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[9] The stereochemical assignment was made on the basis of the ^{1}H NMR analysis and NOE experiment of the product and derivative thereof (see Supporting Information).
[10] In this case the stereoselectivity at the C1′ position is opposite that observed in the pantolactone-derived system. A similar stereochangeover has been observed in the rearrangement of *O*-glycosides derived from primary alcohols; see ref. [2a].
[11] The trapping experiment of enolate **A** (SiMe$_3$Cl, –78 °C) gave an *E*:*Z* mixture (ca. 1:1) of silyl enol ether in 69% yield.

Stereoselective Total Synthesis of Zaragozic Acid A based on an Acetal [1,2] Wittig Rearrangement[**]

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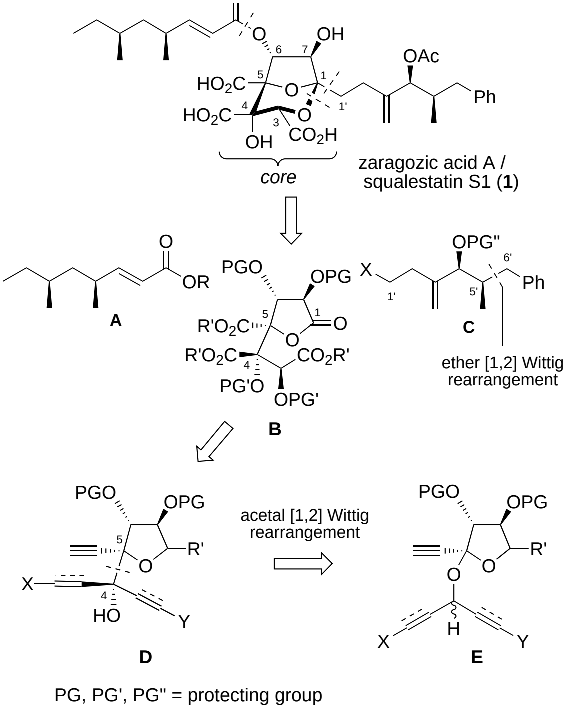
The zaragozic acids and squalestatins are a family of naturally occurring fungal metabolites independently isolated and characterized by researchers at Merck[1] and Glaxo.[2] These natural products are potent inhibitors of squalene synthase and have potential as therapeutic agents for the treatment of hypercholesterolemia.[1a, 2a] All the zaragozic acids and squalestatins have a common 2,8-dioxabicyclo[3.2.1]octane core with an array of six stereogenic centers including contiguous quarternary carbon atoms, and are different only at the alkyl and acyl side chains at C1 and C6, respectively. Therefore, it is not surprising that the these compounds have elicited considerable attention from numerous synthetic chemists.[3, 4] Zaragozic acid A (squalestatin S1; **1**) is a representative example of this novel class of compounds. Herein, we report the efficient, convergent synthesis of **1** by highlighting the acetal [1,2] Wittig rearrangement[5] for forming the C4–C5 bond together with the simultaneous creation of the contiguous quaternary carbon atoms as the key step.

Our strategy is shown in Scheme 1. Disconnection of the C6 side chain **A**, unraveling of the C1 acetal, and cleavage of the C1–C1′ bond led to lactone **B** and an alkyl anion equivalent **C**.[6] Our interest in the carbanion rearrangement of the sugar derivatives led us to consider a strategy for lactone **B** starting from the *C*-glycoside **D**, namely an acetal [1,2] Wittig rearrangement product of the *O*-glycoside **E**. The preceding paper describes the synthesis of this class of highly functionalized *C*-glycosides based on a rearrangement protocol.[7] Furthermore, we planned to construct a C5′–C6′ bond in segment **C** using the original ether [1,2] Wittig rearrangement.[8]



Scheme 1. Retrosynthetic analysis of zaragozic acid A (**1**).

Our synthesis begins from the *O*-glycoside **5a** ($\cong$**E**), which can be prepared from the hemiketal **3** derived from L-arabino-γ-lactone[9] and the protected ethynylvinylmethanol **4** (racemate; Scheme 2). Previous work suggested that the carbanion rearrangement of an *O*-glycoside such as **5a** should produce the [1,2] rearrangement product with high diastereoselectivity and in good yield.[7, 9] In contrast to this expect-

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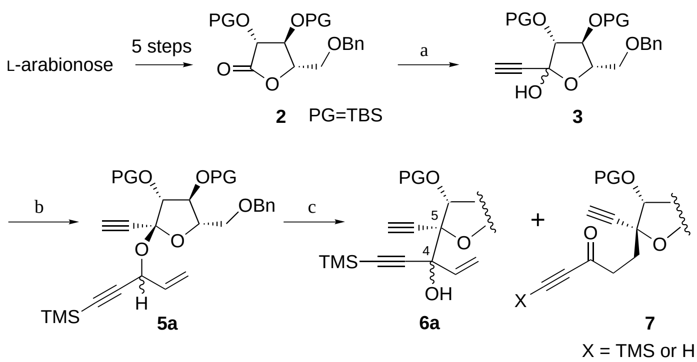
Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.



Scheme 2. Synthesis and rearrangement of *O*-glycoside **5a**. a) Lithium acetylide, $\mathrm{Et_2O}$, $-78\,^{\circ}\mathrm{C}$, 75 %; b) $\mathrm{CH_2{=}CHCH(OH)C{\equiv}C}$-TMS (**4**), montmorillonite K 10, 4 Å-MS, $\mathrm{CH_2Cl_2}$, RT, 55 %; c) *n*BuLi, THF, $-78\,^{\circ}\mathrm{C}$, **6a**: 14 %, **7**: 17 %, recovered **5a**: 46 %. TBS = *tert*-butyldimethylsilyl, Bn = benzyl, TMS = trimethylsilyl.

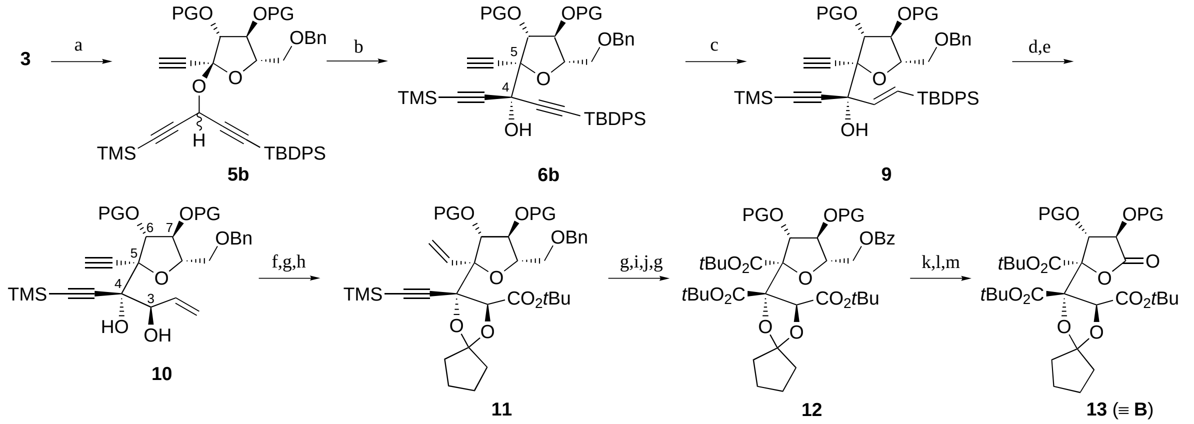
ation, the reaction of *β*-**5a** (*n*BuLi, $-78\,^{\circ}\mathrm{C}$, THF) proceeded to form a 1:1 diastereomeric mixture of the desired [1,2] shift product *β*-**6a** in poor yield, along with a significant amount of the [1,4] rearrangement product **7**. Thus, we tried to redesign the rearrangement system.

Finally, we found that the bis(ethynyl)methanol system satisfied all the requirements as the migrating terminus. The reaction of the *O*-glycoside **5b** (≅**E**), similarly prepared from ketal **3** and the protected bis(ethynyl)methanol **8** (racemate), exclusively afforded the desired [1,2] Wittig product (5*β*,4*S*)-*C*-glycoside **6b** with high diastereoselectivety (> 95 % *β*, 84 % d.r. at C4)[10] in 54 % yield. (Scheme 3). Also significant, the anomeric radical, an intermediate in the rearrangement of **5b**, could efficiently discriminate between the enantiotopic faces of the prochiral bis(ethynyl)methanol radical (that is, differentiation of trimethylsilyl and *tert*-butyldimethylsilyl at the *γ*,*γ*′ positions) during the radical recombination process.

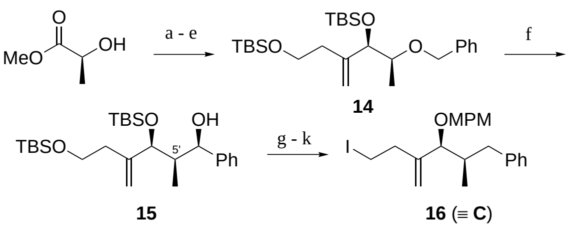
The major diastereomer, separated by column chromatography, was then converted into the key precursor **10**, which has all the stereogenic centers of **B**, by the following sequence. The semireduction of the ethynyl group on **6b** with bis(2-methoxyethoxy)aluminum hydride (Red-Al)in diethyl ether at $-15\,^{\circ}\mathrm{C}$ yielded the *tert*-butyldiphenylvinylsilane **9** with high selectivity.[11] After the ozonolysis of **9**, the addition of vinylmagnesium bromide (toluene, $-78\,^{\circ}\mathrm{C}$) proceeded to give **10** with excellent diastereoselectivity[12] (> 95 % d.r.) with the latent C3 carboxy moiety introduced in the form of a vinyl substituent. After protection of the C3 and C4 hydroxyl groups as a cyclopentylidene acetal, the oxidation of the vinyl group at C3 was accomplished through a three-step sequence which involved ozonolysis to the corresponding aldehyde followed by oxidation with buffered $\mathrm{NaClO_2}$ and esterification with *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea[13] to give the *tert*-butyl monoester. The tris(*tert*-butyl) ester **12** was obtained in good yield following a similar stepwise oxidation of the ethynyl groups at C4 and C5 to the carboxy moieties. The hydrolysis of the benzoate group at C1′[14] and the two-step oxidation (tetrapropylammonium perruthenate (TPAP)/$\mathrm{O_2}$-$\mathrm{Cu(OAc)_2}$[15]) of the resulting hydroxymethyl group afforded the lactone **13** (≅**B**) as a fully elaborated intermediate, to which a nucleophilic side chain equivalent could be added at C1.

Scheme 4 illustrates the synthesis of the C1 side chain equivalent **16** (≅**C**) using the ether [1,2] Wittig rearrangement as the key step (**14**→**15**). The benzyl ether **15** was synthesized from methyl (*S*)-lactate in five steps. The rearrangement of **14** (*n*BuLi, THF, $0\,^{\circ}\mathrm{C}$) afforded **15**, which possesses the desired *R* configuration at the C5′ position (88 % d.r.),[16] in 32 % yield along with 58 % of recovered **14**. The eight-step refunctionalization sequence from **15**, which involved removement of the hydroxyl group at C6′[17] and iodination of the primary alcohol, successfully afforded **16**.

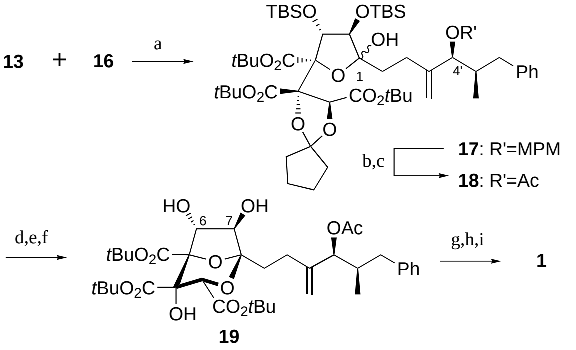
Generation of the alkyllithium side chain (for C1) derived from iodide **16** followed by the addition of a lactone **13** provided the hemiketal **17** as a mixture of anomers (Scheme 5).[18] The oxidative cleavage of the MPM ether followed by acetylation of the hydroxyl group at C4′ completed the assembly of the hemiketal **18**, the precursor



Scheme 3. Synthesis of the lactone **B**. a) TBDPS-$\mathrm{C{\equiv}CCH(OH)C{\equiv}C}$-TMS (**8**), montmorillonite K 10, 4 Å-MS, $\mathrm{CH_2Cl_2}$, RT, 80 %; b) *n*BuLi, THF, $-78\,^{\circ}\mathrm{C}$, 54 % 84:16 at C4; c) Red-Al, $\mathrm{Et_2O}$, $-15\,^{\circ}\mathrm{C}$, 83 %; d) $\mathrm{O_3}$, MeOH, $-78\,^{\circ}\mathrm{C}$ then $\mathrm{Me_2S}$; e) $\mathrm{CH_2{=}CHMgBr}$, toluene, $-78\,^{\circ}\mathrm{C}$, 49 % for two steps; f) cyclopentanone dimethylacetal, *p*TsOH, benzene, RT, 87 %; g) $\mathrm{O_3}$, MeOH, $-78\,^{\circ}\mathrm{C}$ then $\mathrm{Me_2S}$; $\mathrm{NaClO_2}$, $\mathrm{NaH_2PO_4}$, $\mathrm{Me_2C{=}CHMe}$, *t*BuOH/$\mathrm{H_2O}$, RT; *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea, $\mathrm{CH_2Cl_2}$, RT, 73 – 84 % for three steps; h) $\mathrm{H_2}$, cat. Pd/C, MeOH, RT, 88 %; i) 0.1 N TBAF/THF, THF, $0\,^{\circ}\mathrm{C}$, 94 %; j) $\mathrm{H_2}$, Lindlar cat., MeOH, RT, 93 %; k) KOH (aq), MeOH, RT, 78 %; l) cat. TPAP, NMO, 4 Å-MS, $\mathrm{CH_2Cl_2}$, RT, 98 %; m) $\mathrm{O_2}$, $\mathrm{Cu(OAc)_2}$, 2,2′-bipyridyl, DABCO, DMF, $70\,^{\circ}\mathrm{C}$, 72 %. TBDPS = *tert*-butyldiphenylsilyl, Bz = benzoyl, TBAF = tetrabutylammonium fluoride, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine *N*-oxide, DABCO = 1,4-diazabicyclo[2.2.2]octane.



Scheme 4. Synthesis of the C1 side chain (≅**C**). a) $PhCH_2OC(=NH)CCl_3$, cat. CF_3SO_3H, cyclohexane, 0 °C → RT, 90 %; b) *i*PrMgBr, MeO(Me)NH · HCl, THF, −10 °C, 60 %; c) *t*BuLi, $TBSOCH_2CH_2C(=CH_2)Br$, hexane/Et_2O, −78 °C, 92 %; d) $Zn(BH_4)_2$, Et_2O, −78 → −30 °C, 93 %; e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C → RT, 95 %; f) *n*BuLi, THF, −20 → 0 °C, **15**: 32 % recovered, **14**: 58 %; g) TBAF, THF, RT; acetone dimethylacetal, cat. *p*TsOH, benzene, RT; 1 N HCl (aq), THF, 0 °C; TBSCl, imidazole, CH_2Cl_2, RT, 62 % for four steps; h) Li_0, liq. NH_3, −78 → −30 °C, 85 %; i) $MPMOC(=NH)CCl_3$, cat. CF_3SO_3H, cyclohexane, CH_2Cl_2, 0 °C; j) TBAF, THF, RT, 81 % for two steps; k) I_2, imidazole, PPh_3, benzene, RT, 88 %. MPM = *p*-methoxyphenylmethyl.



Scheme 5. Total synthesis of zaragozic acid A (**1**). a) 3.2 equiv of **16**, 5.0 equiv of *t*BuLi, 5:1 hexane:diethyl ether, −40 °C, then **13** , −40 °C, 96 %; b) DDQ, CH_2Cl_2, RT, 96 %; c) Ac_2O, DMAP, CH_2Cl_2, RT, 95 %; d) 10.20:1 TFA:CH_2Cl_2:H_2O, RT; e) *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea, CH_2Cl_2, RT; f) 1 N TBAF, THF, RT, 51 % for three steps; g) $(tBuOCO)_2O$, 4-pyrroridinopyridine, CH_2Cl_2, 0 °C, 81 %; h) **20** (≅**A**, R = H), DCC, DMAP, CH_2Cl_2, RT, 82 %; i) TFA, CH_2Cl_2, RT, 73 %. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = 4-dimethylaminopyridine, TFA = trifluoroacetic acid, DCC = 1,3-dicyclohexylcarbodiimide.

to the bicyclic core and associated C1 side chain. Hydrolysis/ketalization of the hemikatal **18** with trifluoroacetic acid (TFA), followed by the esterification and TBAF treatment provided the desired bicyclic ketal **19**.[19] Selective protection of the hydroxyl group at C7 with a *tert*-butoxycarbonyl (Boc) group[20] followed by acylation with the C6 side chain **20** (≅**A**, R = H),[21] then acid treatment afforded zaragozic acid A (**1**), whose spectroscopic data were in excellent agreement to those of a natural sample (^1H and ^{13}C NMR, IR, HPLC, and $[\alpha]_D$).

In conclusion, we have described the total synthesis of zaragozic acid A, which is highlighted by developing the acetal [1,2] Wittig rearrangement for the construction of the C4–C5 contiguous quaternary chiral centers. This synthetic strategy could be applied to the synthesis of a variety of naturally occurring zaragozic acids as well as designed synthetic analogues.

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[10] The stereochemistry of the major isomer was assigned by X-ray crystallography of a derivative of **6b**. The diastereomeric ratio at C4 was determined by ^1H NMR analysis.

[11] It is worth noting that a similar reaction of simple bis(ethynyl)methanol also preferentially proceeds at the TBDPS side over the TMS side. The investigation into the scope and limitation of the present chemoselective hydroalumination as well as its mechanistic study is now in progress.

[12] The stereochemical outcome of this addition reaction is consistent with chelation control through the hydroxyl group at C4.
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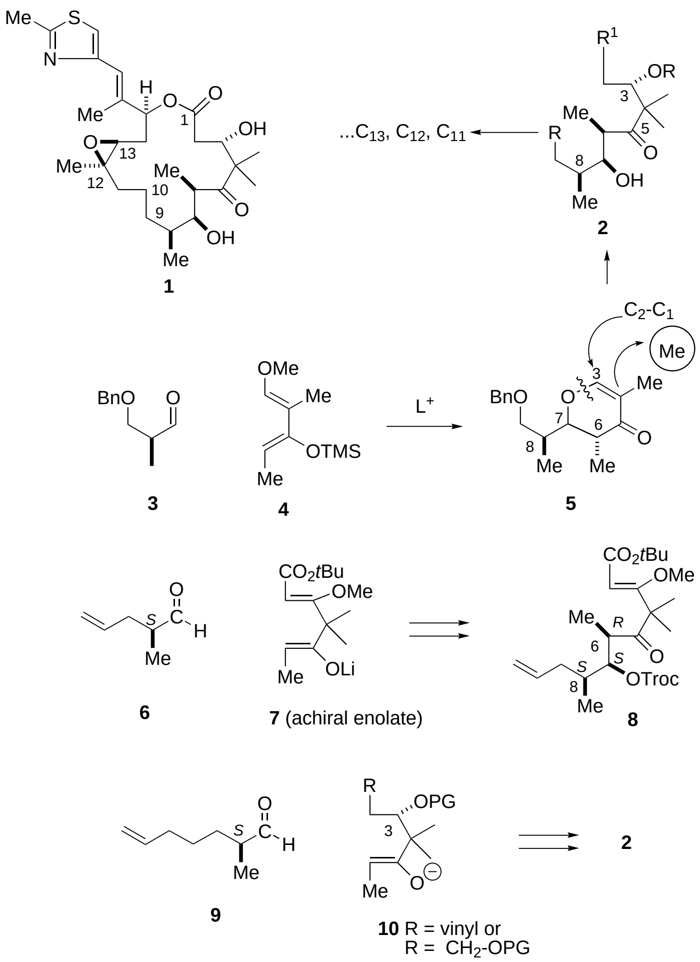
[18] Reaction temperature and the solvent are critical in this step. In fact, the alkyllithium reagent is not reactive to the lactone at −78°C and unstable above −10°C. We have used slightly modified Evans conditions. See ref. [3d].
[19] The spectral data for **19** was identical in all respects to the authentic sample which was prepared from natural zaragozic acid A.
[20] This selective protection was reported by Carreira et al.; see ref. [3c].
[21] Synthesis of the side chain at C6: K. Tomooka, A. Nagasawa, S.-Y. Wei, T. Nakai, *Tetrahedron Lett.* **1996**, *37*, 8895–8898.

Subtle Variations in the Long-Range Transmission of Stereochemical Information: Matched and Mismatched Aldol Reactions[**]

Zhicai Wu, Fei Zhang, and Samuel J. Danishefsky*

In this paper we describe findings with respect to an important question in stereospecific synthesis, that is, how might remote stereogenic loci influence the diastereofacial sense in which covalent bond formation occurs. To address this type of issue in concrete rather than abstract terms, we focused on the very promising antitumor agents, the epothilones (such as epothilone B (**1**), shown in Scheme 1). These compounds have stimulated a great deal of research from the point of view of total synthesis.[1–6] In this paper we do not directly address the total synthesis problem per se. Rather, we focus on the construction of the C6–C7 bond in the acyl sector en route to the natural products, as a paradigm for accomplishing high orders of selection by long-range induction.



Scheme 1. Structure of epothilone B (**1**) and several methods for the construction of the C6–C7 bond in the acyl sector (**2**) of the epothilones. Bn = benzyl, TMS = trimethylsilyl, Troc = trichloroethoxycarbonyl, PG = protecting group.

By way of background we note that, originally,[1a, 1c] the stereochemical information for building the "acyl" sector of the epothilones (see **2** in Scheme 1) was stored in dihydropyrone **5** which itself arose from a cyclocondensation reaction of enantiomerically pure **3** and diene **4**. In our second-generation synthesis,[7] the enantiomerically homogenous **6** reacted with achiral enolate **7**, giving rise selectively (approximate ratio = 5.5:1) to **8**, with the required *R*, *S*, and *S* configurations at C6, C7, and C8, respectively. The configuration at C3 was subsequently induced by catalytic, reagent-based, asymmetric reduction. System **2** can now be prepared in a highly convergent fashion on a multigram scale by this synthesis.[6]

The background result which was central to the program described below was reported by Schinzer and co-workers,[3a] and was subsequently used by others.[4e, 8] The essence of Schinzer's claim[9] was that aldol condensation of the enantiomerically defined lithio enolate system (see **10** in Scheme 1) with the enantiomerically defined aldehyde **9** occurs with high stereoselection in the required sense at the emerging C6–C7 bond, leading, eventually, to a product of type **2**. In essence, in the approach of Schinzer et al., the chirality at C3 had induced the required C6(*R*) and C7(S) configurations. This is in contrast to our second generation approach where the stereogenicity was induced solely by the *S* aldehyde **6**.

We undertook to revisit this type of aldol condensation for several reasons. The role of the pre-C8 *S* methyl group in **9** in delivering the high diastereofacial selectivity at C6 and C7

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