m, 7 H), 1.35 (s, 3 H), 1.32 (s, 3 H), 1.06 (d, 3 H, J = 7.0 Hz), 1.03 (d, 3 H, J = 7.1 Hz), 0.97 (d, 3 H, J = 6.9 Hz), 0.77 (d, 3 H, J = 7.0 Hz); MS, m/e 531 (0.6).

Cyclization of Aldols. A solution of threo aldol **35t** (176 mg, 0.304 mmol) and PPTS (4.7 mg) in benzene (15 mL) was heated to reflux for 4 h. After the mixture was cooled to room temperature the solvent was removed in vacuo, the residue was chromatographed (50% ether–hexanes) to give 124 mg (75%) of trans pyrone **25** as a pale yellow oil, identical in all respects with material prepared previously. In a similar fashion erythro aldol **35e** provided the cis pyrone **25c** in 46% yield as a pale yellow oil: $[\alpha]^{25}_{D}$ +50.56° (c 1.59, $CHCl_3$); IR ($CHCl_3$) 2988, 2940, 2880, 1675, 1600, 1460, 1405, 1382, 1274, 1233 cm^{-1}; NMR ($CDCl_3$) δ 7.50–7.24 (m, 6 H), 5.34 (dd, 1 H, J = 5.9, 1.2 Hz), 4.90 (t, 1 H, J = 4.6 Hz), 4.80 (AB q, 2 H, J = 7.0 Hz, $\Delta\nu_{AB}$ = 31.5 Hz), 4.65 (AB q, 2 H, J = 11.9 Hz, $\Delta\nu_{AB}$ = 42.2 Hz), 4.38 (dd, 1 H, J = 10.9, 2.5 Hz), 4.03–3.80 (m, 5 H), 3.45–3.34 (m, 2 H), 2.51 (ddq, 1 H, J = 7.3, 2.5, 1.2 Hz), 2.18 (app br p, 1 H, J = 6.5 Hz), 1.96–1.55 (m, 6 H), 1.35 (s, 3 H), 1.32 (s, 3 H), 1.17 (d, 3 H, J = 7.0 Hz), 1.12 (d, 3 H, J = 7.3 Hz), 1.01 (d, 3 H, J = 7.1 Hz), 0.77 (d, 3 H, J = 6.4 Hz); MS, m/e 531 (M$^+$ − 15, 21.8).

[4*R*[4α[*R(2*R**,3*R**,4*R**)],5β,6α(1*S**,2*R**)]]-2-[1-[6-[4-(1,3-Dioxolan-2-yl)-1-methyl-2-[(phenylmethoxy)methoxy]butyl]-2,2,5-trimethyl-1,3-dioxan-4-yl]ethyl]-3,4-dihydro-3-methyl-2*H*-pyran-4-ol Acetate (37).** A cold (−78 °C) solution of 105 mg (0.192 mmol) of pyrone **25** and 143 mg (0.384 mmol) of $CeCl_3 \cdot 7H_2O$ in 6 mL of 1:1 ethanol–methylene chloride was treated with a solution of 14.55 mg (0.384 mmol) $NaBH_4$ in 1 mL of ethanol and allowed to warm slowly to −15 °C. After 1 h the reaction mixture was poured into 10 mL of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (4 × 5 mL). The combined extracts were dried ($MgSO_4$), and the solvent was removed in vacuo to give 100 mg of crude alcohol **36**, which was taken up in 2 mL of CH_2Cl_2 and acetylated directly with excess acetic anhydride, triethylamine, and a catalytic amount of DMAP for 1 h at room temperature. The reaction mixture was concentrated at reduced pressure, and the residue was chromatographed (30% ether–hexanes) to give 102 mg (90%) of acetate **37** as a colorless oil.

Alcohol 36: $[\alpha]^{25}_{D}$ +30.91° (c 2.10, $CHCl_3$); IR (neat) 3490 (br), 2985, 2960, 2880, 1649, 1452, 1380 cm^{-1}; NMR ($CDCl_3$) δ 7.40–7.24 (m, 5 H), 6.38 (dd, 1 H, J = 6.1, 1.1 Hz), 4.89 (t, 1 H, J = 4.4 Hz), 4.84 (AB q, 2 H, J = 6.9 Hz, $\Delta\nu_{AB}$ = 45.5 Hz), 4.69 (dd, 1 H, J = 6.1, 2.2 Hz), 4.65, AB q, 2 H, J = 11.9 Hz, $\Delta\nu_{AB}$ = 48.0 Hz), 4.00–3.82 (m, 6 H), 3.50 (dd, 1 H, J = 8.6, 6.3 Hz), 3.41 (dd, 1 H, J = 9.1, 4.4 Hz), 2.13–1.99 (m, 1 H), 1.95–1.60 (m, 7 H), 1.49 (d, 1 H, J = 7.0 Hz), 1.34 (s, 3 H), 1.33 (s, 3 H), 1.02 (d, 3 H, J = 6.4 Hz), 1.00 (d, 3 H, J = 7.2 Hz), 0.96 (d, 3 H, J = 7.1 Hz), 0.87 (d, 3 H. J = 6.5 Hz); MS, m/e 533 (M$^+$ − 15, 6.8); HRMS (EI) calcd for $C_{30}H_{45}O_8$ (M$^+$ − 15) 533.3115, found 533.3118.

Acetate 37: $[\alpha]^{25}_{D}$ −10.61° (c 2.10, $CHCl_3$); IR ($CHCl_3$) 3000, 2975, 2960, 2886, 1722, 1649, 1453, 1380 cm^{-1}; NMR ($CDCl_3$) δ 7.40–7.24 (m, 5 H), 6.43 (d, 1 H, J = 6.2 Hz), 5.07 (dd, 1 H, J = 7.2, 1.1 Hz), 4.89 (m, 1 H), 4.84 (AB q, 2 H, J = 6.8 Hz, $\Delta\nu_{AB}$ = 35.5 Hz), 4.70 (dd, 1 H, J = 6.1, 2.3 Hz), 4.65 (AB q, 2 H, J = 11.8 Hz, $\Delta\nu_{AB}$ = 45.1 Hz), 4.07 (dd, 1 H, J = 9.9, 2.5 Hz), 4.00–3.82 (m, 5 H), 3.49 (dd, 1 H, J = 8.5, 6.7 Hz), 3.41 (dd, 1 H, J = 8.9, 4.5 Hz), 2.07 (s, 3 H), 2.10–2.00 (m, 1 H), 1.95–1.72 (m, 7 H), 1.34 (s, 3 H), 1.32 (s, 3 H), 1.00 (d, 3 H, J = 7.2 Hz), 0.96 (d, 3 H, J = 7.5 Hz), 0.93 (d, 3 H, J = 7.8 Hz), 0.88 (d, 3 H, J = 6.4 Hz); MS, m/e 575 (M$^+$ − 15, 1.3). HRMS calcd for $C_{32}H_{47}O_9$ (M$^+$ − 15) 573.3221, found 575.3190.

[4*R*[4α[*R[2*S**,3*R**,6*S**(*R**)]],5β,6α,(1*S**,2*R**)]]-4-[1-[3,6-Dihydro-3-methyl-6-(1-methyl-2-propenyl)-2*H*-pyran-2-yl]ethyl]-6-[4-(1,3-dioxolan-2-yl)-1-methyl-2-[(phenylmethoxy)methoxy]butyl]-2,2,5-trimethyl-1,3-dioxane (40).** A solution of 42 mg (0.071 mmol) of acetate **37** and 30 mg (0.23 mmol) of *trans*-crotyl silane in 2 mL of nitromethane was cooled to −20 °C and treated with 30 mg of $ZnBr_2$. After warming to −10 °C over 0.5 h, 5 mL of saturated aqueous $NaHCO_3$ was added, and the aqueous phase was extracted with CH_2Cl_2. The combined organics were dried ($MgSO_4$) and concentrated at reduced pressure. Chromatography (30% ether–hexanes) gave 32.3 mg (77%) of olefin **40** as an inseparable 2.8:1 mixture of epimers at C2 (zincophorin numbering). A 60% yield of a 3.5:1 mixture could be obtained if the reaction were conducted in propionitrile at −50 °C with $BF_3 \cdot OEt_2$ catlysis: IR ($CHCl_3$) 3010, 2993, 2968, 2934, 2906, 2878, 1454, 1379, 1253 cm^{-1}; NMR ($CDCl_3$) δ 7.42–7.21 (m, 5 H), 6.08 (ddd, 1 H, J = 16.4, 10.0, 6.5 Hz), 5.80–5.60 (m, 2 H), 5.12–5.00 (m, 2 H), 4.95–4.86 (m, 2 H), 4.75 (d, 1 H, J = 6.5 Hz), 4.66 (AB q, 2 H, J = 11.9 Hz, $\Delta\nu_{AB}$ = 38.8 Hz), 4.02–3.80 (m, 6 H), 3.60 (app t, 1 H, J = 6.5 Hz), 3.46 (dd, 1 H, J = 9.5, 4.1 Hz), 3.39 (dd, 1 H, J = 9.7, 4.0 Hz), 2.50–2.40 (m, 1 H), 2.40–2.30 (m, 1 H), 2.05–1.60 (m, 7 H), 1.35 (s, 3 H), 1.33 (s, 3 H), 1.06 (d, 3 H, J = 6.9 Hz), 1.02 (d, 3 H, J = 6.7 Hz), 1.00 (d, 3 H, J = 7.2 Hz), 0.99 (d, 3 H, J = 6.8 Hz), 0.81 (d, 3 H, J = 6.4 Hz); MS, m/e 571 (M$^+$ − 15, 2.2); HRMS (EI) calcd for $C_{34}H_{51}O_7$ (M$^+$ − 15) 571.3636, found 571.3649.

Aldehyde 41. A solution of 15.0 mg (0.0255 mmol) of olefin **40** in 1 mL of THF was treated with 200 mL of H_2O, 2.69 mg (0.022 mmol) of NMO, and 31 mL (2.5 mmol) of a 0.078 M solution of OsO_4 in THF. After the mixture was stirred for 20 h, solid sodium bisulfite (20 mg) and Florisil (40 mg) were added, and the mixture was stirred vigorously for 1 h. The reaction was then filtered thru a Celite plug, and the filtrate was diluted with 5 mL of ethyl acetate and washed with saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), and the solvent was evaporated at reduced pressure. The crude diol(s) was dissolved in 2 mL of ethanol, and 200 mL of H_2O and treated with 18 mg (0.075 mmol) of $NaIO_4$ and 16 mg (0.19 mmol) of solid $NaHCO_3$. After 0.5 h, the reaction was diluted with 4 mL of saturated aqueous $NaHCO_3$ and extracted with 4 × 3 mL of CH_2Cl_2. The combined organics were dried and concentrated at reduced pressure. Chromatography of the residue (30% ether–hexanes) gave 7.3 mg (49%) of aldehyde **41** as a colorless oil. This material proved to be prone to epimerization and so was used immediately for the next step: IR ($CHCl_3$) 2994, 2967, 2936, 2879, 1710, 1456, 1380 cm^{-1}; NMR ($CDCl_3$) δ 9.92 (d, 1 H, J = 1.5 Hz), 7.40–7.24 (m, 5 H), 5.82–5.60 (m, 2 H), 4.95–4.85 (m, 2 H), 4.70 (d, 1 H, J = 6.0 Hz), 4.73 (AB q, 2 H, J = 11.9 Hz, $\Delta\nu_{AB}$ = 48.0 Hz), 4.33–4.27 (m, 1 H), 4.00–3.80 (m, 5 H), 3.66 (dd, 1 H, J = 7.5, 4.3 Hz), 3.48–3.35 (m, 2 H), 2.66 (app br p, 1 H, J = 7.1 Hz), 2.40–2.28 (m, 1 H), 2.04–1.60 (m, 7 H), 1.35 (s, 3 H), 1.33 (s, 3 H), 1.07 (d, 3 H, J = 7.1 Hz), 0.99 (d, 3 H, J = 7.1 Hz), 0.97 (d, 3 H, J = 7.0 Hz), 0.80 (d, 3 H, J = 6.4 Hz); MX, m/e 573 (M$^+$ − 15, 0.5).

[4*R*[4α[*R[2*S**,5*S**,6*S**]],5β,6α(1*S**,2*R**)]]-6-[1-[6-[4-(1,3-Dioxolan-2-yl)-1-methyl-2-[(phenylmethoxy)methoxy]butyl]-2,2,5-trimethyl-1,3-dioxan-4-yl]ethyl]-5,6-dihydro-α,5-dimethyl-2*H*-pyran-2-acetic Acid Methyl Ester (42).** A solution of aldehyde **41** (9.3 mg, 5.2 mmol) in 0.5 mL of acetone at 0 °C was treated with 14 mL of Jones reagent (2.67 M). After 10 min, 2-propanol (100 μL) was added followed by 2 mL of pH 7 buffer. The aqueous phase was extracted with 4 × 2 mL CH_2Cl_2, the combined organics were dried over $MgSO_4$, and the solvent was removed in vacuo. The crude acid was then dissolved in 1 mL of CH_2Cl_2 and treated with 0.5 mL of an ethereal solution of diazomethane. After 5 min, the reaction was concentrated at reduced pressure and the residue was chromatographed (30% ether–hexanes) to give 9.0 mg (91%) of methyl ester **42** as a colorless oil: IR ($CHCl_3$) 2980, 2950, 2880, 1725, 1460, 1380, cm^{-1}; NMR ($CDCl_3$) δ 7.40–7.24 (m, 5 H), 5.81–5.60 (m, 2 H), 4.89 (t, 1 H, J = 4.2 Hz), 4.82 (AB q, 2 H, J = 7.0 Hz, $\Delta\nu_{AB}$ = 39.3 Hz), 4.66 (AB q, 2 H, J = 11.8 Hz, $\Delta\nu_{AB}$ = 46.3 Hz), 4.40–4.30 (m, 1 H), 4.00–3.80 (m, 5 H), 3.68 (s, 3 H), 3.53–3.35 (m, 3 H), 2.72 (app p, 1 H, J = 7.3 Hz), 2.42–2.28 (m, 1 H), 2.08–1.60 (m, 7 H), 1.36 (s, 3 H), 1.32 (s, 3 H), 1.17 (d, 3 H, J = 7.1 Hz), 1.00 (d, 3 H, J = 7.1 Hz), 0.99 (d, 6 H, J = 7.1 Hz), 0.79 (d, 3 H, J = 6.3 Hz); MS, m/e 603 (M$^+$ − 15, 0.7).

[4*R*[4α[*R[2*S*(*S**,5*S**,6*S**]]5β,6α(1*S**,2*R**)]]-6-[1-[6-[4-(1,3-Dioxolan-2-yl)-1-methyl-2-(benzoyloxy)butyl]-2,2,5-trimethyl-1,3-dioxan-4-yl]ethyl]-2,3,5,6-tetrahydro-α,5-dimethyl-2*H*-pyran-2-acetic Acid Methyl Ester (43).** A mixture consisting of 9.0 mg (14.5 mmol) of methyl ester **42** and 12 mg of 10% Pd/C was kept under a balloon of H_2 for 3 h at room temperature. The catalyst was filtered off, and the filtrate was concentrated at reduced pressure. Chromatography (60% ether–hexanes) gave 4.8 mg (66%) of the alcohol as a colorless oil: IR ($CHCl_3$) 3490 (br), 2992, 2970, 2952, 2937, 2870, 1723, 1457, 1381, 1254 cm^{-1}; NMR ($CDCl_3$) δ 4.91 (t, 1 H, *J* = 4.4 Hz), 4.04–3.85 (m, 5 H), 3.80–3.65 (m, 1 H), 3.69 (s, 3 H), 3.54–3.40 (m, 3 H), 2.65 (dq, 1 H, *J* = 9.0, 7.1 Hz), 2.25–2.13 (m, 1 H), 1.99–1.40 (m, 12 H), 1.37 (s, 3 H), 1.35 (s, 3 H), 1.09 (d, 3 H, *J* = 7.1 Hz), 1.06 (d, 3 H, *J* = 6.9 Hz), 1.02 (d, 3 H, *J* = 7.2 Hz), 0.99 (d, 3 H, *J* = 77.1 Hz), 0.75 (d, 3 H, *J* = 6.5 Hz); MS, *m/e* 585 (M$^+$ – 15, 2.2); HRMS (EI) calcd for $C_{26}H_{45}O_8$ 485.3115, found 485.3107.

A solution of alcohol (7.2 mg, 14 mmol) in pyridine (1 mL) was treated with 20 mg (140 mmol) of benzoyl chloride and 3.5 mg (28 mmol) of DMAP. After 9 h at room temperature, the solvent was removed at reduced pressure, and the residue was chromatographed (35% ether–hexanes) to give 6.1 mg (70%) of benzoate **43** as a colorless oil. The epimers could be separated at this stage by HPLC (16% ethyl acetate/hexanes).

Major isomer 43a: $[\alpha]^{25}{}_{D}$ 14.85° (*c* 0.35, $CHCl_3$); IR ($CHCl_3$) 2991, 2969, 2938, 2875, 1714, 1454, 1378 cm^{-1}; NMR ($CDCl_3$) δ 8.04–8.00 (m, 2 H), 7.58–7.49 (m, 1 H), 7.48–7.35 (m, 2 H), 5.50–5.40 (m 1 H), 4.89 (app, t, 1 H, *J* = 4.4 Hz), 4.01–3.82 (m, 4 H), 3.68 (s, 3 H), 3.43 (dd, 1 H, *J* = 9.2, 2.4 Hz), 3.37–3.30 (m, 2 H), 2.58 (dq, 1 H, *J* = 8.6, 7.2 Hz), 2.20 (app p, 1 H, *J* = 7.3 Hz), 2.10–1.80 (m, 4 H), 1.80–1.63 (m, 4 H), 1.60–1.40 (m, 3 H), 1.23 (s, 3 H), 1.17 (d, 3 H, *J* = 7.1 Hz), 1.08 (d, 3 H, *J* = 7.0 Hz), 1.03 (d, 3 H, *J* = 6.9 Hz), 0.97 (d, 3 H, *J* = 6.9 Hz), 0.91 (s, 3 H), 0.75 (d, 3 H, *J* = 6.4 Hz); MS, *m/e* 589 (M$^+$ – 15, 1.4). HRMS (EI) calcd for $C_{33}H_{49}O_9$ 589.3377, found 589.3374.

Minor isomer 43s: IR ($CHCl_3$) 2990, 2936, 2874, 1713, 1456, 1378, 1275 cm^{-1}; NMR ($CDCl_3$) δ 8.05–8.00 (m, 2 H), 7.56–7.50 (m, 1 H), 7.48–7.36 (m, 2 H), 5.48–5.38 (m, 1 H), 4.89 (app t, 1 H, *J* = 4.5 Hz), 4.00–3.82 (m, 4 H), 3.82–3.70 (m, 1 H), 3.68 (s, 3 H), 3.45–3.30 (m, 3 H), 2.89 (dq, 1 H, *J* = 9.1, 7.0 Hz), 2.15–1.85 (m, 5 H), 1.85–1.40 (m, 7 H), 1.26 (d, 3 H, *J* = 6.8 Hz), 1.25 (s, 3 H), 1.17 (d, 3 H, *J* = 7.0 Hz), 1.01 (s, 3 H), 0.97 (d, 3 H, *J* = 6.6 Hz), 0.89 (d, 3 H, *J* = 6.6 Hz), 0.74 (d, 3 H, *J* = 6.5 Hz); MS, *m/e* 589 (M$^+$ – 15, 1.4).

[4*R*[4α[*R[2*S*(*S**,5*S**,6*S**]],5β,6α(1*S**,2*R**)]]-6-[1-[6-[2-(Benzoyloxy)-1-methyl-5-oxopentyl]-2,2,5-trimethyl-1,3-dioxan-4-yl]ethyl]tetrahydro-α,5-dimethyl-2*H*-pyran-2-acetic Acid Methyl Ester (2a).** A solution of **43** (3.5 mg, 5.8 mmol) in 0.5 mL of acetone was treated with a catalytic amount of *p*-TsOH. After 36 h at room temperature, 2 mL of saturated aqueous $NaHCO_3$ was added, and the aqueous phase was extracted with CH_2Cl_2 (4 × 1 mL). The combined organics were dried ($MgSO_4$) and concentrated at reduced pressure. Chromatography (20% ethyl acetate–hexanes) gave 2.9 mg (89%) of aldehyde **2a** as a colorless oil, which was identical in all respects with an authentic sample prepared by degradation of natural zincophorin.[8]

Olefin 45. A solution of sulfone **3** (55 mg, 0.124 mmol) in 1.6 mL of dry THF under argon at –78 °C, was treated with 1.75 M *n*-butyllithium (71 mL, 0.124 mmol). After 10 min the resulting yellow solution was treated with 1 M magnesium bromide (124 mL, 0.124 mmol), upon which a white precipitate formed. After 45 min at –78 °C, the cold bath was removed, and the reaction mixture was allowed to warm until the precipitate had dissolved, upon which the reaction mixture was immediately recooled to –78 °C. After 15 min, a solution of aldehyde **2a** (46 mg, 0.0824 mmol) in dry THF (400 mL, 200 mL wash) was added, discharging the yellow color. After 30 min, the reaction was allowed to warm to room temperature. After 15 min, the reaction was poured into saturated NH_4Cl (10 mL) and extracted with Et_2O (4 × 15 mL). The extracts were combined and dried ($MgSO_4$), and the solvent was removed in vacuo. Chromatography of the residue (5% Et_2O–petroleum ether) afforded 19.5 mg of recovered sulfone **3**. Further elution with 40% Et_2O–petroleum ether afforded 71.2 mg (88%) of hydroxy sulfones **44** as a mixture of diastereomers. The mixture was carried on to the next reaction.

A solution of hydroxy sulfones **44** (71.2 mg, 0.072 mmol) in 4 mL of a 3:1 mixture of THF/MeOH was treated with 6% Na–Hg (300 mg) at –40 °C. After 10 min, 50 mg more of amalgam was added, and after 10 min more, the solution was diluted with ether (cold) and filtered. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (10% ether–hexanes) to afford 30 mg of alkene **45** (50%) as an 8:1 mixture of *E*/*Z* isomers: 1H NMR (490 MHz) δ 8.1 (m, 2 H), 7.5 (, 1 H), 7.4 (m, 3 H), 5.4 (m, 3 H), 4.97 (d, 1 H, *J* = 9.3 Hz), 3.7 (m, 1 H), 3.67 (s, 3 H), 3.55 (d, 1 H, *J* = 8.2 Hz), 3.44 (m, 1 H), 3.35 (m, 2 H), 2.6 (apparent dq, 1 H, *J* = 10.8, 7.0 Hz), 2.35 (m, 1 H), 2.2 (m, 2 H), 2.1–1.2 (m, 19 H), 1.25 (s, 3 H), 1.15 (d, 3 H, *J* = 7 Hz), 1.08 (d, 3 H, *J* = 7 Hz), 1.02 (d, 3 H, *J* = 7 Hz), 0.97 (d, 3 H, *J* = 7 Hz), 0.94 (s, 3 H), 0.91 (d, 3 H, *J* = 6.7 Hz), 0.85 (s, 9 H), 0.83 (m, 5 H), 0.77 (t, 3 H, *J* = 6.6 Hz), –0.02 (s, 3 H), –0.05 (s, 3 H); IR ($CHCl_3$) 2900, 1720, 1460, 1385, 1285, 1255, 1070, 840, 715 cm^{-1}.

Zincophorin Methyl Ester (1b). A solution of **45** (25 mg, 0.03 mmol) in 2 mL of 1:1:2 1 N HCl–MeOH–THF was heated to 50 °C for 10 h. The reaction mixture was cooled, poured into H_2O (10 mL), and extracted with ether (4 × 15 mL). The extracts were combined, dried (Na_2SO_4), and concentrated in vacuo. The crude triol was treated with 2 mL of 1:1:2 2 N LiOH–MeOH–THF at 50 °C for 1 h. The reaction mixture was poured into 1 N HCl (10 mL) and extracted with ether (4 × 15 mL). The extracts were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in ether and treated with excess diazomethane. The solution was concentrated, and the residue was chromatographed (40% ether–hexanes) to give 10.2 mg zincophorin methyl ester (60%): $[\alpha]^{25}{}_{D}$ +22.4° (*c* 0.89, $CHCl_3$) [lit.[1] $[\alpha]_D$ +20.9° (*c* 2.0, $CHCl_3$)]; ^1H NMR (500 MHz) δ 5.93 (s, 1 H), 5.62 (app dt, 1 H, *J* = 15.0, 3.2 Hz), 5.35 (dd, 1 H, *J* = 15.0, 9.0 Hz), 5.11 (d, 1 H, *J* = 9.3 Hz), 4.43 (d, 1 H, *J* = 8.1 Hz), 4.1 (m, 3 H), 3.76 (d, 1 H, *J* = 10.1 Hz), 3.73 (s, 3 H), 3.63 (dd, 1 H, *J* = 8.6, 1.7 Hz), 3.56 (d, 1 H, *J* = 9.2 Hz), 3.44 (app, dt, 1 H, *J* = 9.0, 1.8 Hz), 3.23 (ap, dq, 1 H, *J* = 10.8, 7 Hz), 2.42 (m, 1 H), 2.22 (m, 3 H), 2.12 (br s, 1 H), 2.01 (m, 2 H), 1.75 (m, 4 H), 1.6 (d, 3 H, *J* = 1.3 Hz), 1.3 (m, 6 H), 1.11 (d, 3 H, *J* = 7.0 Hz), 1.10 (d, 3 H, *J* = 7.2 Hz), 1.07 (d, 3 H, *J* = 8.0 Hz), 0.95 (d, 3 H, *J* = 6.6 Hz), 0.88 (m, 5 H), 0.85 (d, 3 H, *J* = 6.8 Hz), 0.82 (d, 3 H. *J* = 6.6 Hz), 0.67 (d, 3 H, *J* = 7.0 Hz); IR ($CHCl_3$) 3400, 1730, 1460, 1385, 1280, 1260, 1120, 1085, 1020, 975 cm^{-1}.

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