Facile Entry to the Zaragozic Acids. Asymmetric Total Synthesis of 6,7-Dideoxysqualestatin H5

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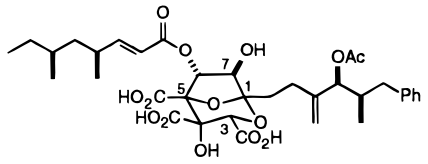
The zaragozic acids[2] and the squalestatins[3] constitute a novel family of fungal metabolites that exhibit extraordinary potency as inhibitors of squalene synthase, as antifungal agents, and as inhibitors of farnesyl protein transferase.[4] The unusual structure of these highly functionalized metabolites coupled with their promising biological activitities, especially their potential as leads for hypercholesterolemic therapy, have inspired numerous efforts directed toward their synthesis. Consequent to these efforts, a variety of approaches to the central 2,8-dioxabicyclo[3.2.1]octane core have been recorded,[5] and several total syntheses of zaragozic acid A (squalestatin S1) (**1**) and zaragozic acid C (**2**) have been reported.[6,7] Despite these elegant successes, we were attracted to the considerable challenge of devising a more concise and general approach to members of the zaragozic acid family. In this context, we targeted the bicyclic lactone **10** as a potentially versatile gateway because it contains the requisite absolute chiralty at C(3)−C(5) as well as appropriate functional handles for introducing the remaining substituents and side chains of the zaragozic acids. We envisaged that this compact intermediate might be assembled via the intramolecular vinylogous aldol reaction of the 5-substituted-2-furoate **9** (Scheme 1).[8] We now report the implementation of such a cyclization as a key step in a concise synthesis of 6,7-dideoxysqualestatin H5 (**3**).[3c]



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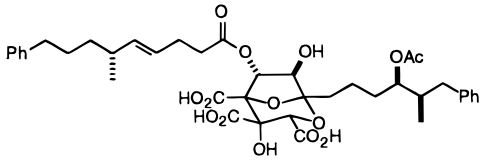

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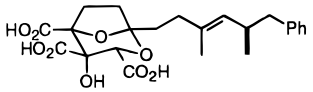

3

As the point of departure en route to the pivotal vinylogous aldol reaction, dimethyl D-tartrate was converted to the monoprotected derivative **5** (69%).[9,10] Selective reduction of the ester α to the free hydroxyl group in **5** was best achieved using borane−dimethyl sulfide complex in the presence of catalytic sodium borohydride,[10] although under the best conditions an inseparable mixture (4:1) of the 1,2- and 1,3-diols was obtained. Fortunately, protection of the primary alcohols as their *tert*-butyldiphenylsilyl ethers (TBDPS) led to a mixture from which **6** was isolated by chromatography in 50% overall yield. Esterification of **6** with the known acid **7**, which is available in three steps from commercially available 5-bromo-2-furancarboxylic acid,[11] proceeded in 96% yield to give **8**. Removal of the tetrahydropyranyl protecting group[12] followed by oxidation of the intermediate alcohol with Dess−Martin periodinane[13] gave **9** (94% overall yield).

The key cyclization of **9** via an intramolecular vinylogous aldol reaction was now at hand, and after some experimentation, we found that this transformation proceeded most efficiently in the presence of 3 equiv of $TiCl_4$ (CH_2Cl_2, 0 °C → rt, 2 h) to give **10** in 40% yield. Less than 5% of the other three diastereomeric adducts were obtained under these conditions, whereas use of other Lewis acids such as $ZnCl_2$, $ZnBr_2$, $SnCl_4$, $BF_3{\cdot}OEt_2$, and TMS−OTf either returned starting material or complex mixtures containing other diastereomeric adducts. Interestingly, the presence of the phenylthio group on the furan ring was critical to the success of this reaction, as the cyclization of the corresponding methoxyfuran furnished mixtures containing comparable quantities of each of the four possible adducts. Reduction of the double bond followed by protection of the tertiary hydroxyl group gave **11** (75% overall yield); the structure of **11** was confirmed by X-ray analysis.

The requisite (C1) side chain of **3** was prepared according to a straightforward sequence of reactions consisting of four

(1) On leave from Sankyo Co., Ltd., Tokyo, Japan.

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(9) The structure assigned to each compound was in accord with its spectral (^1H and ^{13}C NMR, IR, MS) characteristics. Analytical samples of new compounds were obtained by distillation, recrystallization, or preparative HPLC and gave satisfactory combustion analysis (C, H) and/or identification by high-resolution mass spectrometry. Yields are based on purified materials.

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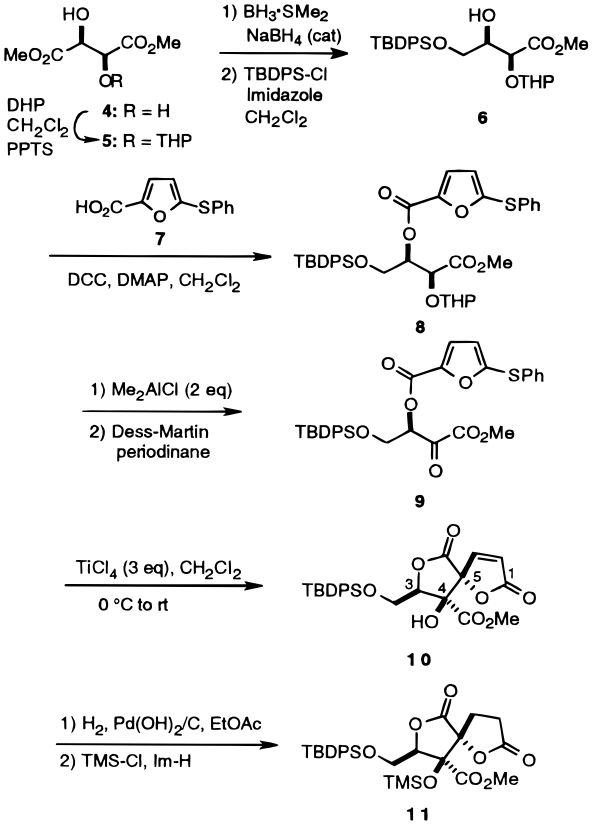
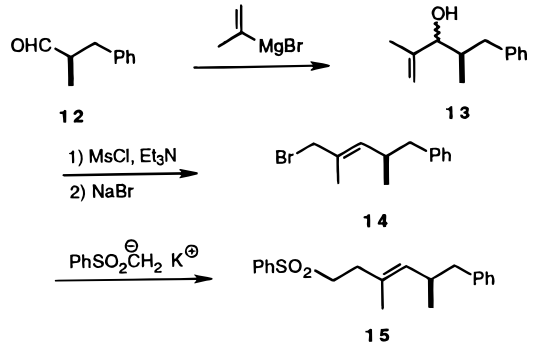
Scheme 1



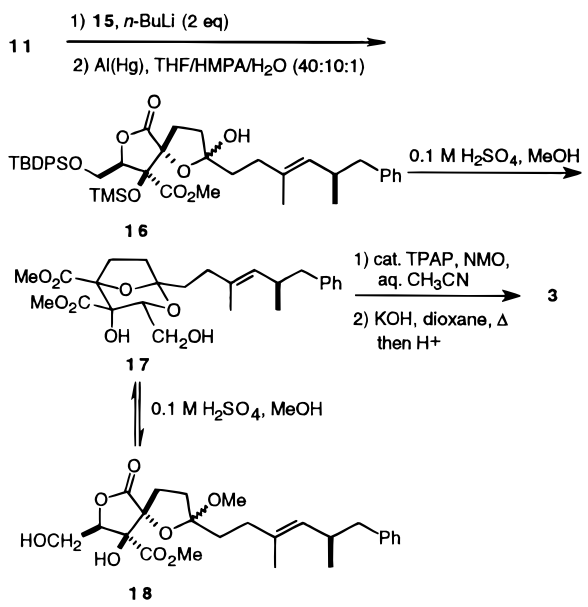
Scheme 2



steps from the known aldehyde **12** (>95% ee) (Scheme 2).[14] Thus, isopropenylmagnesium bromide added to **12** without epimerization of the stereocenter bearing the methyl group to give **13** as a mixture (ca. 1:1) of epimers (75%).[15] Compound **13** was then converted in two steps (81% overall yield) to the allyl bromide **14**, which was alkylated with the potassium salt of methyl phenyl sulfone to give the monoalkylated product **15** (89% yield).[16]

Coupling the C(1) side chain with the spiro bicyclic subunit **11** was then achieved by selective addition of the dianion of the sulfone **15** to the less hindered lactone moiety of **11** to give, following reductive desulfonylation,[17] the hemiketal **16** in 73% overall yield (Scheme 3). Treatment of **16** with methanolic acid led to an equilibrium mixture

Scheme 3



(1:2.5) of the desired bicyclic ketal **17** (25% yield) together with a mixture (ca. 1:1, 65%) of epimeric methyl ketals that have been tentatively identified as **18**. Obtention of this mixture was somewhat surprising inasmuch as all other acid-catalyzed transformations leading to zaragozic acids A and C reportedly delivered exclusively the desired 2,8-dioxabicyclo[3.2.1]octane core.[6,7] On the other hand, in various model studies directed toward the zaragozic acids, mixtures of isomeric ketals have been reported.[5b,d,e,g] Thus, the presence of the hydroxyl groups at C(6) and C(7) in synthetic intermediates may play an important role in dictating the thermodynamic course of these transketalizations. In any event, the mixture of **17** and **18** was readily separable by chromatography, and the undesired ketals **18** could be reequilibrated upon exposure to methanolic acid to give additional quantities of **17**. Oxidation of the primary alcohol function of **17** to the corresponding carboxyl group[18] and hydrolysis of the methyl esters gave synthetic **3** (62% overall yield), which gave ^{1}H and ^{13}C NMR spectra identical with those of an authentic sample.[19]

The total asymmetric synthesis of the natural product 6,7-dideoxysqualestatin H5 (**3**) has been completed by a concise approach in which the longest linear sequence is 14 steps. The synthesis highlights a novel strategy for assembling the core of the zaragozic acids and provides a compelling example of the power and versatility of intramolecular vinylogous aldol reactions in organic synthesis.

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Supporting Information Available: Complete experimental procedures and characterization (^{1}H and ^{13}C NMR and IR spectra and mass spectral data) (9 pages).

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