

ABCD-bis(spiroketal) and the completion of the althoyrtin C synthesis is described in the following communication.^[22]

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Keywords: althoyrtin • antitumor agents • natural products • spongistatin • total synthesis

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- [4] Abbreviations: *dr* = diastereomer ratio; TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl; TMS = trimethylsilyl; DIBALH = diisobutylaluminum hydride; Tr = trityl = triphenylmethyl; Tf = trifluoromethanesulfonyl; Bn = benzyl; PPTS = pyridinium *p*-toluenesulfonate; CSA = camphorsulfonic acid; LDBB = di-*tert*-butylbiphenyllithium; DMAP = 4-dimethylaminopyridine; 9-BBN = 9-borabicyclo[3.3.1]nonane; *m*-CPBA = *m*-chloroperbenzoic acid; LDA = lithium diisopropylamide HMPA = hexamethylphosphoric triamide.
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Enantioselective Synthesis of Althoyrtin C (Spongistatin 2): Fragment Assembly and Revision of the Spongistatin 2 Stereochemical Assignment**

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Dedicated to Professor Dieter Seebach and Professor Yoshito Kishi on the occasion of their 60th birthdays

With convergent syntheses of the AB,^[1] CD,^[1] and EF^[2] spongipyran fragments in hand, the assembly of these subunits to the althoyrtin C skeleton was addressed (Figure 1). While the C₄₄–C₅₁ side chain had been successfully

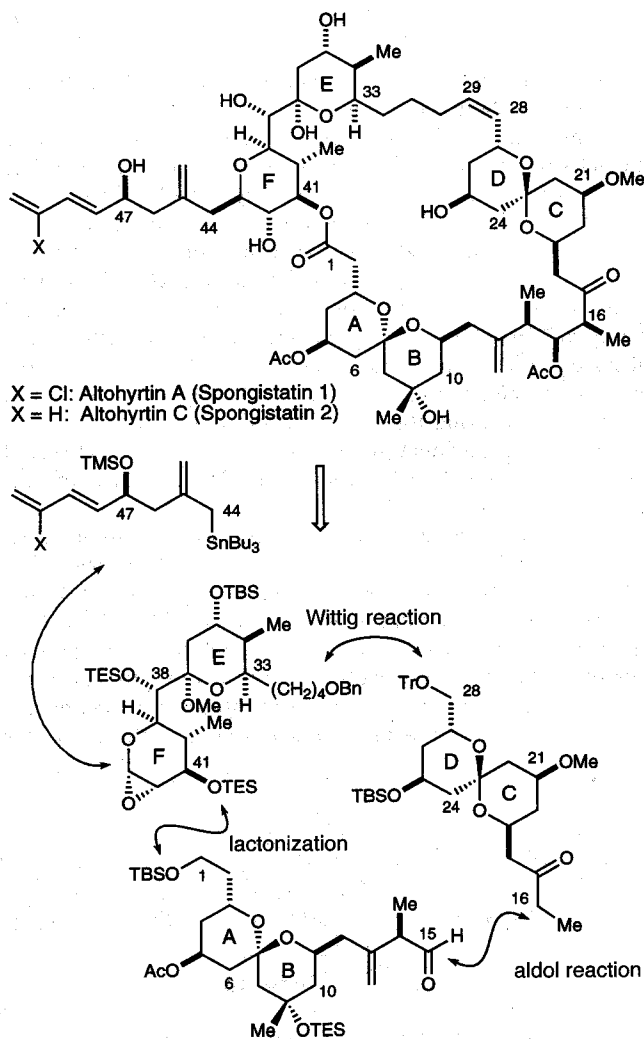


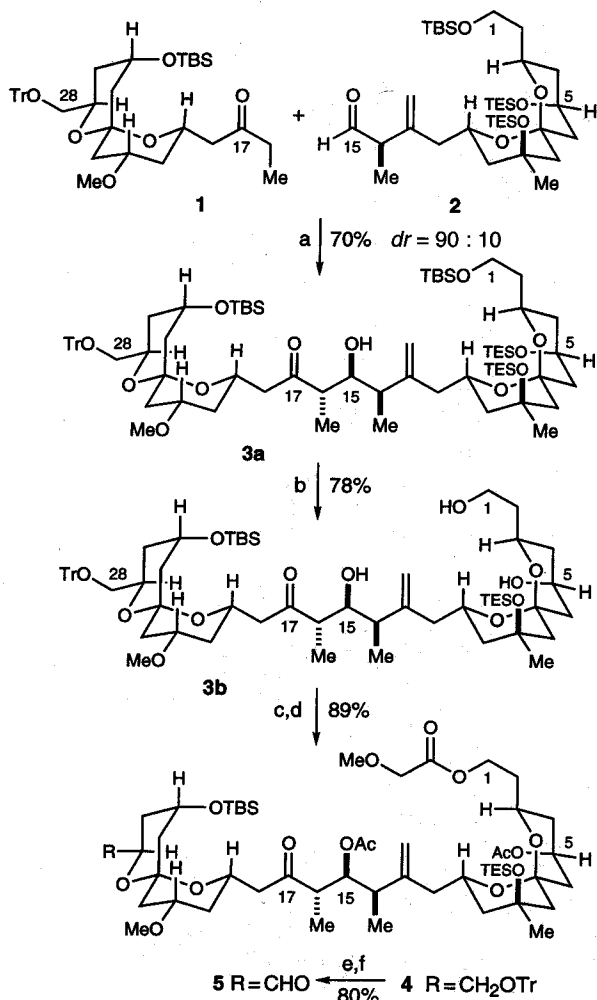
Figure 1. Assembly of the althoyrtin subunits. (See ref. [4] for abbreviations.)

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incorporated into the isolated EF bis(pyran),^[2] we planned to delay the introduction of this fragment until later in the assembly process. Since data obtained for the altohyrtins and spongistatins reveal that the identity of the side-chain substituent X exhibits a significant influence on the cytotoxic potency of these molecules,^[3] we intend to develop syntheses of other side-chain analogues of these macrolides in forthcoming investigations. We report here the completion of the total synthesis of altohyrtin C (spongistatin 2), which employs a diastereoselective aldol union of the AB- and CD-spiroketal subunits, a Wittig coupling of the ABCD and EF fragments, a late-stage addition of the C₄₄-C₅₁ side chain to the fully elaborated ABCDEF system, and a regioselective macro-lactonization, which exhibits fortuitous discrimination between the unprotected C₄₁ and C₄₂ diol functionalities of the F ring.

The aldol coupling of CD-spiroketal ethyl ketone **1**^[1] with AB-spiroketal aldehyde **2**^[1] was first addressed (Scheme 1).^[4]

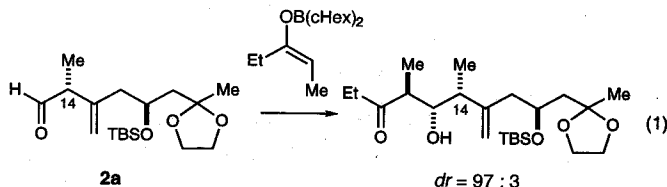


Scheme 1. AB/CD aldol fragment coupling. a) (cHex)₂BCl, Et₃N, pentane, 0°C, 90 min, then -78°C, addition of **2**; b) HF·pyridine, THF, 0°C; c) (MeOCH₂-CO)₂O, *i*Pr₂EtN, CH₂Cl₂; d) Ac₂O, DMAP, pyridine, 22°C; e) Me₂AlCl, CH₂Cl₂, -78°C; f) Dess-Martin periodinane, CH₂Cl₂. (See ref. [4] for abbreviations.)

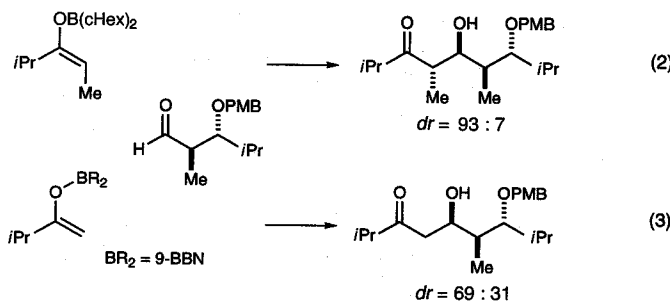
Ample precedent exists for establishment of the 1,2-*anti* relationship between C₁₅ and C₁₆ through the use of *E* boron enolates;^[5] however, control of the incipient C₁₅-hydroxyl configuration was a concern. Because each reacting partner in this proposed aldol reaction has stereocenters that can

potentially influence the stereochemical outcome of the reaction, the stereochemical preferences of each fragment were separately examined.

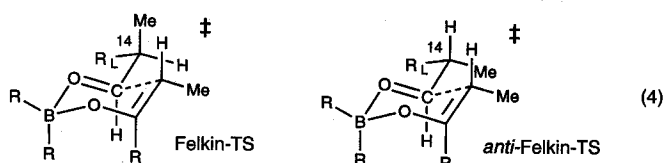
An investigation of the intrinsic diastereofacial bias of the *E* boron enolate derived from **1** indicated that remote chirality on **1** would not significantly influence the stereochemical outcome of the proposed aldol union.^[6] In contrast, treatment of model aldehyde **2a** with the *E* boron enolate of 3-pentanone gave the corresponding Felkin *anti* aldol adduct in 97:3 diastereoselectivity [Eq. (1); the *dr* value gives the ratio



of the given isomer to all other isomers].^[7] Control experiments demonstrate that *E* substituted boron enolates [Eq. (2)] exhibit enhanced Felkin selectivities in additions to chiral α -substituted aldehydes relative to their unsubstituted counterparts [Eq. (3)]. This increased selectivity can be



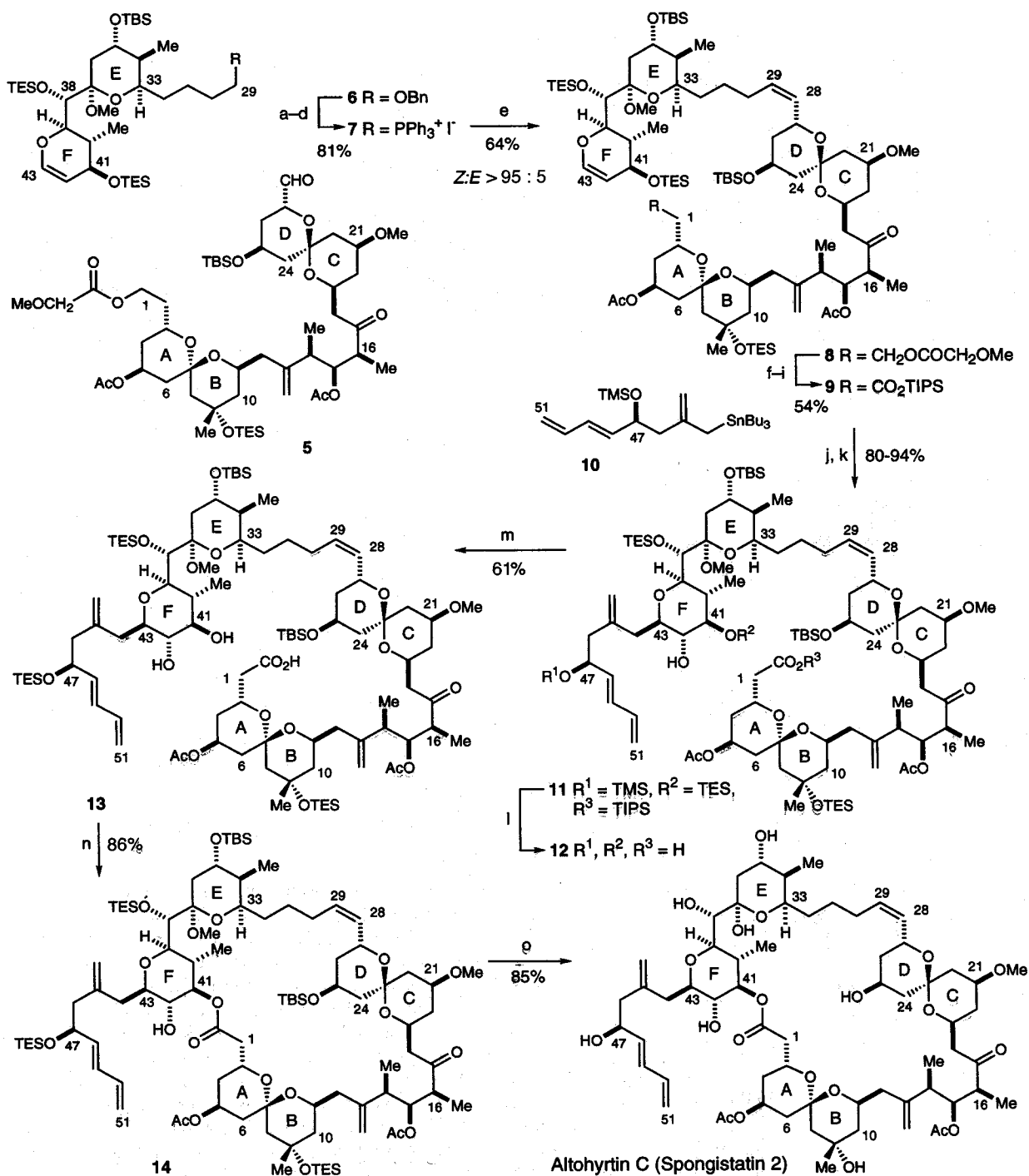
attributed to destabilization of the Felkin *anti* transition state by a developing *syn* pentane interaction [Eq. (4)].^[8]



In the event, selective formation of the *E* boron enolate of ethyl ketone **1** with dicyclohexylchloroborane,^[9] followed by the addition of aldehyde **2**^[10] afforded a 9:1 mixture of product diastereomers (Scheme 1) favoring the desired Felkin adduct **3a** (70%). At this point in the synthesis, incorporation of the C₅ and C₁₅ acetate residues present in the altohyrtin structure was addressed. Selective desilylation of **3a** at C₁ and C₅ with buffered HF·pyridine proceeded in good yield to give triol **3b** (78%).^[11] Selective monoacetylation at the C₁-hydroxyl with methoxyacetic anhydride was followed by bis(acetylation) at C₅ and C₁₅ with acetic anhydride to afford **4** (89%). The selection of the methoxyacetyl residue for interim protection of the C₁ (carboxyl) terminus was made after difficulties were encountered in the selective hydrolysis of the corresponding C₁ acetate, which required extended reaction times. Under these conditions significant β -elimination of the C₁₅ acetate residue was noted.

Refuctionalization of the C₁–C₂₈ bis(spiroketal) **4** in preparation for the Wittig reaction was then undertaken. Removal of the C₂₈ trityl ether with Me₂AlCl^[12] under carefully controlled conditions afforded the corresponding alcohol,^[13] which was oxidized with the Dess–Martin periodinane to give aldehyde **5**, the substrate required for the projected Wittig reaction. The requisite phosphonium salt **7** was prepared from EF-bis(pyran) benzyl ether **6**^[12] (Scheme 2) by successive debenzylation (LDBB, 96%), mesylation

(MsCl, Et₃N, 99%), sodium iodide displacement (NaI, acetone, 94%), and displacement by triphenylphosphane (PPh₃, MeCN, 91%). Deprotonation of **7** (1.26 equiv) with LiHMDS followed by addition of aldehyde **5** provided the desired Wittig product **8** in 64% yield (>95:5 Z:E).^[14] Removal of the methoxyacetate C₁ protecting group was accomplished with NH₃/MeOH in 82% yield. While hydrolysis of the secondary acetates at C₅ and C₁₅ was not observed, a minor by-product resulting from β-elimination of the C₁₅



Scheme 2. Final assembly: a) LDBB, THF, -78°C; b) MsCl, Et₃N, CH₂Cl₂; c) NaI, NaHCO₃, Na₂SO₃, acetone; d) PPh₃, CH₃CN; e) LiHMDS, THF, -78°C, then 5, -20°C; f) NH₃, MeOH; g) Dess–Martin periodinane, pyridine, CH₂Cl₂; h) NaClO₂, 2-methyl-2-butene, ethyl-1-propenyl ether, *t*BuOH, pH 5.5; i) TIPSCl, Et₃N, THF; j) dimethyldioxirane, acetone, CH₂Cl₂; k) 16 equiv of **10**, 2 equiv of Bu₃SnOTf, -78°C; l) HF·pyridine, pyridine, THF, 0°C; m) TESCl, imidazole, CH₂Cl₂, 0°C (61% from **11**); n) 2,4,6-trichlorobenzoyl chloride, *i*Pr₂NEt, benzene, then DMAP, benzene, reflux; o) HF, H₂O, MeCN. (See ref. [4] for abbreviations.)

ester was isolated. Dess–Martin oxidation (92%) followed by buffered Kraus oxidation^[2] and silyl protection (TIPSCl, Et₃N) provided TIPS ester **9** (72%, two steps).

At this stage, introduction of the C₄₄–C₅₁ side chain was undertaken. Epoxidation of the C₄₂–C₄₃ dihydropyran was accomplished with complete chemo- and stereoselectivity (as judged by ¹H NMR analysis) by addition of approximately 1.5 equivalents of dimethyldioxirane. Immediate treatment of the resulting epoxide with allylstannane **10**^[2] (16 equiv) and tributylstannyl triflate (2 equiv) afforded the desired adduct **11**, comprising the full altohyrtin carbon skeleton, in 80–94% yield of isolated product as a single diastereomer. The excess allylstannane was recovered in quantitative yield after column chromatography.

As a prelude to macrocycle formation, a complex series of silyl deprotection operations on ester **11** was implemented. Treatment of this intermediate with buffered HF·pyridine (THF, 0°C), afforded selective deprotection of the TIPS ester at the C-terminus, the C₄₇ TMS ether, and the C₄₁ TES ether,^[15] while retaining the four silyl protecting groups at C₉, C₂₅, C₃₅, and C₃₈ (Scheme 2). Subjection of acid triol **12** to Yamaguchi macrolactonization conditions (2,4,6-trichlorobenzoyl chloride, *i*Pr₂NEt, DMAP)^[16] provided a product tentatively identified as the desired cyclization product bearing a trichlorobenzoyl group at the C₄₇ oxygen. Accordingly, selective protection of acid triol **12** at the C₄₇ hydroxyl was performed prior to macrolactonization to give TES ether **13** (TESCl, imidazole, 0°C, 61% from **11**).^[17]

Exposure of **13** to Yamaguchi conditions provided a single regioisomeric lactone **14** in 86% yield. Deprotection (HF/H₂O/MeCN) provided the desired natural product, which was isolated in 85% yield after reverse phase HPLC. The regiochemical outcome of the macrocyclization was unambiguously established by observation of the coupling patterns among the C₄₀–C₄₄ protons in the COSY spectrum of the deprotected compound ([D₆]DMSO). This allowed an unambiguous assignment of resonances of hydrogen atoms at the C₄₁ and C₄₂ atoms; both the diagnostic downfield shift of the C₄₁H resonance ($\delta = 4.68$ for C₄₁H, 3.04 for C₄₂H) and the presence of a C₄₂H–C₄₂OH coupling verified that macrolactonization had occurred at the C₄₁-hydroxyl group. Our observation that the seco acid **13**, carrying an unprotected hydroxyl function at C₄₂, may be cyclized directly to the macrolactone **14** simplifies the later stages of the synthesis plan. The motivation for attempting this cyclization as part of the original plan was based on the conviction that any protecting group appended to the C₄₂-hydroxyl would add sufficient steric hindrance to the C₄₁-hydroxyl group to impair the macrolactonization process.

The synthetic material was identical to a sample of natural spongistatin 2^[18] as judged by ¹H NMR (500 MHz, CD₃CN), HPLC, electrospray mass spectroscopy, and ultraviolet spectroscopy. Comparison of optical rotations confirmed that the synthetic and natural compounds possessed the same absolute stereochemistry (synthetic: $[\alpha]_D^{24} + 21.3^\circ$ ($c = 0.03$ in MeOH); natural: $[\alpha]_D^{24} + 29.2^\circ$ ($c = 0.12$ in MeOH)). Further, detailed comparison of one-dimensional ¹H NMR and two-dimensional COSY spectra (500 MHz, [D₆]DMSO) confirmed that our synthetic material was also identical to natural altohyrtin C.^[19] We thus conclude that spongistatin 2 and altohyrtin C are identical compounds and speculate that the altohyrtin stereochemical assignment can be extended to the remaining members of the spongipyran family.

The route to altohyrtin C outlined here should be readily applicable to the side-chain congeners altohyrtin A (spongis-

tatin 1) and altohyrtin B,^[3] with dihydropyran **9** serving as a common intermediate for the synthesis of these compounds and additional unnatural analogues.^[20]

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- [3] Representative IC₅₀ values against tumor cell lines: a) M. Kobayashi, S. Aoki, K. Gato, I. Kitagawa, *Chem. Phar. Bull.* **1996**, *44*, 2142–2149; altohyrtin A (X = Cl) 0.01 ng mL⁻¹, altohyrtin B (X = Br) 0.02 ng mL⁻¹, altohyrtin C (X = H) 0.40 ng mL⁻¹; b) R. Bai, G. F. Taylor, Z. A. Cichacz, C. L. Herald, J. A. Kepler, G. R. Pettit, E. Hamel, *Biochemistry* **1995**, *34*, 9714–9721; spongistatin 1 (X = Cl) 0.13 nM, spongistatin 2 (X = H) 0.85 nM.
- [4] Abbreviations: dr = diastereomer ratio, 9-BBN = 9-borabicyclo[3.3.1]nonane, cHex = cyclohexyl, TIPS = triisopropylsilyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TMS = trimethylsilyl, Tr = trityl = triphenylmethyl, Tf = trifluoromethanesulfonyl, Bn = benzyl, LDBB = lithium di-*tert*-butylbiphenyl, DMAP = 4-dimethylaminopyridine, MsCl = methanesulfonyl chloride, LiHMDS = lithium hexamethyldisilazide.
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- [10] Aldehyde **2** was used directly in these experiments without purification. Exposure of **2** to silica gel led to isomerization to the α,β -unsaturated aldehyde.
- [11] The desilylation was interrupted before completion. Some monodesilylated material (hydroxy group at C₃) was recovered (15%).
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- [14] Unchanged aldehyde **5** (11%) was also recovered in diastereomerically pure form.
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- [17] The initial product of the reaction is the corresponding C₁ TES ester, which is cleaved during purification on silica gel.
- [18] We thank Professor G. R. Pettit for providing a natural sample of spongistatin 2.
- [19] We thank Professor M. Kobayashi for providing copies of spectra of natural altohyrtin C.
- [20] While addition of the side chain at an even later stage may be possible, preliminary investigations of an alternative route involving lactonization of the dihydropyran seco acid corresponding to **9** and subsequent side-chain addition suggest that the epoxidation/allylstannane addition sequence may be more difficult.