Novel Approach to the Zaragozic Acids. Enantioselective Total Synthesis of 6,7-Dideoxysqualestatin H5

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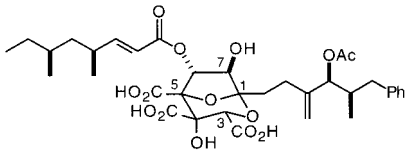
Received December 18, 2001

The total synthesis of 6,7-dideoxysqualestatin H5 (**3**) has been completed by a concise approach that features the stereoselective intramolecular vinylogous aldol reaction of the furoic ester **25a** to give **30** or its trimethylsilyl ether derivative **34**, which possess the requisite absolute stereochemistry at C(3)−C(5) of **3**. Compound **34** was reduced to the saturated bislactone **39**, and the C(1) side chain subunit **47** was introduced leading to a mixture of the hemiacetals **48** and the corresponding ketone **49**. When this mixture was stirred with methanolic acid, transketalization occurred to give a mixture of **50** and the spirocyclic methyl acetals **51a**,**b**. Oxidation of the primary alcohol group in **50** followed by saponification of the two remaining ester groups gave **3**. The longest linear sequence in the synthesis commences with commercially available erythronolactone (**26**) and requires 17 chemical steps with only 10 isolated intermediates.

Introduction

The isolation and identification of natural products having biological activity is an important undertaking that has led to the discovery of numerous leads for new drugs. One therapeutic area of particular importance is the development of novel agents for treating cardiovascular disease, which is among the leading causes of death in developed countries. Antihypertensive agents have a long and successful record of use for reducing high blood pressure, and more recently hypercholesterolemic agents have emerged as highly efficacious drugs for reducing serum levels of cholesterol and the risk of coronary heat disease. Many of the successful drugs in this latter area are inhibitors of HMG CoA reductase. However, because this enzyme plays a key role in the early steps of the biosynthesis of cholesterol, the production of steroids other than cholesterol may be affected, thereby leading to side effects. Hence, there has been considerable interest in finding agents that intervene at a latter stage of the biosynthetic pathway, and attention has recently focused on inhibiting squalene synthase, an enzyme that catalyzes the first committed step in cholesterol biosynthesis.

One of the most potent classes of such inhibitors was discovered as a result of random screening procedures that led to the discovery of a new family of fungal metabolites. These compounds were named zaragozic acids by Merck scientists,[1] who isolated the compounds from a fungus found in a river in the Zaragoza province of Spain, and squalestatins,[2] by Glaxo scientists who isolated them from a soil sample from Portugal. These compounds not only exhibit extraordinary potency as inhibitors of squalene synthase, but they also are inhibitors of farnesyl protein transferase.[3] The first member of this class was compound **1**, which was named zaragozic acid A by the Merck group and squalestatin S1 by the Glaxo group. A large number of related compounds have since been isolated, including zaragozic acid C (**2**) and 6,7-dideoxysqualestatin H5 (**3**).



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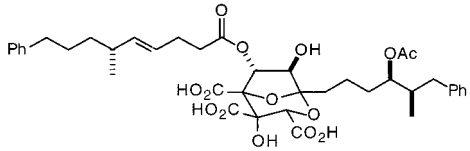

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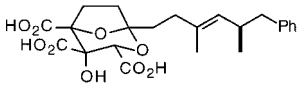

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The unusual structure of these highly functionalized fungal metabolites coupled with their promising biologi-

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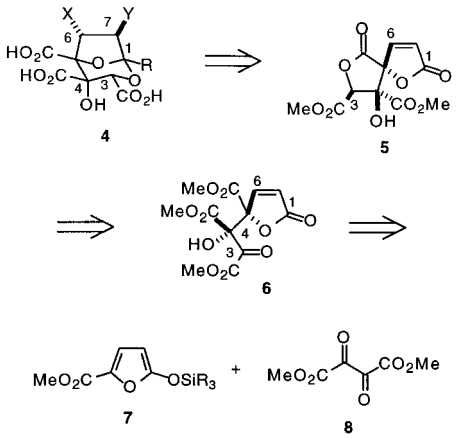
10.1021/jo011157s CCC: $22.00
Published on Web 05/10/2002

Scheme 1

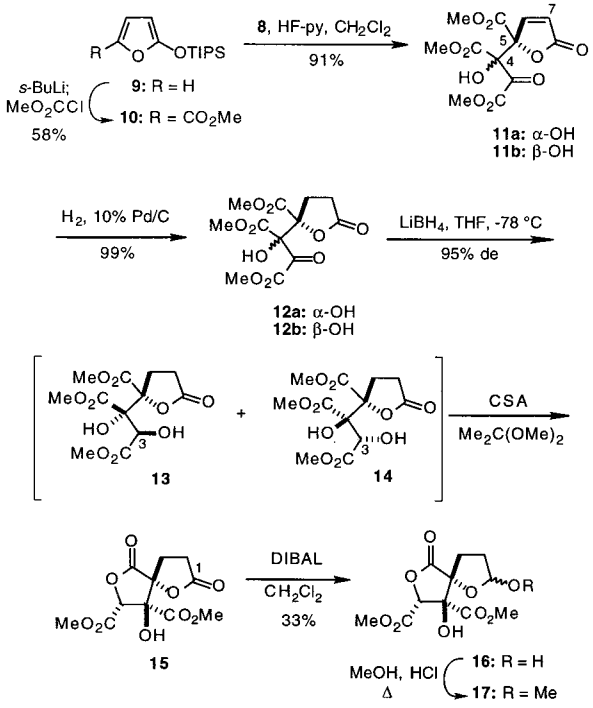


cal activities inspired numerous efforts directed toward their synthesis. Consequent to these efforts, a variety of ingenious approaches to the central 2,8-dioxabicyclo-[3.2.1]octane core have been recorded,[4] and total syntheses of zaragozic acid A (squalestatin S1) (**1**), zaragozic acid C (**2**), and other naturally occurring derivatives have been reported.[5,6] Despite these successes, we were attracted to the considerable challenge of devising a more concise and general approach to members of the zaragozic acid family utilizing vinylogous aldol reactions as a key construction. We now report the details of our work in this area and a concise synthesis of 6,7-dideoxysqualestatin H5 (**3**).[2d]

Results and Discussion

First Generation Approach. In our first approach to the various zaragozic acids **4**, we targeted the bicyclic lactone **5** as a potentially versatile gateway because it contains the requisite absolute chirality at C(3)−C(5) as well as appropriate functional handles for introducing the remaining substituents and side chains of all the zaragozic acids (Scheme 1). We envisaged that this compact intermediate might be assembled via reduction and cyclization of **6**, which would in turn be assembled using a vinylogous aldol reaction of the furan **7** with the dioxosuccinate **8**.

Scheme 2



In accordance with the above retrosynthetic analysis, the requisite furan **10** was readily prepared by metalation and carbomethoxylation of the known furan **9** (Scheme 2).[7] The second building block, dimethyl dioxosuccinate (**8**), was prepared in one step by the acid-catalyzed dehydration of dihydroxytartrate according to the method of Beak.[8] With compounds **8** and **10** in hand, the stage was set to examine the feasibility and the stereoselectivity of the key vinylogous aldol reaction, but a series of initial attempts to catalyze this reaction with a variety of Lewis acids, including $SnCl_4$, $BF_3{\cdot}OEt_2$, Me_2AlCl, $TiCl_4$, and $AlCl_3$ were unsuccessful. However, we were delighted to discover that the vinylogous aldol addition could be induced using excess HF·pyridine to provide an inseparable mixture (ca. 2.3:1) of the diastereomeric adducts **11a**,**b** in 91% yield. At this stage it was not possible to assign the relative stereochemistry of the two adducts, but subsequent experiments revealed that the major isomer was in fact the desired **11a** (vide infra). Unfortunately, these adducts were extremely labile toward retro-aldolization under both acidic and basic conditions. The hydroxyl group at C(4) presumably serves as the trigger for this reversal that is driven to relieve steric congestion about the newly formed C(4)−C(5) bond. We reasoned that reduction of the double bond of the butenolide moiety in **11a**,**b** would stabilize the system and indeed found that the mixture of saturated lactones **12a**,**b**, which were prepared in essentially quantitative yield by catalytic hydrogenation of **11a**,**b**, were stable and amenable to further manipulation.

The stereoselectivity of the reduction of the carbonyl group at C(3) of **12a**,**b** was then examined using a variety of hydride reducing agents, but reduction with $LiBH_4$ was

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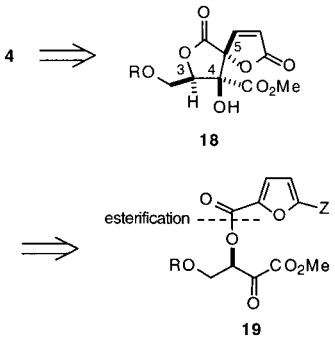
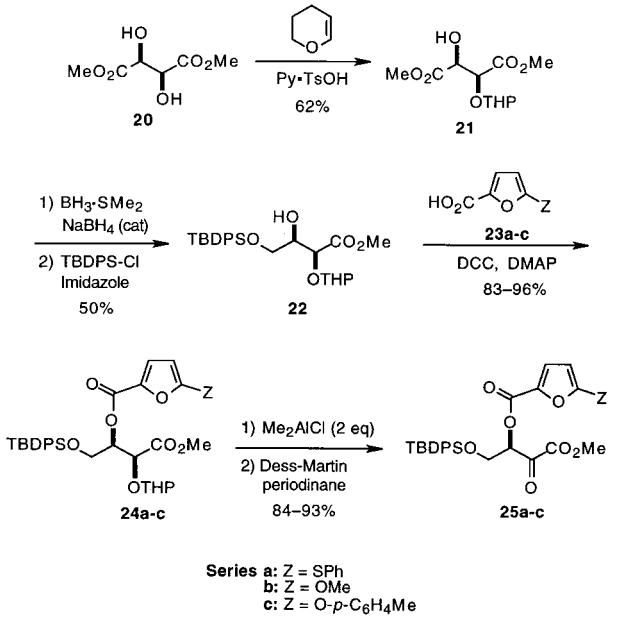
Scheme 3



Scheme 4



found to be the most diastereoselective giving an inseparable mixture of **13** and **14** as the only identifiable products. At this point, we were fortunate to find that small quantities of crystals of the derived lactone **15** separated from the mixture of **13** and **14**, and the structure of this substance was unequivocally established by X-ray analysis. When we attempted to convert **13** and **14** to their respective acetonides using camphorsulfonic acid in 2,2-dimethoxypropane, we unexpectedly isolated a mixture (ca. 2.2:1) of **15** together with the corresponding lactone derived from **14**. Pure **15** could thus be isolated in 26% overall yield from furan **10** after crystallization from chloroform.

The X-ray structure of **15** revealed that the vinylogous aldol reaction had proceeded predominantly in the desired stereochemical sense, but the hydride reduction of the carbonyl group at C(3) proceeded with apparent chelation control to give the incorrect relative stereochemistry. We reasoned that it would either be possible to reverse the stereochemistry of the reduction or to invert this center later in the synthesis, so we examined the feasibility of converting **15** into the 2,8-dioxabicyclo-[3.2.1]octane system characteristic of the zaragozic acids. Thus, selective reduction at C(1) of the less substituted lactone ring of **15** using DIBAL proceeded smoothly to give a mixture of hemiacetals, but subjecting this mixture to refluxing methanolic HCl gave a mixture of methyl acetals rather than the desired oxabicyclic core, presumably because the ester group at C(3) would be axial in such a product. It was thus apparent that an alternate strategy that efficiently delivered an intermediate with the correct configuration at all centers was needed.

Second Generation Approach. Inasmuch as the bimolecular vinylogous aldol reaction of **8** and **10** proceeded with only modest selectivity, we queried whether an intramolecular variant of this process might be more stereoselective. Hence, a different entry to the zaragozic acids was envisioned in which an intermediate such as **18**, which has the requisite stereochemistry at C(3)−C(5), might be formed by the cyclization of a furoic ester related to **19** (Scheme 3). Preparation of **19** by esterification of substituted furoic acids with the appropriate alcohols was envisioned as being straightforward. The activating group Z on the furan ring could be varied as a tactical device to optimize the cyclization.

Several routes to the alcohol component of the ester generally represented by **19** were developed. In the first, dimethyl tartrate (**20**) was protected as its mono-THP derivative **21** (Scheme 4). Chemoselective reduction of the ester moiety α to the hydroxy group in **21** was best achieved using BH_3·SMe_2 in the presence of catalytic $NaBH_4$ to give an inseparable mixture (3:1) of the 1,2 and 1,3-diols.[9] After selective protection of the primary alcohol as its TBDPS ether, the diprotected alcohol **22** was isolated in 50% yield by column chromatography. At the outset of these studies, it was not clear what the optimal nature of the activating group Z on the furan ring would be, so the series of furoate esters **24a**−**c** was prepared by esterification of **22** with the known furoic acids **23a**−**c**[10] in the presence of dicyclohexylcarbodimide (DCC) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP). The tetrahydropyranyl group was removed from the esters **24a**−**c** by the action of Me_2AlCl.[11] Because the intermediate secondary alcohols exhibited a tendency to suffer an intramolecular 1,2-acyl transfer, they were typically oxidized directly without extensive handling using Dess−Martin periodinane to deliver the α-ketoesters **25a**−**c**.[12]

While the above route to **25a**−**c** could be used to make the necessary quantities of material for cyclization studies, the problems associated with the somewhat inefficient monoprotection of dimethyl tartrate coupled with the modest regioselectivity in the hydride reduction of **21** persuaded us to examine other avenues to these α-keto esters. In the event, erythronolactone (**26**)[13] was selectively protected in a modification of a literature procedure by reacting the derived stannylidene acetal with *p*-methoxybenzyl chloride to give a mixture of regioisomers (6:1) that were readily separable by recrystallization to give pure lactone **27**.[14] Protection of the remaining secondary alcohol and methanolysis of the lactone under basic conditions proceeded with migration of the silyl protecting group to the primary alcohol to provide alcohol **28** in 78% yield over the two steps. The alcohol **28** was coupled with furoic acid **23a** as before, and subsequent

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Scheme 5

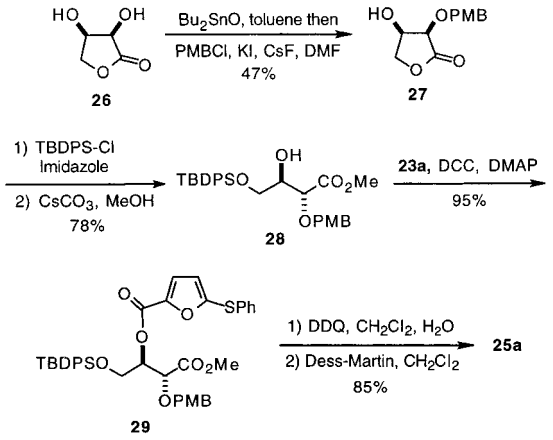


Table 1. Stereochemistry of Vinylogous Aldol Cyclizations of 25a−c

compd	Lewis acid (equiv)	conditions[a]	isomer ratio[b] (**30**:**31**:**32**:**33**)	isolated isomer (%yield)[b]
25a	$TiCl_4$ (1.0)	rt, 3 h	6:2:1:0	**30** (11)
	$TiCl_4$ (2.5)	0 °C→rt, 1.5 h	14:1:1:0	**30** (33)
	$TiCl_4$ (3.0)	0 °C→rt, 1.5 h	>20:1:2:0	**30** (42)
	$TiCl_4$ (5.0)	0 °C→rt, 2 h	>20: 2:1:0	**30** (43)
	$SnCl_4$ (2.0)	rt, 4 h	1:2:1:1	
25b	$TiCl_4$ (3.0)	−78→0 °C, 2 h	0:0:2:1	**32** (56), **33** (30)
	$SnCl_4$ (1.0)	−78 °C→rt, 3 h	trace:1:4:5	
	$BF_3{\cdot}OEt_2$ (1.0)	rt, 3 h	0:1:0:3.4	**31** (19), **33** (40)
	TMS−I (1.2)	0 °C→rt, 1 h	0:3:0:1	**31** (39), **33** (12)
25c	$TiCl_4$ (3.0)	−78→0 °C, 2 h	1:1:>20:1	**32** (65)
	$SnCl_4$ (3.0)	−78 °C→rt, 2 h	2:1:5:6	
	$BF_3{\cdot}OEt_2$ (1.2)	rt, 12 h	0:1:trace:3	**31** (12), **33** (32)

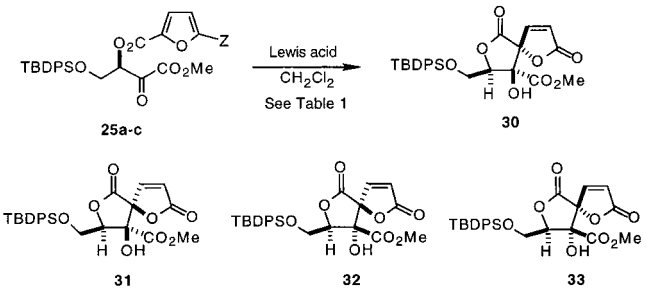
[a] The reactants were combined in dichloromethane at the lower temperature and then stirred at the final temperature for the time indicated. [b] Ratio determined by ^1H NMR of crude reaction mixture.

deprotection of the resulting ester with DDQ and oxidation with Dess−Martin periodinane gave **25a** in 85% yield. This route to **25a** was both chemically and operationally more efficient than the previous one.

The intramolecular vinylogous aldol reactions of **25a−c** were then examined using different Lewis acids to catalyze the addition (Table 1). When **25a** was employed as the starting material, Lewis acids as $BF_3{\cdot}OEt_2$, $ZnCl_2$, $Sc(OTf)_3$, and TMS-I did not induce cyclization, and either starting **25a** or unidentified products were obtained. However, both $TiCl_4$ and $SnCl_4$ effected cyclization although the latter was not selective and gave a mixture of all four possible diastereomers in approximately equal amounts. The $TiCl_4$-induced cyclization proceeded to give the highest ratio of the desired adduct **30**, and the stereoselectivity was dependent upon the number of equivalents of $TiCl_4$. Poorer selectivities and lower yields were observed when fewer than 3 equiv of $TiCl_4$ were employed, but use of larger quantities of catalyst had little effect upon the reaction.

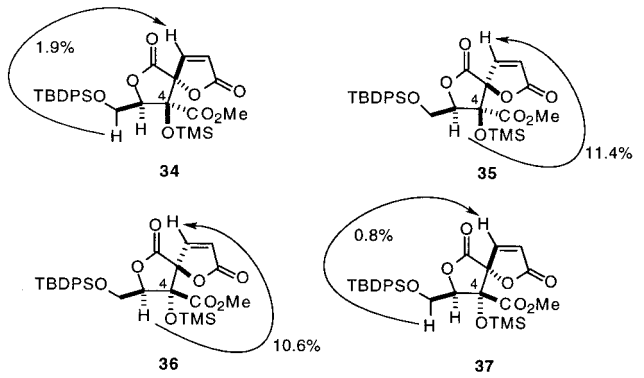
That the number of equivalents and the Lewis acid had an effect upon the course of the cyclization was somewhat expected, but it was surprising that the nature of the activating group Z on the C(5) position of the furan had a major impact upon the stereochemical outcome of the reaction. For example, a methoxy group on the furan led to the preferential formation of **32** and **33** in roughly comparable amounts using $TiCl_4$, but significant amounts of **31** were isolated when TMS-I was employed to initiate the reaction. The presence of a 4′-methylphenoxy group

Scheme 6



on the furan led to the formation of **32** as the major product when $TiCl_4$ was used as the catalyst, whereas other acid catalysts led to mixtures of products. Activation of the furan ring with an electron-donating group was clearly necessary, as when Z = H or Br, no cyclization was observed.

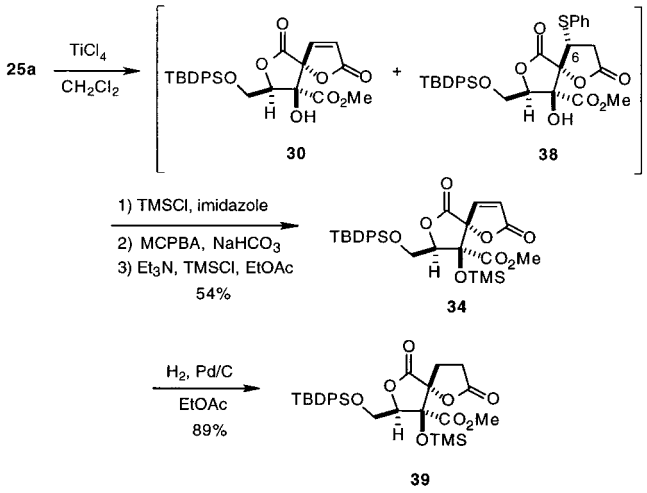
To facilitate structure determination of the adducts **30−33**, they were converted into their respective trimethylsilyl ethers **34−37**. The structures of the adducts **34−37** were first tentatively assigned based upon the observed NOEs as shown. However, it was not possible to assign the stereochemistry at C(4) based upon NMR alone. Consequently, the structures of **34**, **36**, and **37** were unequivocally established by X-ray crystallographic analysis.



Although the spirocyclic adducts **30−33** could be isolated in pure form, they were somewhat unstable and prone to suffer retroaldolization, especially in the presence of base. For example, if either pure **30** or **32** was heated in pyridine at 50 °C, a mixture containing all four diastereomers **30−33** was obtained in a ratio (5:10:5:1) that reflects their corresponding relative stabilities in the order **31**>**30** = **32**>**33**. When either pure **30** or **32** was resubjected to the conditions of the initial cyclization, no isomerization occurred, and hence we assume these reactions were conducted under kinetically controlled conditions.

Careful analysis of the reaction mixtures obtained in the cyclizations of **25a** revealed that the sulfide **38** was formed in nearly 20% yield. Presumably the thiophenoxide anion that is released during the course of the reaction adds in a 1,4-sense to the desired product **30** to give **38**. To circumvent this problem and to increase the yield of **30**, various thiophiles including Hg(II) and Cu(II) salts were added in hopes of trapping this anion prior to its reaction with **30**. Ultimately, all efforts to reduce the amount of **38** formed during the reaction or workup and increase the yield of **30** were unsuccessful, and a modified protocol was developed for converting **38** into

Scheme 7

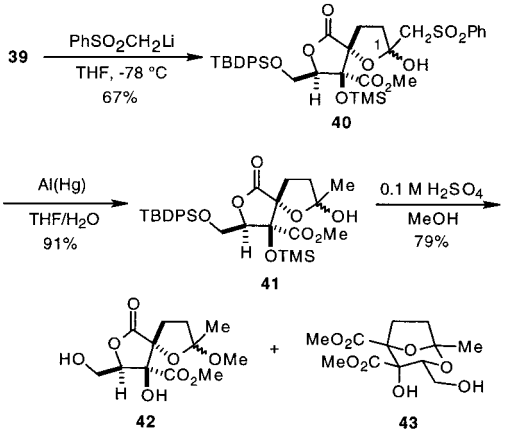


the more stable trimethylsilyl ether **34**. In the event, upon completion of the usual cyclization of **25a** in the presence of $TiCl_4$, the crude product mixture was sequentially treated with TMS-Cl and imidazole, MCPBA, and then Et_3N and TMS-Cl to give **34** in 54% overall yield from **25a**. It was necessary to add TMS-Cl in the last step because some deprotection of the tertiary alcohol at C(4) occurred during the sequence. Catalytic hydrogenation of the butenolide **34** then gave **39**, thereby setting the stage for installation of the C(1) side chain. The structure of **39** was also secured by X-ray crystallography.

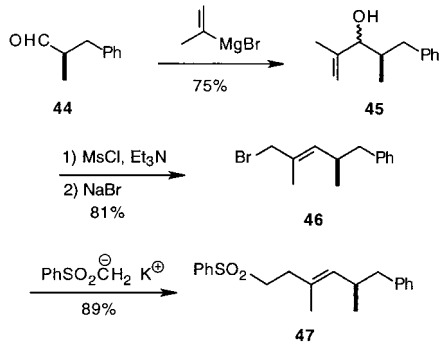
In preliminary work directed toward introducing the aliphatic side chain at C(1), we examined the additions of various aliphatic Grignard, organolithium, and cerium reagents to **39**. However, starting **39** was typically recovered, although low yields of the cyclic hemiacetals arising from addition to the desired lactone carbonyl group were sometimes obtained. Anions of phenyl sulfones are also known to react with lactones,[15] and we found that the monoanion of methyl phenyl sulfone added cleanly to **39** providing **40**. Reductive desulfonylation of **40** then furnished the desired lactol **41** in 61% overall yield.[16] When **41** was treated with methanolic sulfuric acid, a mixture (2:1) of **42** and **43** was obtained, the latter of which possesses the zaragozic acid core. That a mixture of products was obtained in this model study occasioned no serious alarm as the position of the equilibria in related systems were known to be finely balanced and dependent upon the specific substituents.[4a,c,d,f,17] Indeed, the equilibrium generally favors the desired dioxabicyclo-[3.2.1]octane ring system in the natural series.[5]

In light of these positive results, we set to the task of preparing the sulfone of the requisite C(1) side chain. Thus, addition of 2-propenylmagnesium bromide to the

Scheme 8



Scheme 9



known aldehyde **44** afforded alcohol **45**.[18] The optical purity of **45** (>95% ee) was established by degradation ($NaIO_4$, $RuO_2 \cdot xH_2O$) to the corresponding carboxylic acid derivative of **44** and NMR analysis of its methyl (*S*)-(+)-mandelate derivative.[19] Mesylation of **45** followed by reaction of the intermediate mesylate with NaBr gave the allyl bromide **46**. Initial attempts to convert **46** into **47** by alkylation of the lithiated monoanion of methyl phenyl sulfone gave significant quantities of dialkylated material. The potassium salts of sulfones were known to undergo selective monoalkylation,[20] and indeed we found reaction of **46** with the potassium salt of methyl phenyl sulfone proceeded cleanly to give **47** in 89% yield.

The spirobicycle **39** was then coupled with the C(1) side chain by selective addition of the dianion of the sulfone **47** to the less hindered lactone moiety of **39**. Reductive desulfonylation with aluminum amalgam then gave a mixture of hemiacetals **48** together with the ring opened ketone **49**. This mixture was then treated with methanolic sulfuric acid to give a mixture (1:2.5) of the desired bicyclic ketal **50** (25% yield) along with two methyl acetals of formula **51** (1:1, 65% yield). Obtention of this mixture was somewhat surprising inasmuch as all other acid catalyzed transformations leading to natural zaragozic acids reportedly delivered either exclusively or predominantly the desired 2,8-dioxabicyclo[3.2.1]octane core.[5] Thus, the presence of the hydroxyl groups at C(6) and C(7) in synthetic intermediates leading to

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(14) Flasche, M.; Scharf, H. *Tetrahedron: Asymmetry* **1995**, *6*, 1543−1546.
(15) (a) Thompson, C. M. *Dianion Chemistry in Organic Synthesis*; CRC Press: Boca Raton, 1994; Chapter 2. (b) Mussatto, M. C.; Savoia, D.; Tronbini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1980**, *45*, 4002−4005. (c) Cavicchioli, S.; Savoia, D.; Tronbini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1984**, *49*, 1246−1251. (d) Alzérreca, A.; Avilés, M.; Collazo, L. *J. Heterocycl. Chem.* **1990**, *27*, 1729−1731. (e) Alzérreca, A.; Martínez, J.; Velázquez, L.; Prieto, J. A.; Arias, L. *J. Heterocycl. Chem.* **1994**, *31*, 45−48.
(16) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1964**, *86*, 1639−1640. (b) Wuonola, M. A.; Woodward, R. B. *Tetrahedron* **1976**, *32*, 1085−1095.
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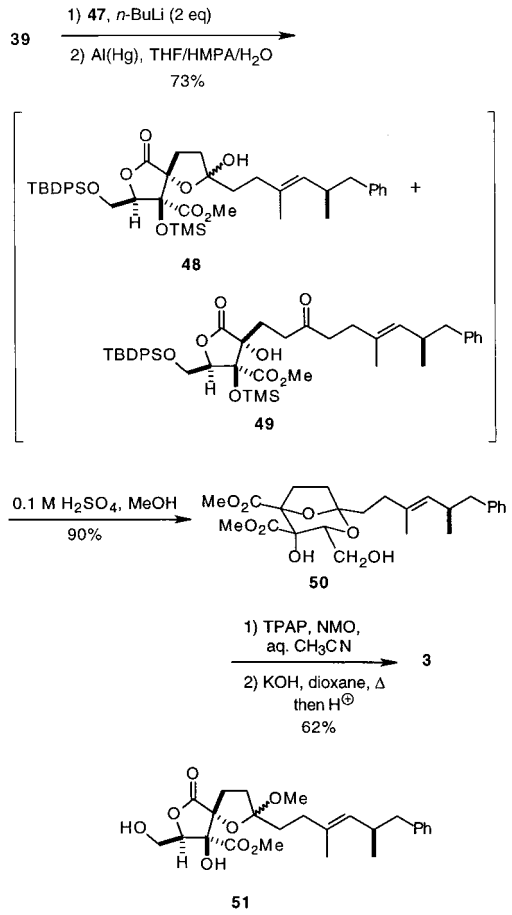
(20) Pine, S. H.; Shen, G.; Bautista, J.; Sutton, C. Jr.; Yamada, W.; Apodaca, L. *J. Org. Chem.* **1990**, *55*, 2234−2237.

Scheme 10

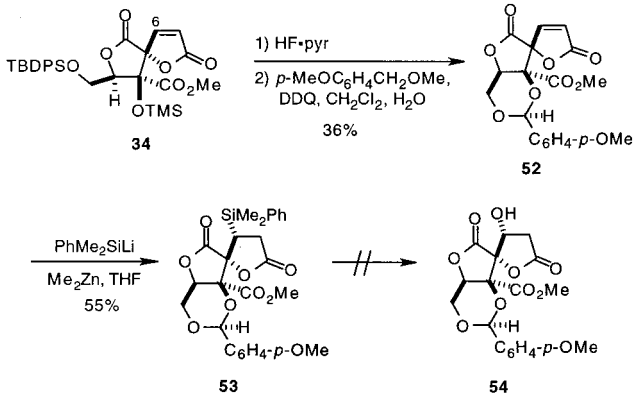


zaragozic acids A and C may play an important role in dictating the kinetic and/or the thermodynamic course of these intramolecular transketalizations. In any event, the mixture of **50** and **51** was readily separable by chromatography, and the undesired ketals **51** could be partially reequilibrated upon exposure to methanolic acid to give additional quantities of **50**. Oxidation of the primary alcohol moiety in **50** with TPAP in the presence of H_2O and subsequent saponification of the methyl esters gave 6,7-dideoxysqualestatin H5 (**3**) in 62% yield from **50**.[21] The synthetic **3** thus obtained gave ^1H and ^{13}C NMR spectra identical with those of an authentic sample.[22]

Having successfully completed the enantioselective total synthesis of 6,7-diedeoxysqualestatin H5, we turned our attention to the possibility that the spirocyclic intermediate **34** might be converted into other naturally occurring zaragozic acids containing hydroxyl groups at C(6) and C(7). We selected 7-deoxyzaragozic acid A as our initial target as tactics developed for its synthesis could be applied to the preparation of other zaragozic acids. We envisioned that the C(6)−C(7) double bond in **34** would serve as a suitable functional handle for the introduction of the requisite oxygen functionality at these sites.

Initial efforts directed toward oxidation of the butenolide consisted of various attempts to epoxidize the double bond. Unfortunately, all these experiments were unsuccessful, frequently leading to mixtures of uncharacterized compounds that were believed to arise from loss of the TMS protecting group from the C(4) hydroxyl group of **34** and subsequent retroaldolization or attack upon one or both the lactone carbonyl groups. To avoid such side reactions, the two silyl protecting groups on the 1,3-diol array in **34** were removed using HF·pyridine and replaced with the more stable cyclic *p*-methoxybenzylidene acetal to give **52**. Although it was not possible to epoxidize the double bond of **52**, we found that **52** underwent 1,4-addition of a dimethylphenylsilyl zincate to furnish the silane **53**,[23] the structure of which was confirmed by X-ray analysis. Unfortunately, all attempts to transform the silyl moiety at C(6) in **53** into the requisite hydroxy group to give **54** by applying a variety of known procedures were unsuccessful,[24] and either starting material or unidentified products were typically obtained. Hence, additional studies directed toward functionalizing the double bond of intermediates related to **34** must be pursued in order to extend our approach to the syntheses of the more complex zaragozic acids.

Scheme 11



The total enantioselective synthesis of the natural product 6,7-dideoxysqualestatin H5 (**3**) has been completed by a concise approach in which the longest linear sequence is 17 steps from commercially available erythronolactone (**26**) and proceeds via only 10 isolated intermediates. The synthesis highlights a novel strategy for rapidly assembling the core of the zaragozic acids by a stereoselective intramolecular vinylogous aldol reaction, thereby providing a compelling example of the power and versatility of such constructions in organic synthesis. Other applications of this and related reactions are the subjects of current investigations, the results of which will be reported in due course.

Experimental Section

General. Unless otherwise noted, solvents and reagents were reagent grade and used without purification. Tetrahydrofuran (THF) was distilled from potassium/benzophenone ketyl under nitrogen, and dichloromethane (CH_2Cl_2) was

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(22) We thank Dr. Philip J. Sidebottom (GlaxoWellcome, UK) for ^1H and ^{13}C NMR spectra of authentic 6,7-dideoxysqualestatin H5.

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distilled from calcium hydride prior to use. Reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of argon in glassware that had been oven or flame dried. Melting points are uncorrected. Infrared (IR) spectra were recorded either neat on sodium chloride plates or as solutions in $CHCl_3$ as indicated and are reported in wavenumbers (cm^{-1}) referenced to the 1601.8 cm^{-1} absorption of a polystyrene film. ^1H and ^{13}C NMR spectra were obtained as solutions in $CDCl_3$ unless otherwise indicated, and chemical shifts are reported in parts per million (ppm, δ) downfield from internal standard Me_4Si (TMS). Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as s, singlet; br, broad; d, doublet; t, triplet; q, quartet; m, multiplet; and comp, complex multiplet. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh ASTM).[25] Percent yields are given for compounds that were ≥95% pure as judged by NMR.

(3*R*,4*R*)-4-Hydroxy-3-(4-methoxybenzyloxy)dihydro-2(3*H*)-furanone (27). A suspension of erythronolactone (**26**) (5.90 g, 50.0 mmol) and dibutyltin oxide (12.45 g, 50.0 mmol) in toluene (250 mL) was heated at reflux for 6 h in an apparatus equipped with a Dean−Stark trap. After cooling, the solvent was removed under reduced pressure to give a tan solid that was combined with CsF (14.43 g, 95.0 mmol) and dried under reduced pressure. The solids were suspended in DMF (150 mL), and KI (11.05 g, 66.5 mmol) and *p*-$MeOC_6H_4CH_2Cl$ (10.17 mL, 75.0 mmol) were added. The mixture was stirred for 5 h at room temperature, EtOAc (350 mL) was added, and the mixture was poured into H_2O (300 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide a yellow solid that was purified by column chromatography eluting with hexanes/EtOAc (1:1−1:4) to afford 8.49 g of a mixture (6:1) of regioisomers. Recrystallization from hot EtOAc provided 5.65 g (47%) of **27** as white needles: mp 100−103 °C; ^1H NMR (250 MHz) δ 7.35 (dd, J = 1.9, 6.6 Hz, 2 H), 7.32 (dd, J = 2.0, 6.6 Hz, 2 H), 4.96 (d, J = 11.6 Hz, 1 H), 4.76 (d, J = 11.6 Hz, 1 H), 4.33−4.19 (comp, 3 H), 4.14 (d, J = 4.8 Hz, 1 H), 3.81 (s, 3 H); ^{13}C NMR (63 MHz) δ 173.5, 159.9, 130.1, 128.1, 114.1, 73.7, 72.6, 67.7, 55.3; IR (neat) 3462, 2958, 1781, 1612, 1514, 1465 cm^{-1}; mass spectrum (CI) *m*/*z* 238.0846 [$C_{12}H_{15}O_5$ (M + 1) requires 238.0841] (base), 161, 154, 149, 137.

(3*R*,4*R*)-4-*tert*-Butyldiphenylsiloxy-3-(4-methoxybenzyloxy)dihydro-2(3*H*)-furanone. A solution of **27** (5.65 g, 23.7 mmol) in CH_2Cl_2 (85.0 mL) containing imidazole (2.02 g, 29.6 mmol) and TBDPSCl (7.40 mL, 28.5 mmol) was stirred for 5 h at room temperature. The mixture was poured into a mixture of EtOAc (200 mL) and H_2O (100 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the residual oil was purified by flash chromatography eluting with hexanes/EtOAc (9:1) to afford 9.88 g (87%) of diprotected lactone as a colorless oil; ^1H NMR (250 MHz) δ 7.73−7.62 (comp, 4 H), 7.47−7.23 (comp, 6 H), 7.17 (d J = 8.7 Hz, 2 H), 6.82 (d, J = 8.7 Hz, 2 H), 4.67 (s, 2 H), 4.40 (ddd, J = 1.1, 3.0, 4.4 Hz, 1 H), 4.13 (dd, J = 1.1, 10.2 Hz, 1 H), 3.98 (dd, J = 3.0, 10.2 Hz, 1 H), 3.90 (d, J = 4.4 Hz, 1 H), 3.77 (s, 3 H), 1.07 (s, 9 H); ^{13}C NMR (63 MHz) δ 173.8, 159.4, 135.9, 135.6, 133.1, 132.5, 130.0, 129.9, 129.7, 128.6, 127.8, 127.6, 113.7, 74.0, 71.9, 71.5, 69.1, 55.1, 26.7, 19.2; IR (neat) 2333, 2858, 1790, 1613, 1514, 1464, 1428 cm^{-1}; mass spectrum (CI) *m*/*z* 475.1932 [$C_{28}H_{32}O_5Si$ (M + 1) requires 475.1941] (base), 257, 241.

Methyl (2*R*,3*R*)-4-*tert*-Butyldiphenylsiloxy-3-hydroxy-2-(4′-methoxybenzyoxy)butanoate (28). A solution of Cs_2CO_3 (0.4 g, 1.0 mmol) and the diprotected lactone from the preceding experiment (9.88 g, 20.7 mmol) in MeOH (70 mL) was stirred for 1 h at 0 °C. Brine (200 mL) and CH_2Cl_2 (100 mL) were added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give 10.84 g of a light yellow oil that was purified by flash chromatography eluting with hexanes/EtOAc (4:1) to afford 10.01 g (95%) of **28** as a colorless oil;^1H NMR (250 MHz) δ 7.65−7.62 (comp, 4 H), 7.44−7.35 (comp, 6 H), 7.19 (d, J = 8.6 Hz, 2 H), 6.83 (d, J = 8.6 Hz, 2 H), 4.57 (d, J = 11.1 Hz, 1 H), 4.34 (d, J = 11.1 Hz, 1 H), 4.09 (d, J = 6.9 Hz, 1 H), 3.98−3.94 (m, 1 H), 3.80−3.77 (m, 2 H), 3.79 (s, 3 H), 3.74 (s, 3 H), 2.56 (d, J = 6.9 Hz, 1 H), 1.05 (s, 9 H); ^{13}C NMR (63 MHz) δ 171.6, 159.4, 135.5, 133.0, 132.9, 129.8, 129.8, 129.0, 127.8, 113.8, 78.3, 72.5, 72.3, 63.7, 55.2, 52.0, 26.8, 19.2; IR (neat) 3490, 2952, 2932, 2856, 1750, 1611, 1513, 1427 cm^{-1}; mass spectrum (CI) *m*/*z* 507.2203 [$C_{29}H_{36}O_6Si$ (M + 1) requires 507.2203] (base), 311, 251, 233.

Methyl (2*R*,3*R*)-4-*tert*-Butyldiphenylsiloxy-3-(5-phenylthio-2-furoyloxy)-2-(4′-methoxybenzyloxy)butanoate (29). A solution of **28** (10.01 g, 19.7 mmol), **23a** (4.77 g, 21.6 mmol), DMAP (1.20 g, 9.8 mmol), and DCC (4.87 g, 23.6 mmol) in CH_2Cl_2 (200 mL) was stirred at room temperature for 12 h. The mixture was filtered, and the filtrate was concentrated to give 16.4 g of a light tan oil that was purified by flash chromatography eluting with hexanes/EtOAc (85:15) to afford 11.95 g (95%) of **29** as a colorless oil; ^1H NMR (250 MHz) δ 7.64−7.60 (comp, 4 H), 7.42−7.21 (comp, 11 H), 7.11 (d, J = 3.4 Hz, 1 H), 6.79 (d, J = 8.7 Hz, 2 H), 6.65 (d, J = 3.4 Hz, 1 H), 5.45 (dt, J = 4.5, 9.9 Hz, 1 H), 4.71 (d, J = 11.5 Hz, 1 H), 4.46 (d, J = 11.5 Hz, 1 H), 4.38 (d, J = 5.4 Hz, 1 H), 3.99 (dd, J = 5.4, 11.1 Hz, 2 H), 3.93 (dd, J = 4.5, 11.1 Hz), 3.76 (s, 3 H), 3.66 (s, 3 H), 1.00 (s, 9 H); ^{13}C NMR (63 MHz) δ 170.2, 159.3, 156.6, 150.2, 146.4, 135.6, 135.5, 135.4, 133.4, 132.9, 132.8, 129.7, 129.6, 129.6, 129.2, 128.8, 127.6, 127.5, 127.5, 119.6, 118.5, 113.7, 75.7, 74.4, 72.5, 61.3, 55.1, 52.0, 26.6, 19.0; IR (neat) 3070, 3012, 2931, 2856, 1731, 1612, 1577, 1513 cm^{-1}; mass spectrum (CI) *m*/*z* 711.2459 [$C_{40}H_{43}O_8SSi$ (M + 1) requires 711.2448] (base), 653, 302, 207.

Methyl (2*R*,3*R*)-4-*tert*-Butyldiphenylsiloxy-3-(5-phenylthio-2-furoyloxy)-2-hydroxybutanoate. A solution of **29** (13.31 g, 18.7 mmol) and DDQ (8.50 g, 37.4 mmol) in CH_2Cl_2/H_2O (270 mL, 10:1) was stirred at 35 °C for 12 h. The solvent was removed under reduced pressure, and the residue was dissolved in Et_2O (300 mL) and poured into saturated $NaHCO_3$ (200 mL). The layers were separated, and the organic layer was washed with saturated $NaHCO_3$ (5 × 100 mL). The organic layer was then stirred vigorously with saturated $NaHSO_3$ solution (500 mL) until no *p*-methoxybenzaldehyde could be detected by TLC. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give 9.86 g (89%) of alcohol as a yellow oil that was used in the next reaction without further purification; ^1H NMR (250 MHz) δ 7.69−7.63 (comp, 4 H), 7.44−7.22 (comp, 11 H), 7.17 (d, J = 3.5 Hz, 1 H), 6.63 (d, J = 3.5 Hz, 1 H), 5.43 (dt, J = 3.7, 9.4 Hz, 1 H), 4.58 (dd, J = 3.7, 6.5 Hz, 1 H), 3.93 (dd, J = 1.4, 5.8 Hz, 2 H), 3.72 (s, 3 H), 3.37 (d, J = 6.5 Hz, 1 H), 1.03 (s, 9 H); ^{13}C NMR (63 MHz) δ 172.3, 157.0, 150.5, 146.2, 135.4, 135.4, 133.3, 132.5, 129.7, 129.2, 127.7, 127.5, 119.9, 118.4, 74.8, 70.2, 61.5, 52.7, 26.7, 26.5, 19.0; IR (neat) 3489, 3070, 2953, 2856, 1736, 1566, 1463 cm^{-1}; mass spectrum (CI) *m*/*z* 591.1883 [$C_{32}H_{35}O_7SSi$ (M + 1) requires 591.1873] (base), 513, 435, 302, 279.

Methyl (3*R*)-4-*tert*-Butyldiphenylsiloxy-3-(5-phenylthio-2-furoyloxy)-2-oxobutanoate (25a). Dess−Martin periodinane (7.03 g, 16.6 mmol) was added to a stirred solution of the preceding alcohol (6.53 g, 11.1 mmol) in CH_2Cl_2 (110 mL) at 0 °C. After 10 min, wet CH_2Cl_2 (200 μL H_2O in 200 mL CH_2Cl_2) was added dropwise, and stirring was continued for 2 h. The solvents were removed under reduced pressure, and the residue was dissolved in Et_2O (200 mL). The solution was washed with 10% $NaHSO_3$ (100 mL) and saturated $NaHCO_3$ (100 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give 6.24 g (96%) of **25a** as a yellow oil; ^1H NMR (300 MHz) δ 7.69−7.61 (comp, 4 H), 7.46−7.24 (comp, 11 H), 7.22 (d, J = 3.4 Hz, 1 H), 6.66 (d, J = 3.4 Hz, 1 H), 5.99 (dd, J = 3.4, 4.6 Hz, 1 H), 4.43 (dd, J = 4.6, 11.4 Hz, 1 H), 4.09 (dd, J = 3.4, 11.4 Hz, 1 H), 3.89 (s, 3 H),

(25) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

0.99 (s, 9 H); ^{13}C NMR (75 MHz) δ 187.1, 160.1, 156.9, 151.2, 145.7, 135.6, 135.4, 133.2, 132.6, 132.2, 130.0, 129.4, 127.9, 120.8, 118.6, 77.2, 63.2, 53.2, 26.5, 19.2; IR ($CHCl_3$) 1736, 1577, 1463, 1296, 1114 cm^{-1}; mass spectrum (CI) *m*/*z* 589.1720 [$C_{32}H_{33}O_7SiS$ (M + 1) requires 589.1716] (base), 511, 279, 177.

(5*R*,8*R*,9*S*)-8-*tert*-Butyldiphenylsiloxymethyl-9-methoxycarbonyl-9-trimethylsiloxy-1,7-dioxaspiro[4.4]non-3-ene-2,6-dione (34). Neat $TiCl_4$ (1.79 mL, 16.3 mmol) was added dropwise to a stirred solution of α-ketoester **25a** (3.20 g) in CH_2Cl_2 (25 mL) at 0 °C. The solution was stirred at 0 °C for 30 min and then at room temperature for 2 h. The reaction was cooled in an ice-H_2O bath, and ice-cold H_2O (100 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (1 × 50 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (25 mL) at 0 °C, and TMSCl (2.36 g, 2.76 mL, 21.7 mmol) and imidazole (2.69 g, 43.4 mmol) were added with stirring. The reaction was stirred at 0 °C for 1.5 h, and then EtOAc (50 mL) was added. The mixture was washed with H_2O (30 mL), saturated $NaHCO_3$ (30 mL), 1 M HCl solution (10 mL), and brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in CH_2Cl_2 (30 mL) at 0 °C, and $NaHCO_3$ (1.82 g, 21.7 mmol) and MCPBA (3.90 g) were added. The mixture was stirred at 0 °C for 30 min, whereupon EtOAc (100 mL) and 10% $Na_2S_2O_3$ (30 mL) were added. The layers were separated, and the organic layer was washed with saturated $NaHCO_3$ (2 × 30 mL), dried (Na_2SO_4) and concentrated. The residue was dissolved in EtOAc (25 mL) at 0 °C, and Et_3N (2.20 g, 3.0 mL 21.7 mmol) and TMSCl (0.69 mL, 5.43 mmol) were added with stirring. The mixture was stirred at room temperature for 30 min, and then EtOAc (50 mL) was added. The reaction mixture was washed with H_2O (30 mL), 1 M HCl solution (20 mL), and brine (20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes/EtOAc (6:1) to give 1.98 g of mixture of trimethylsilyl ethers. Crystallization of the mixture from hexanes/EtOAc (4:1) (19 mL) gave 1.41 g (46%) of **34**. The mother liquor was concentrated, and the residue was resubjected to chromatography eluting with hexanes/EtOAc (5:1) to give 0.37 g of **34**, which was recrystallized from hexanes/EtOAc (5:1) (2 mL) to give 0.26 g of **34**. The total recovery of **34** was 1.67 g (54%); mp 132−133 °C; ^{1}H NMR (300 MHz) δ 7.68−7.65 (comp, 4 H), 7.54 (d, J = 5.7 Hz, 1 H), 7.44−7.36 (comp, 6 H), 6.29 (d, J = 5.7 Hz, 1 H), 4.96 (dd, J = 4.5, 5.0 Hz, 1 H), 3.95−3.85 (m, 2 H), 3.75 (s, 3 H), 1.06 (s, 9 H), 0.02 (s, 9H); ^{13}C NMR (75 MHz) δ 169.8, 167.5, 167.1, 150.4, 135.6, 132.4, 130.2, 128.0, 124.2, 90.1, 83.2, 83.0, 61.6, 53.6, 26.9, 19.3, 1.6; IR ($CHCl_3$) 1798, 1770, 1102 cm^{-1}; mass spectrum (CI) *m*/*z* 569.2037 [$C_{29}H_{37}O_8Si_2$ (M + 1) requires 569.2027] (base), 491.

(5*R*,8*R*,9*S*)-8-*tert*-Butyldiphenylsiloxymethyl-9-methoxycarbonyl-9-trimethylsiloxy-1,7-dioxaspiro[4.4]nonane-2,6-dione (39). A mixture of butenolide **34** (1.28 g, 2.25 mmol) in EtOAc (10 mL) containing 10% Pd/C (0.48 g, 0.45 mmol) was stirred under H_2 (1 atm) at room temperature for 15 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The crude product was purified by recrystallization from a mixture (1:1) of hexanes and EtOAc (12 mL) to give 0.86 g of **39** as white crystals. The filtrate was concentrated, and the residue was recrystallized from a mixture (2:1) of hexanes and EtOAc (6 mL) to give an additional 0.28 g of **39**. The total recovery of **39** was 1.14 g (89%); mp 142−145 °C; ^{1}H NMR (300 MHz) δ 7.67−7.65 (comp, 4 H), 7.43−7.36 (comp, 6 H), 5.01 (dd, J = 3.6, 7.5 Hz, 1 H), 3.89 (dd, J = 3.6, 11.6 Hz, 1 H), 3.75 (dd, J = 7.5, 11.6 Hz, 1 H), 3.74 (s, 3 H), 2.82−2.23 (comp, 2 H), 1.06 (s, 9 H), −0.02 (s, 9 H); ^{13}C NMR (75 MHz) δ 174.2, 171.2, 168.1, 135.7, 135.6, 132.9, 132.6, 130.0, 127.9, 86.3, 83.5, 81.5, 62.5, 53.4, 27.2, 26.8, 23.4, 19.3, 1.4; IR ($CHCl_3$) 1796, 1748, 1216, 1113 cm^{-1}; mass spectrum (CI) *m*/*z* 571.2179 [$C_{29}H_{39}O_8Si_2$ (M + 1) requires 571.2184] (base), 513, 493.

(4*R*)-2,4-Dimethyl-5-phenyl-1-penten-3-ol (45). A solution of 2-bromopropene (605 mg, 5.00 mmol) in THF (2 mL) was added slowly (ca 1 h) to a stirred suspension of magnesium (152 mg, 6.25 mmol) in THF (3 mL) at room temperature. The mixture was stirred at room temperature for 1 h and then cooled to 0 °C, whereupon a solution of aldehyde **44**[18] (380 mg, 2.56 mmol) in THF (5 mL) was added. The mixture was stirred at 0 °C for 10 min, at room temperature for 10 min and poured into H_2O (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 40 mL). The extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (4:1) to give 366 mg (75%) of diastereomeric mixture (∼1:1) of alcohols **45**; ^{1}H NMR (300 MHz) δ 7.31−7.16 (comp, 5 H), 5.00−4.90 (comp, 2 H), 3.90−3.84 (comp, 1 H), 3.07 (dd, J = 3.4, 13.2 Hz, 0.5 H), 2.76 (dd, J = 6.0, 13.4 Hz, 0.5 H), 2.43 (dd, J = 8.6, 13.4 Hz, 0.5 H), 2.29 (dd, J = 10.0, 13.2 Hz, 0.5 H), 2.00−1.86 (comp, 1 H), 1.75 (s, 1.5 H), 1.70 (s, 1.5 H), 1.59 (br s, 0.5 H), 1.58 (br d, J = 4.1 Hz, 0.5 H), 0.84 (d, J = 6.8 Hz, 1.5 H), 0.75 (d, J = 6.8 Hz, 1.5 H); ^{13}C NMR (75 MHz) δ 146.7, 146.5, 141.1, 141.0, 129.4, 129.1, 128.2, 128.1, 125.8, 125.7, 112.7, 111.3, 80.6, 77.9, 40.1, 38.2, 38.0, 37.6, 18.6, 17.4, 15.9, 13.4; IR ($CHCl_3$) 3606, 1650, 1602, 1495, 1453, 1010, 907 cm^{-1}; mass spectrum (CI) *m*/*z* 190.1352 [$C_{13}H_{18}O$ (M^+) requires 190.1358], 185, 173 (base), 153.

(2*R*,3*E*)-5-Bromo-2,4-dimethyl-3-pentenylbenzene (46). MsCl (223 μL, 2.88 mmol) was added to a stirred solution of epimeric alcohols **45** (366 mg, 1.92 mmol) and Et_3N (455 μL, 3.26 mmol) in dry CH_2Cl_2 (6 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h and then poured into a mixture of EtOAc (50 mL) and H_2O (50 mL). The layers were separated, and the organic layer was washed with 1 M HCl (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give 512 mg of crude mesylates. The mesylates were dissolved in 2-butanone (10 mL) containing NaBr (395 mg, 3.84 mmol) and 18-crown-6 ether (50 mg, 0.19 mmol), and the mixture was heated under reflux for 6 h. The mixture was cooled to room temperature and poured into a mixture of EtOAc (50 mL) and H_2O (50 mL). The layers were separated, and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes to give 395 mg (81%) of bromide **46**; ^{1}H NMR (300 MHz) δ 7.28−7.11 (comp, 5 H), 5.43 (d, J = 8.4 Hz, 1 H), 3.92 (s, 2 H), 2.65−2.54 (comp, 3 H), 1.54 (d, J = 1.3 Hz, 3 H), 0.97 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz) δ 140.3, 136.6, 131.2, 129.3, 128.2, 125.9, 43.4, 41.9, 35.0, 20.2, 14.7; IR ($CHCl_3$) 1603, 1495, 1452 cm^{-1}; mass spectrum (CI) *m*/*z* 253.0592 [$C_{13}H_{18}Br$ (M + 1) requires 253.0592], 173 (base).

(2*R*,3*E*)-2,4-Dimethyl-6-phenylsulfonyl-3-hexenylbenzene (47). A solution of methylphenyl sulfone (244 mg, 1.56 mmol) in THF (2 mL) was added to a suspension of KH (57 mg, 1.42 mmol) in THF (2 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, whereupon a solution of **46** (180 mg, 0.71 mmol) in THF (1 mL) was added at 0 °C. The reaction mixture was stirred at room temperature for 10 h and then saturated aqueous NH_4Cl (20 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (5:1) to give 208 mg (89%) of **47**; ^{1}H NMR (300 MHz) δ 7.93−7.25 (comp, 5 H), 7.24−7.05 (comp, 5 H), 4.95 (br d, J = 8.9 Hz, 1 H), 3.14−2.98 (m, 2 H), 2.61−2.40 (comp, 3 H), 2.32−2.27 (m, 2 H), 1.31 (d, J = 1.3 Hz, 3 H), 0.91 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz) δ 140.7, 139.1, 133.7, 132.6, 130.0, 129.3, 129.2, 128.1, 128.0, 125.7, 55.2, 43.7, 34.6, 32.2, 20.6, 15.9; IR ($CHCl_3$) 1603, 1495, 1448, 1307, 1151, 1086 cm^{-1}; mass spectrum (CI) *m*/*z* 329.1584 [$C_{20}H_{25}O_2S$ (M + 1) requires 329.1575], 187 (base), 143.

(1*S*,3*R*,4*S*,5*R*)-1-[(3*E*,5*R*)-3,5-Dimethyl-6-phenyl-3-hexenyl]-4-hydroxy-3-hydroxymethyl-4,5-bis(methoxycarbonyl)-2,8-dioxabicyclo[3.2.1]octane (50) and (2*R*/*S*,5*R*,-8*R*,9*S*)-2-[(3*E*,5*R*)-3,5-Dimethyl-6-phenyl-3-hexenyl]-9-hydroxy-8-(hydroxymethyl)-2-methoxy-9-methoxycarbonyl-1,7-dioxaspiro[4.4]nonan-6-one (51a,b). A solution of *n*-BuLi in hexanes (0.60 mL, 0.84 mmol) was added to a solution of **47** (138 mg, 0.42 mmol) in THF (1 mL) at −78 °C. The solution

was stirred at −78 °C for 1.5 h, and a solution of **39** (239 mg, 0.42 mmol) in THF (2 mL) was added. The reaction was stirred at −78 °C for 1 h and then allowed to warm to 0 °C over 1 h. Saturated aqueous NH_4Cl (10 mL) was added at 0 °C, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 30 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in THF (8 mL), and the resulting solution was added to aluminum amalgam, which was prepared from small pieces of aluminum foil (1.56 g, 57.7 mmol) and 2% aqueous $HgCl_2$ (14 mL). HMPA (2 mL) and H_2O (0.2 mL) were then added, and the reaction was stirred at room temperature for 3 h, and the solids were removed by vacuum filtration through a Celite pad, which was washed with Et_2O (1 × 50 mL). The combined filtrate and washings were washed with H_2O (2 × 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 232 mg (73%) of a mixture of epimeric hemiacetals **48** and ketone **49**. A portion of the above mixture of **48** and **49** (49 mg, 0.065 mmol) was dissolved in MeOH (5 mL) containing concentrated H_2SO_4 (49 mg, 0.5 mmol), and the solution was stirred at room temperature for 40 h. Pyridine (119 mg, 121 μL, 1.5 mmol) was added, and the solvents were removed under reduced pressure. The residue was dissolved in EtOAc (30 mL), and the resulting solution was washed with H_2O (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (1:2) to give 7.6 mg (25%) of **50** and a total of 19.3 mg (65%) of the epimeric methyl acetals **51a** and **51b**.

For **50:** ^{1}H NMR (300 MHz) δ 7.26−7.12 (comp, 5 H), 5.01 (d, J = 9.1 Hz, 1 H), 4.28 (t, J = 5.7 Hz, 1 H), 3.85 (s, 3 H), 3.79 (s, 3 H), 3.80−3.60 (m, 2 H), 3.12−3.03 (m, 1 H), 2.64−2.51 (comp, 3 H), 2.21−1.85 (comp, 7 H), 1.44 (d, J = 1.1 Hz, 3 H), 0.95 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz) δ 170.8, 169.4, 141.1, 133.2, 130.6, 129.3, 128.0, 125.7, 109.0, 88.1, 75.1, 74.1, 61.6, 53.2, 52.8, 44.0, 35.4, 34.5, 33.5, 31.6, 29.3, 20.9, 16.1; IR ($CHCl_3$) 3538, 1737, 1439, 1268, 1229, 1124, 1036 cm^{-1}; mass spectrum (CI) m/z 463.2323 [$C_{25}H_{35}O_8$ (M + 1) requires 463.2332] (base), 445.

For **51a:** (less polar): mp, 100−102 °C; ^{1}H NMR (300 MHz) δ 7.25−7.11 (comp, 5 H), 4.98 (d, J = 8.4 Hz, 1 H), 4.84 (t, J = 4.4 Hz, 1 H), 4.54 (s, 1 H), 4.10−4.07 (m, 2 H), 3.86 (s, 3 H), 3.22 (s, 3 H), 2.70−1.64 (comp, 11 H), 1.41 (d, J = 1.2 Hz, 3 H), 0.96 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz) δ 173.9, 170.9, 141.1, 133.3, 130.6, 129.3, 128.0, 125.6, 112.4, 87.6, 81.0, 78.9, 60.9, 53.4, 48.9, 44.0, 35.7, 34.6, 33.0, 31.7, 27.7, 22.7, 14.2; IR ($CHCl_3$) 3335, 1793, 1741, 1453, 1286, 1077, 1041, 1032 cm^{-1}; mass spectrum (CI) m/z 463.2335 [$C_{25}H_{35}O_8$ (M + 1) requires 463.2332], 431 (base), 403.

For **51b:** (more polar) ^{1}H NMR (300 MHz) δ 7.26−7.12 (comp, 5 H), 4.99 (d, J = 7.7 Hz, 1 H), 4.76 (t, J = 5.0 Hz, 1 H), 4.11 (s, 1 H), 3.98−3.93 (m, 2 H), 3.92 (s, 3 H), 3.12 (s, 3 H), 2.75−1.70 (comp, 11 H), 1.43 (d, J = 1.3 Hz, 3 H), 0.94 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz) δ 174.2, 171.4, 141.1, 133.2, 130.6, 130.5, 129.3, 128.0, 125.7, 112.6, 87.0, 80.1, 79.4, 61.1, 53.8, 49.2, 44.0, 35.5, 34.6, 34.3, 32.8, 29.3, 20.8, 16.3; IR ($CHCl_3$) 3498, 1792, 1744, 1453, 1288, 1058, 1032 cm^{-1}; mass spectrum (CI) m/z 463.2326 [$C_{25}H_{35}O_8$ (M + 1) requires 463.2332], 431 (base), 403.

6,7-Dideoxysqualestatin H5 Dimethyl Ester. *N*-Methylmorpholine *N*-oxide (25 mg, 0.22 mmol) and tetrapropylammonium perruthenate (2 mg, 0.005 mmol) were added to a solution of alcohol **50** (25 mg, 0.05 mmol) in a mixture of CH_3CN (1 mL) and H_2O (2 mg, 0.11 mmol). The solution was stirred at room temperature for 5 h, and then EtOAc (30 mL) and 0.1 M HCl (10 mL) were added. The layers were separated, and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (5:1) to give 23 mg (88%) of 6,7-dideoxysqualestatin H5 dimethyl ester as a glass; ^{1}H NMR (300 MHz) δ 7.28−7.12 (comp, 5 H), 5.03 (d, J = 8.6 Hz, 1 H), 4.83 (s, 1 H), 3.94 (s, 3 H), 3.79 (s, 3 H), 3.12−3.01 (m, 1 H), 2.70−2.47 (m, 3 H), 2.22−1.96 (comp, 7 H), 1.46 (d, J = 1.1 Hz, 3 H), 0.95 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz) δ 169.8, 168.8, 165.9, 141.1, 132.9, 131.0, 129.3, 128.1, 125.8, 109.5, 88.1, 74.6, 53.8, 53.0, 44.0, 34.8, 34.5, 33.4, 31.4, 29.1, 20.9, 16.1; IR ($CHCl_3$) 3525, 1740, 1603, 1439, 1271, 1124 cm^{-1}; mass spectrum (CI) m/z 477.2107 [$C_{25}H_{33}O_9$ (M + 1) requires 477.2125] (base), 459, 385.

6,7-Dideoxysqualestatin H5 (3). 6,7-Dideoxysqualestatin H5 dimethyl ester (10 mg, 0.021 mmol) was dissolved in dioxane (1 mL) containing H_2O (1.5 mg, 0.084 mmol), and potasium *tert*-butoxide (24 mg, 0.21 mmol) was added. The reaction mixture was heated at reflux for 1 d. The solvent was evaporated, and H_2O (10 mL) was added. The aqueous mixture was washed with Et_2O (1 × 10 mL), acidified with 0.1 M HCl (4 mL), and extracted with EtOAc (2 × 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by reverse phase (C18) HPLC eluting with MeOH/H_2O/AcOH (850:150:2) to give 6.6 mg (70%) of **3**; ^{1}H NMR (500 MHz, CD_3OD) δ 7.23−7.11 (comp, 5 H), 5.03 (d, J = 9.0 Hz, 1 H), 4.87 (s, 1 H), 3.19−3.15 (m, 1 H), 2.68−2.60 (m, 1 H), 2.58 (dd, J = 6.1, 13.0 Hz, 1 H), 2.47 (dd, J = 8.3, 13.0 Hz, 1 H), 2.21−1.83 (comp, 7 H), 1.42 (d, J = 1.1 Hz, 3 H), 0.95 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.4, 172.4, 171.1, 142.4, 135.0, 131.7, 130.3, 129.0, 126.7, 109.9, 89.5, 76.2, 75.9, 45.1, 36.5, 35.9, 34.7, 32.2, 30.3, 21.4, 16.1; IR ($CHCl_3$) 3397, 1733, 1603, 1276, 1129 cm^{-1}; mass spectrum (FAB) m/z 447.1642 [$C_{23}H_{27}O_9$ (M − 1) requires 447.1655] (base), 403.

Acknowledgment. We thank the National Institutes of Health, the Robert A. Welch Foundation, Pfizer, Inc., and Merck Research Laboratories for their generous support of this research. We are also grateful to the Sankyo Co., Ltd. (Tokyo, Japan) for financial support for Dr. Satoru Naito.

Supporting Information Available: Complete experimental details and characterization (^{1}H and ^{13}C NMR spectra, IR spectra, mass spectra) and copies of the ^{1}H NMR spectra of **10**−**17**, **21**, **22**, **24a**−**c**, **25a**−**c**, **27**−**43**, **45**−**47**, **50**−**53** and X-ray structural data for **15**, **34**, **36**, **37**, **39**, and **53**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO011157S