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

Received: October 22, 1997 [Z11066IE]  
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**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] Recent synthesis of the C<sub>36</sub>–C<sub>46</sub> (F ring) fragment: I. Paterson, L. Keown, *Tetrahedron Lett.* 1997, 38, 5727–5730.
- [3] The relative stereochemical relationship between the C<sub>44</sub>–C<sub>38</sub> (F ring) and the C<sub>27</sub>–C<sub>29</sub> (E ring) segments has been assigned differently in the altohyrtin, spongistatin, and cinachyrolide series: a) M. Kobayashi, S. Aoki, K. Gato, I. Kitagawa, *Chem. Phar. Bull.* 1996, 44, 2142–2149; 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; c) N. Fusetani, K. Shinoda, S. Matsunaga, *J. Am. Chem. Soc.* 1993, 115, 3977–3981.
- [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.
- [5] a) R. Halcomb, S. Danishefsky, *J. Am. Chem. Soc.* 1989, 111, 6661–6666; b) I. Kim, T. Park, S. Hu, K. Abrampah, S. Zhang, P. Livingston, S. Danishefsky, *J. Org. Chem.* 1995, 60, 7716–7717; c) T. Park, I. Kim, S. Hu, M. Bilodeau, J. Randolph, O. Kwon, S. Danishefsky, *J. Am. Chem. Soc.* 1996, 118, 11488–11500.
- [6] D. A. Evans, W. C. Black, *J. Am. Chem. Soc.* 1993, 115, 4497–4513.
- [7] T. Fukuyama, S. C. Lin, L. Li, *J. Am. Chem. Soc.* 1990, 112, 7050–7051.
- [8] S. Hanessian, Y. Guindon, *Carbohydr. Res.* 1980, 86, C3–C6. Addition of Bu<sub>4</sub>NI was found to be unnecessary for this transformation.
- [9] D. A. Evans, J. A. Murry, M. C. Kozlowski, *J. Am. Chem. Soc.* 1996, 118, 5814–5815.
- [10] a) M. Zuger, T. Weller, D. Seebach, *Helv. Chim. Acta* 1980, 63, 2005–2009; b) G. Frater, *Tetrahedron Lett.* 1981, 22, 425–428.
- [11] D. A. Evans, M. J. Dart, J. L. Duffy, M. G. Yang, *J. Am. Chem. Soc.* 1996, 118, 4322–4343.
- [12] J. R. Parikh, W. von E. Doering, *J. Am. Chem. Soc.* 1967, 89, 5505–5507.
- [13] B. S. Bal, W. E. Childers, H. W. Pinnick, *Tetrahedron* 1981, 37, 2091–2096. The use of ethyl-1-propenyl ether prevented decomposition of the acid-sensitive dihydropyran.
- [14] 1-chloro-*N,N*-trimethylpropenylamine: A. Devos, J. Rémon, A.-M. Frisque-Hesbain, A. Colens, L. Ghosez, *J. Chem. Soc. Chem. Commun.* 1979, 1180–1181.
- [15] A. Lubineau, J. Auge, N. Lubin, *J. Chem. Soc. Perkin Trans. 1* 1990, 3011–3015. Diol 19 is prepared in three steps from (*S*)-glyceraldehyde acetonide.
- [16] E. Rouvier, J.-C. Giacomoni, A. Cambon, *Bull. Soc. Chim. France*, 1971, 1717–1723.
- [17] a) L. E. Overman, P. A. Renhowe, *J. Org. Chem.* 1994, 59, 4138–4142; b) S. Weigand, R. Bruckner, *Synthesis* 1996, 475–482.
- [18] a) S. V. Ley, B. Lygo, A. Wonnacott, *Tetrahedron Lett.* 1985, 26, 535–538; b) C. Greck, P. Grice, S. V. Ley, A. Wonnacott, *ibid.* 1986, 27, 5277–5280; c) J.-M. Beau, P. Sinay, *ibid.* 1985, 26, 6185–6188; d) J.-M. Beau, P. Sinay, *ibid.* 1985, 26, 6189–6192; e) J.-M. Beau, P. Sinay, *ibid.* 1985, 26, 6193–6196.
- [19] The two anomers of 25 underwent methanolysis at different rates. The mixture of anomers was subjected to ZnI<sub>2</sub>/MeOH at room temperature, which converted the major anomer into 26 (>95:5 *a*). The minor anomer of 25 was then separated and treated with MgBr<sub>2</sub>·Et<sub>2</sub>O in refluxing MeOH to provide additional 26 (2:1 *a*). 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.
- [20] The authors wish to thank Kevin R. Campos for performing the X-ray analysis of 27.
- [21] M. Kobayashi, S. Aoki, H. Sakai, N. Kihara, T. Sasaki, I. Kitagawa, *Chem. Phar. Bull.* 1993, 41, 989–991.
- [22] D. A. Evans, B. W. Trotter, B. Côté, P. J. Coleman, L. C. Dias, and A. N. Tyler, *Angew. Chem.* 1997, 109, 2957–2961; *Angew. Chem. Int. Ed. Engl.* 1997, 36, 2744–2747.

## 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,<sup>[1]</sup> CD,<sup>[1]</sup> and EF<sup>[2]</sup> spongipyran fragments in hand, the assembly of these subunits to the altohyrtin C skeleton was addressed (Figure 1). While the C<sub>44</sub>–C<sub>51</sub> side chain had been successfully

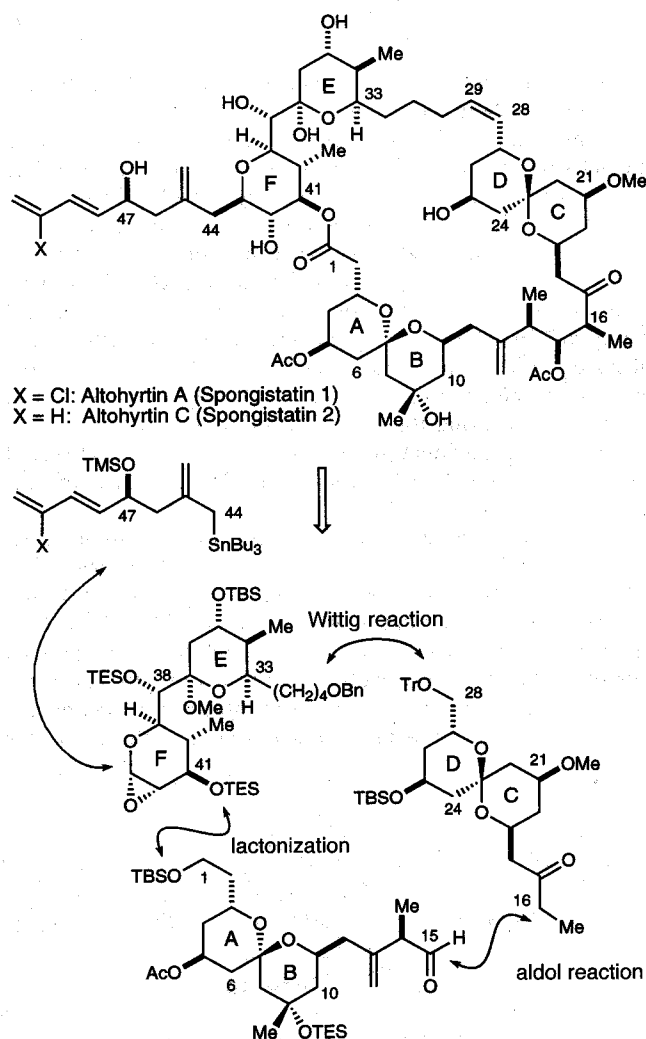


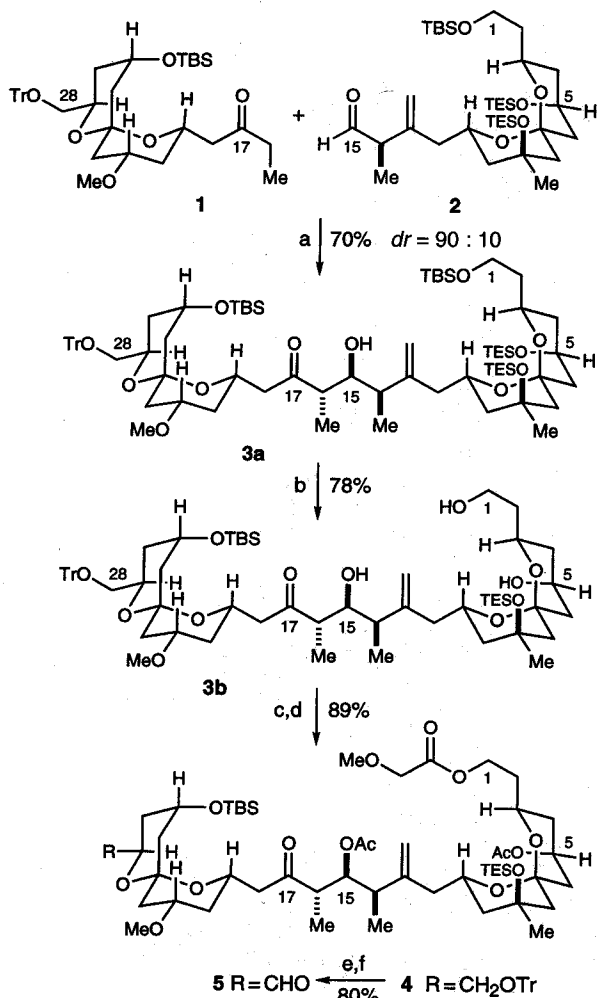
Figure 1. Assembly of the altohyrtin subunits. (See ref. [4] for abbreviations.)

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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.

incorporated into the isolated EF bis(pyran),<sup>[2]</sup> 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,<sup>[3]</sup> 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<sub>44</sub>–C<sub>51</sub> side chain to the fully elaborated ABCDEF system, and a regioselective macrolactonization, which exhibits fortuitous discrimination between the unprotected C<sub>41</sub> and C<sub>42</sub> diol functionalities of the F ring.

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

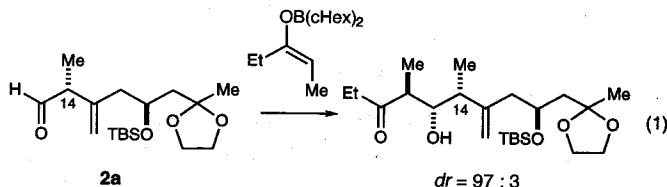


Scheme 1. AB/CD aldol fragment coupling. a) (cHex)<sub>2</sub>BCl, Et<sub>3</sub>N, pentane, 0°C, 90 min, then –78°C, addition of **2**; b) HF·pyridine, THF, 0°C; c) (MeOCH<sub>2</sub>CO)<sub>2</sub>O, *i*Pr<sub>2</sub>EtN, CH<sub>2</sub>Cl<sub>2</sub>; d) Ac<sub>2</sub>O, DMAP, pyridine, 22°C; e) Me<sub>2</sub>AlCl, CH<sub>2</sub>Cl<sub>2</sub>, –78°C; f) Dess–Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>. (See ref. [4] for abbreviations.)

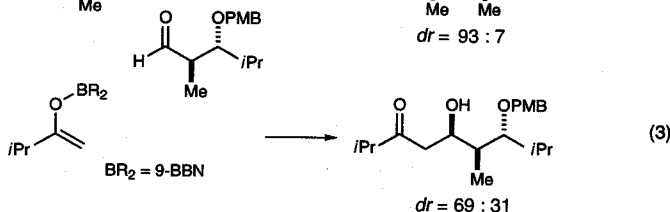
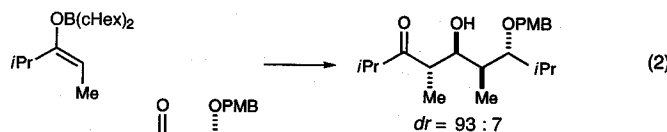
Ample precedent exists for establishment of the 1,2-*anti* relationship between C<sub>15</sub> and C<sub>16</sub> through the use of *E* boron enolates;<sup>[5]</sup> however, control of the incipient C<sub>15</sub>-hydroxyl configuration was a concern. Because each reacting partner in this proposed aldol reaction has stereocenters that can

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

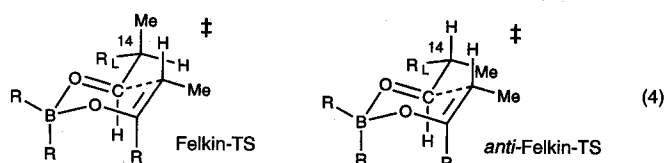
An investigation of the intrinsic diastereofacial bias of the *E* boron enolate derived from **1** indicated that remote chirality on **1** would not significantly influence the stereochemical outcome of the proposed aldol union.<sup>[6]</sup> In contrast, treatment of model aldehyde **2a** with the *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].<sup>[7]</sup> Control experiments demonstrate that *E* substituted boron enolates [Eq. (2)] exhibit enhanced Felkin selectivities in additions to chiral  $\alpha$ -substituted aldehydes relative to their unsubstituted counterparts [Eq. (3)]. This increased selectivity can be



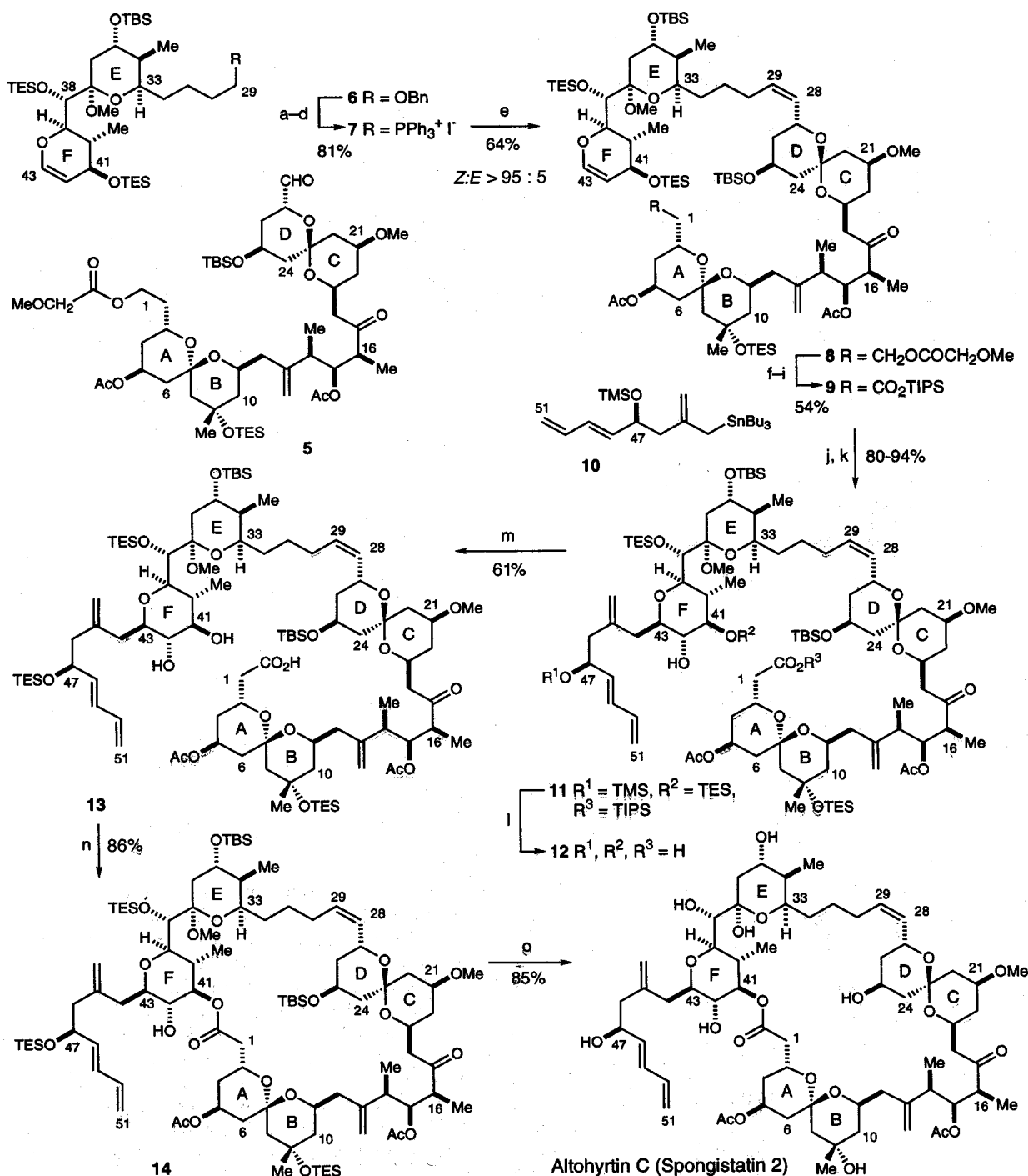
attributed to destabilization of the Felkin *anti* transition state by a developing *syn* pentane interaction [Eq. (4)].<sup>[8]</sup>



In the event, selective formation of the *E* boron enolate of ethyl ketone **1** with dicyclohexylchloroborane,<sup>[9]</sup> followed by the addition of aldehyde **2**<sup>[10]</sup> 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<sub>5</sub> and C<sub>15</sub> acetate residues present in the altohyrtin structure was addressed. Selective desilylation of **3a** at C<sub>1</sub> and C<sub>5</sub> with buffered HF·pyridine proceeded in good yield to give triol **3b** (78%).<sup>[11]</sup> Selective monoacetylation at the C<sub>1</sub>-hydroxyl with methoxyacetic anhydride was followed by bis(acylation) at C<sub>5</sub> and C<sub>15</sub> with acetic anhydride to afford **4** (89%). The selection of the methoxyacetyl residue for interim protection of the C<sub>1</sub> (carboxyl) terminus was made after difficulties were encountered in the selective hydrolysis of the corresponding C<sub>1</sub> acetate, which required extended reaction times. Under these conditions significant  $\beta$ -elimination of the C<sub>15</sub> 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  $\text{Me}_2\text{AlCl}$ <sup>[12]</sup> under carefully controlled conditions afforded the corresponding alcohol,<sup>[13]</sup> 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**<sup>[2]</sup> (Scheme 2) by successive debenzylation (LDBB, 96%), mesylation

( $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ , 99%), sodium iodide displacement ( $\text{NaI}$ , acetone, 94%), and displacement by triphenylphosphane ( $\text{PPh}_3$ ,  $\text{MeCN}$ , 91%). Deprotonation of **7** (1.26 equiv) with  $\text{LiHMDS}$  followed by addition of aldehyde **5** provided the desired Wittig product **8** in 64% yield ( $>95:5$   $Z:E$ ).<sup>[14]</sup> Removal of the methoxyacetate  $C_1$  protecting group was accomplished with  $\text{NH}_3/\text{MeOH}$  in 82% yield. While hydrolysis of the secondary acetates at  $C_5$  and  $C_{15}$  was not observed, a minor by-product resulting from  $\beta$ -elimination of the  $C_{15}$



Scheme 2. Final assembly: a) LDBB, THF,  $-78^\circ\text{C}$ ; b)  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ; c)  $\text{NaI}$ ,  $\text{NaHCO}_3$ ,  $\text{Na}_2\text{SO}_3$ , acetone; d)  $\text{PPh}_3$ ,  $\text{CH}_3\text{CN}$ ; e)  $\text{LiHMDS}$ , THF,  $-78^\circ\text{C}$ , then **5**,  $-20^\circ\text{C}$ ; f)  $\text{NH}_3$ ,  $\text{MeOH}$ ; g) Dess–Martin periodinane, pyridine,  $\text{CH}_2\text{Cl}_2$ ; h)  $\text{NaClO}_2$ , 2-methyl-2-butene, ethyl-1-propenyl ether,  $t\text{BuOH}$ , pH 5.5; i)  $\text{TIPSCl}$ ,  $\text{Et}_3\text{N}$ , THF; j) dimethyldioxirane, acetone,  $\text{CH}_2\text{Cl}_2$ ; k) 16 equiv of **10**, 2 equiv of  $\text{Bu}_3\text{SnOTf}$ ,  $-78^\circ\text{C}$ ; l)  $\text{HF} \cdot \text{pyridine}$ , pyridine, THF,  $0^\circ\text{C}$ ; m)  $\text{TESCl}$ , imidazole,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  (61% from **11**); n) 2,4,6-trichlorobenzoyl chloride,  $i\text{Pr}_2\text{NEt}$ , benzene, then DMAP, benzene, reflux; o)  $\text{HF}$ ,  $\text{H}_2\text{O}$ ,  $\text{MeCN}$ . (See ref. [4] for abbreviations.)

ester was isolated. Dess–Martin oxidation (92 %) followed by buffered Kraus oxidation<sup>[2]</sup> and silyl protection (TIPSCl, Et<sub>3</sub>N) provided TIPS ester **9** (72 %, two steps).

At this stage, introduction of the C<sub>44</sub>–C<sub>51</sub> side chain was undertaken. Epoxidation of the C<sub>42</sub>–C<sub>43</sub> dihydropyran was accomplished with complete chemo- and stereoselectivity (as judged by <sup>1</sup>H NMR analysis) by addition of approximately 1.5 equivalents of dimethyldioxirane. Immediate treatment of the resulting epoxide with allylstannane **10**<sup>[2]</sup> (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<sub>47</sub> TMS ether, and the C<sub>41</sub> TES ether,<sup>[15]</sup> while retaining the four silyl protecting groups at C<sub>9</sub>, C<sub>25</sub>, C<sub>35</sub>, and C<sub>38</sub> (Scheme 2). Subjection of acid triol **12** to Yamaguchi macrolactonization conditions (2,4,6-trichlorobenzoyl chloride, iPr<sub>2</sub>NEt, DMAP)<sup>[16]</sup> provided a product tentatively identified as the desired cyclization product bearing a trichlorobenzoyl group at the C<sub>47</sub> oxygen. Accordingly, selective protection of acid triol **12** at the C<sub>47</sub> hydroxyl was performed prior to macrolactonization to give TES ether **13** (TESCl, imidazole, 0 °C, 61 % from **11**).<sup>[17]</sup>

Exposure of **13** to Yamaguchi conditions provided a single regioisomeric lactone **14** in 86 % yield. Deprotection (HF/H<sub>2</sub>O/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<sub>40</sub>–C<sub>44</sub> protons in the COSY spectrum of the deprotected compound ([D<sub>6</sub>]DMSO). This allowed an unambiguous assignment of resonances of hydrogen atoms at the C<sub>41</sub> and C<sub>42</sub> atoms; both the diagnostic downfield shift of the C<sub>41</sub>H resonance ( $\delta$  = 4.68 for C<sub>41</sub>H, 3.04 for C<sub>42</sub>H) and the presence of a C<sub>42</sub>H–C<sub>42</sub>OH coupling verified that macrolactonization had occurred at the C<sub>41</sub>-hydroxyl group. Our observation that the seco acid **13**, carrying an unprotected hydroxyl function at C<sub>42</sub>, 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<sub>42</sub>-hydroxyl would add sufficient steric hindrance to the C<sub>41</sub>-hydroxyl group to impair the macrolactonization process.

The synthetic material was identical to a sample of natural spongistatin 2<sup>[18]</sup> as judged by <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>CN), 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 <sup>1</sup>H NMR and two-dimensional COSY spectra (500 MHz, [D<sub>6</sub>]DMSO) confirmed that our synthetic material was also identical to natural altohyrtin C.<sup>[19]</sup> 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,<sup>[3]</sup> with dihydropyran **9** serving as a common intermediate for the synthesis of these compounds and additional unnatural analogues.<sup>[20]</sup>

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<sub>50</sub> 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<sup>-1</sup>, altohyrtin B (X = Br) 0.02 ng mL<sup>-1</sup>, altohyrtin C (X = H) 0.40 ng mL<sup>-1</sup>; 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.
- [5] D. A. Evans, E. Vogel, J. V. Nelson, *J. Am. Chem. Soc.* **1979**, *101*, 6120–6123.
- [6] Reaction of the *E* boron enolate derived from **1** with isobutyraldehyde gave low stereoselection (2:1).
- [7] High levels of 1,2-diastereoselection in the addition of various nucleophiles to  $\alpha$ -methyl- $\beta$ -methylene substrates are preceded: 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  $\alpha,\beta$ -unsaturated aldehyde.
- [11] The desilylation was interrupted before completion. Some monodesilylated material (hydroxy group at C<sub>3</sub>) was recovered (15 %).
- [12] For removal of trityl ethers with Et<sub>3</sub>AlCl 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<sub>1</sub> 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.