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

Received: October 22, 1997 [Z11066IE]
German version: *Angew. Chem.* **1997**, *109*, 2954–2957

Keywords: altohyrtin · 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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[19] The two anomers of **25** underwent methanolysis at different rates. The mixture of anomers was subjected to ZnI_2/MeOH at room temperature, which converted the major anomer into **26** (>95:5 α). The minor anomer of **25** was then separated and treated with $MgBr_2 \cdot Et_2O$ in refluxing MeOH to provide additional **26** (2:1 α). The major side product in these reactions was the enone product of sulfone elimination: D. S. Brown, S. V. Ley, S. Vile, M. Thompson, *Tetrahedron* **1991**, *47*, 1329–1342.

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Enantioselective Synthesis of Altohyrtin C (Spongistatin 2): Fragment Assembly and Revision of the Spongistatin 2 Stereochemical Assignment**

David A. Evans,* B. Wesley Trotter, Bernard Côté, Paul J. Coleman, Luiz Carlos Dias, and Andrew N. Tyler

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 altohyrtin C skeleton was addressed (Figure 1). While the C_{44}–C_{51} side chain had been successfully

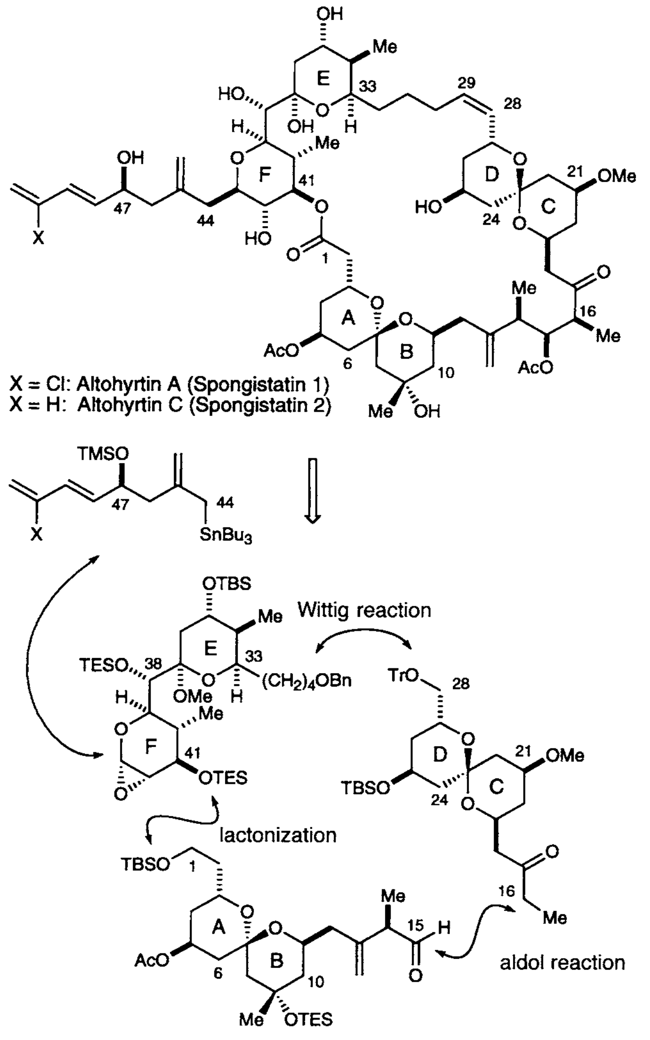

Figure 1. Assembly of the altohyrtin subunits. (See ref. [4] for abbreviations.)

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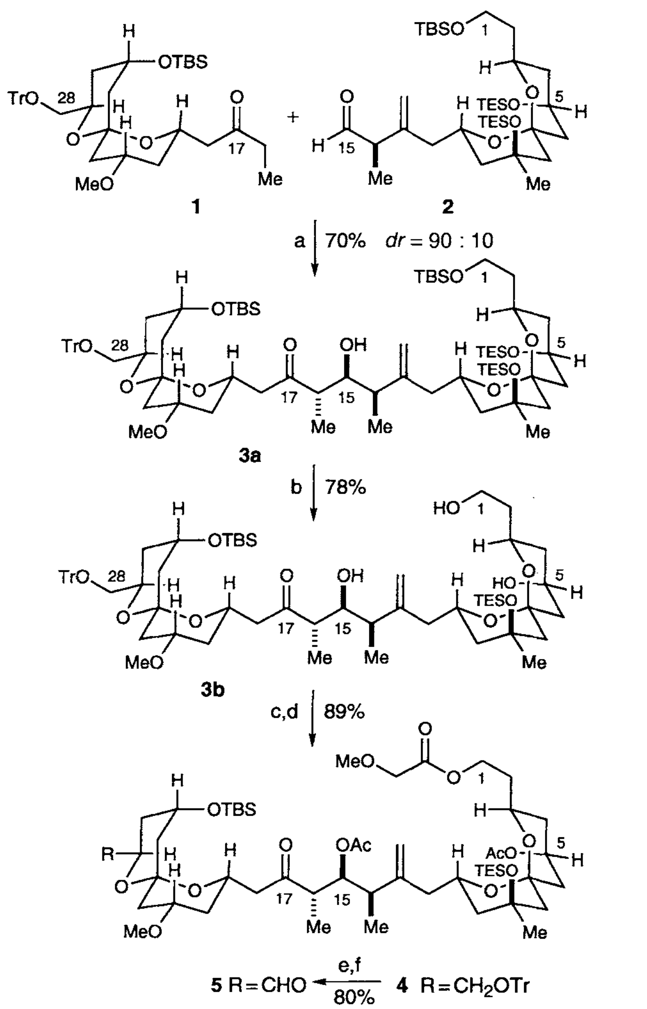
[**] Financial support has been provided by the National Institutes of Health (NIH) and the National Science Foundation (NSF). The NIH BRS Shared Instrumentation Grant Program 1-S10-RR04870 and the NSF (CHE 88-14019) are acknowledged for providing NMR facilities.

  0570-0833/97/3624-2744 $ 17.50+.50/0

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 $C_{44}-C_{51}$ side chain to the fully elaborated ABCDEF system, and a regioselective macrolactonization, which exhibits fortuitous discrimination between the unprotected C_{41} and C_{42} diol functionalities of the F ring.

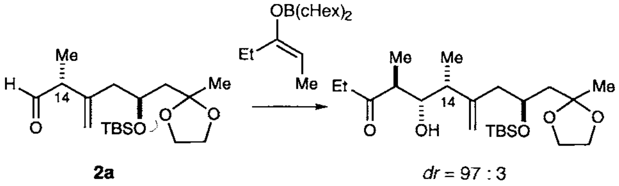
The aldol coupling of CD-spiroketal ethyl ketone **1**[1] with AB-spiroketal aldehyde **2**[1] was first addressed (Scheme 1).[4]



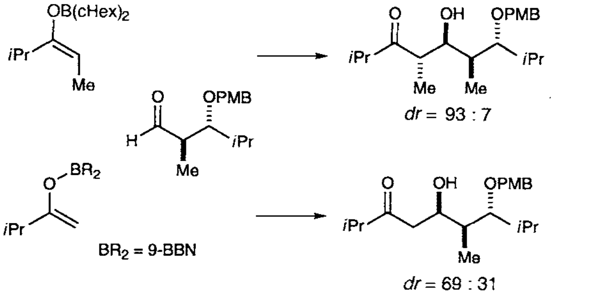
Scheme 1. AB/CD aldol fragment coupling. a) $(cHex)_2BCl$, Et_3N, pentane, 0°C, 90 min, then −78°C, addition of **2**; b) HF·pyridine, THF, 0°C; c) $(MeOCH_2CO)_2O$, iPr_2EtN, CH_2Cl_2; d) Ac_2O, DMAP, pyridine, 22°C; e) Me_2AlCl, CH_2Cl_2, −78°C; f) Dess–Martin periodinane, CH_2Cl_2. (See ref. [4] for abbreviations.)

Ample precedent exists for establishment of the 1,2-*anti* relationship between C_{15} and C_{16} through the use of *E* boron enolates;[5] however, control of the incipient C_{15}-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

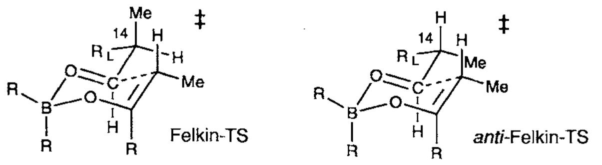

(1)

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


(2)

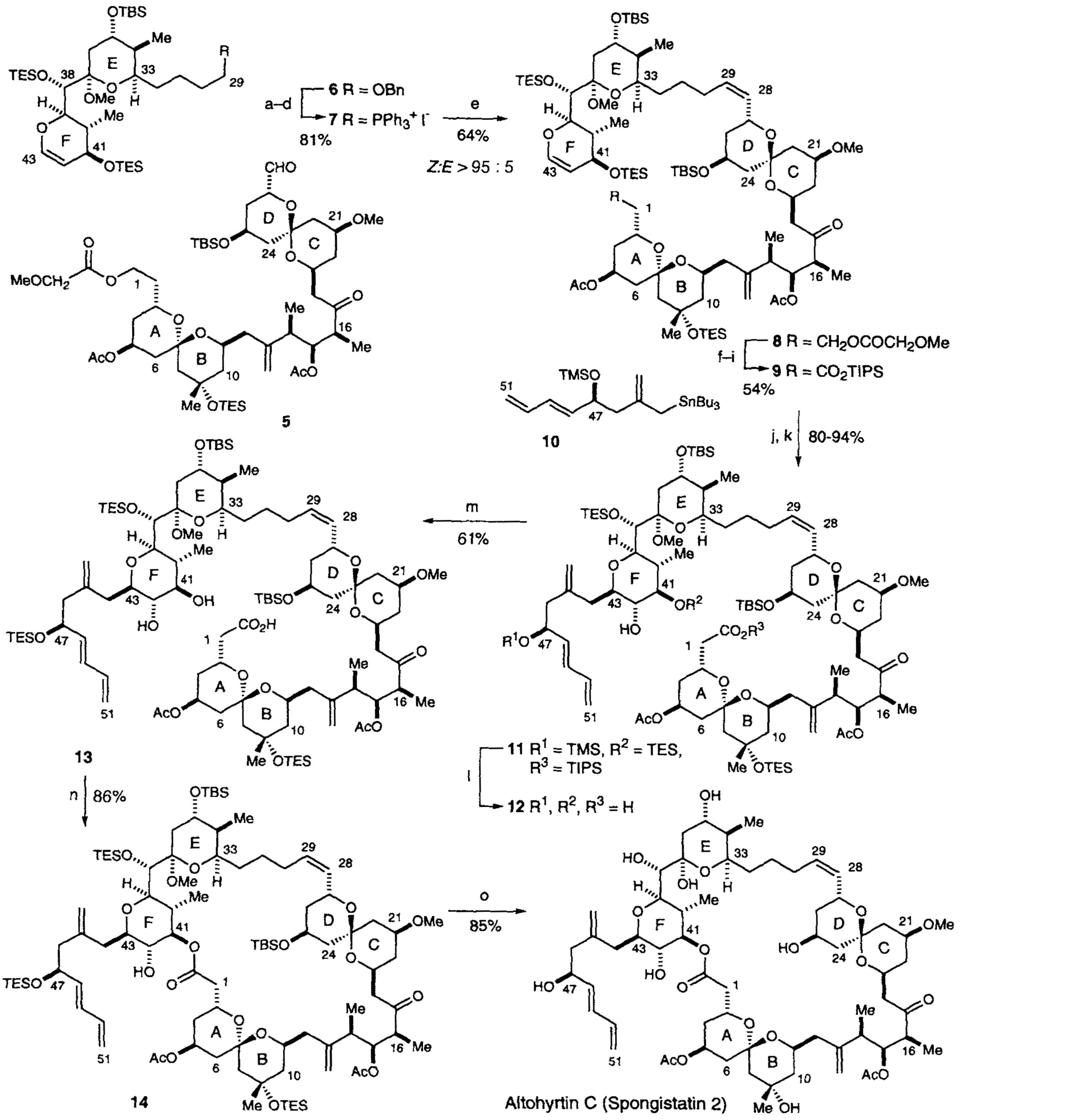
(3)

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


(4)

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 C_5 and C_{15} acetate residues present in the altohyrtin structure was addressed. Selective desilylation of **3a** at C_1 and C_5 with buffered HF·pyridine proceeded in good yield to give triol **3b** (78%).[11] Selective monoacetylation at the C_1-hydroxyl with methoxyacetic anhydride was followed by bis(acylation) at C_5 and C_{15} with acetic anhydride to afford **4** (89%). The selection of the methoxyacetyl residue for interim protection of the C_1 (carboxyl) terminus was made after difficulties were encountered in the selective hydrolysis of the corresponding C_1 acetate, which required extended reaction times. Under these conditions significant β-elimination of the C_{15} acetate residue was noted.

Refunctionalization of the C_1-C_{28} bis(spiroketal) **4** in preparation for the Wittig reaction was then undertaken. Removal of the C_{28} trityl ether with Me_2AlCl[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**[2] (Scheme 2) by successive debenzylation (LDBB, 96%), mesylation (MsCl, Et_3N, 99%), sodium iodide displacement (NaI, acetone, 94%), and displacement by triphenylphosphane (PPh_3, 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 C_1 protecting group was accomplished with NH_3/MeOH in 82% yield. While hydrolysis of the secondary acetates at C_5 and C_{15} was not observed, a minor by-product resulting from β-elimination of the C_{15}



Scheme 2. Final assembly: a) LDBB, THF, −78°C; b) MsCl, Et_3N, CH_2Cl_2; c) NaI, $NaHCO_3$, Na_2SO_3, acetone; d) PPh_3, CH_3CN; e) LiHMDS, THF, −78°C, then **5**, −20°C; f) NH_3, MeOH; g) Dess–Martin periodinane, pyridine, CH_2Cl_2; h) $NaClO_2$, 2-methyl-2-butene, ethyl-1-propenyl ether, *t*BuOH, pH 5.5; i) TIPSCl, Et_3N, THF; j) dimethyldioxirane, acetone, CH_2Cl_2; k) 16 equiv of **10**, 2 equiv of Bu_3SnOTf, −78°C; l) HF·pyridine, pyridine, THF, 0°C; m) TESCl, imidazole, CH_2Cl_2, 0°C (61% from **11**); n) 2,4,6-trichlorobenzoyl chloride, *i*Pr_2NEt, benzene, then DMAP, benzene, reflux; o) HF, H_2O, MeCN. (See ref. [4] for abbreviations.)

  0570-0833/97/3624-2746 $ 17.50+.50/0 *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, No. 24

ester was isolated. Dess–Martin oxidation (92%) followed by buffered Kraus oxidation[2] and silyl protection (TIPSCl, Et_3N) provided TIPS ester **9** (72%, two steps).

At this stage, introduction of the $C_{44}-C_{51}$ side chain was undertaken. Epoxidation of the $C_{42}-C_{43}$ 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 C_{47} TMS ether, and the C_{41} TES ether,[15] while retaining the four silyl protecting groups at C_9, C_{25}, C_{35}, and C_{38} (Scheme 2). Subjection of acid triol **12** to Yamaguchi macrolactonization conditions (2,4,6-trichlorobenzoyl chloride, *i*Pr_2NEt, DMAP)[16] provided a product tentatively identified as the desired cyclization product bearing a trichlorobenzoyl group at the C_{47} oxygen. Accordingly, selective protection of acid triol **12** at the C_{47} 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/H_2O/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 $C_{40}-C_{44}$ protons in the COSY spectrum of the deprotected compound ([D_6]DMSO). This allowed an unambiguous assignment of resonances of hydrogen atoms at the C_{41} and C_{42} atoms; both the diagnostic downfield shift of the $C_{41}H$ resonance ($\delta = 4.68$ for $C_{41}H$, 3.04 for $C_{42}H$) and the presence of a $C_{42}H-C_{42}OH$ coupling verified that macrolactonization had occurred at the C_{41}-hydroxyl group. Our observation that the seco acid **13**, carrying an unprotected hydroxyl function at C_{42}, 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 C_{42}-hydroxyl would add sufficient steric hindrance to the C_{41}-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, CD_3CN), 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° ($c = 0.03$ in MeOH); natural: $[\alpha]_D^{24}$ +29.2° ($c = 0.12$ in MeOH)). Further, detailed comparison of one-dimensional ^1H NMR and two-dimensional COSY spectra (500 MHz, [D_6]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 (spongistatin 1) and altohyrtin B,[3] with dihydropyran **9** serving as a common intermediate for the synthesis of these compounds and additional unnatural analogues.[20]

Received: October 22, 1997 [Z11067IE]
German version: *Angew. Chem.* **1997**, *109*, 2957–2961

Keywords: altohyrtin · antitumor agents · natural products · spongistatin · total synthesis

[1] D. A. Evans, P. J. Coleman, L. C. Dias, *Angew. Chem.* **1997**, *109*, 2951–2954; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2738–2741.

[2] D. A. Evans, B. W. Trotter, B. Côté, P. J. Coleman, *Angew. Chem.* **1997**, *109*, 2954–2957; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2741–2744.

[3] Representative IC_{50} 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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[6] Reaction of the *E* boron enolate derived from **1** with isobutyraldehyde gave low stereoinduction (2:1).

[7] High levels of 1,2-diastereoselection in the addition of various nucleophiles to α-methyl-β-methylene substrates are precedented: a) F. Sato, Y. Takeda, H. Uchiyama, Y. Kobayashi, *J. Chem Soc. Chem. Commun.* **1984**, 1132–1134; b) F. Sato, M. Kusakabe, Y. Kobayashi, *ibid.* **1984**, 1130–1131; c) F. Sato, M. Kusakabe, T. Kato, Y. Kobayashi, *ibid.* **1984**, 1331–1332.

[8] a) D. A. Evans, J. L. Duffy, M. J. Dart, unpublished results; b) D. A. Evans, J. V. Nelson, T. Taber, in *Topics in Stereochem.* **1982**, *13*, pp. 1–115; c) W. R. Roush, *J. Org. Chem.* **1991**, *56*, 4151–4157.

[9] K. Ganesan, H. C. Brown, *J. Org. Chem.* **1993**, *58*, 7162–7169.

[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 C_5) was recovered (15%).

[12] For removal of trityl ethers with Et_2AlCl see H. Köster, N. D. Sinha, *Tetrahedron Lett.* **1982**, *23*, 2641–2644.

[13] The use of aqueous Rochelle's salt in the isolation was essential for removing the organoaluminum salts prior to concentration; otherwise, residual aluminum-promoted spiroketal isomerization to the undesired diaxial anomer took place.

[14] Unchanged aldehyde **5** (11%) was also recovered in diastereomerically pure form.

[15] The moderate yield for this transformation may be partly due to difficulties in isolating the polar acid triol on small scale. TLC analysis of the reaction suggests a clean and selective transformation.

[16] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

[17] The initial product of the reaction is the corresponding C_1 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.

