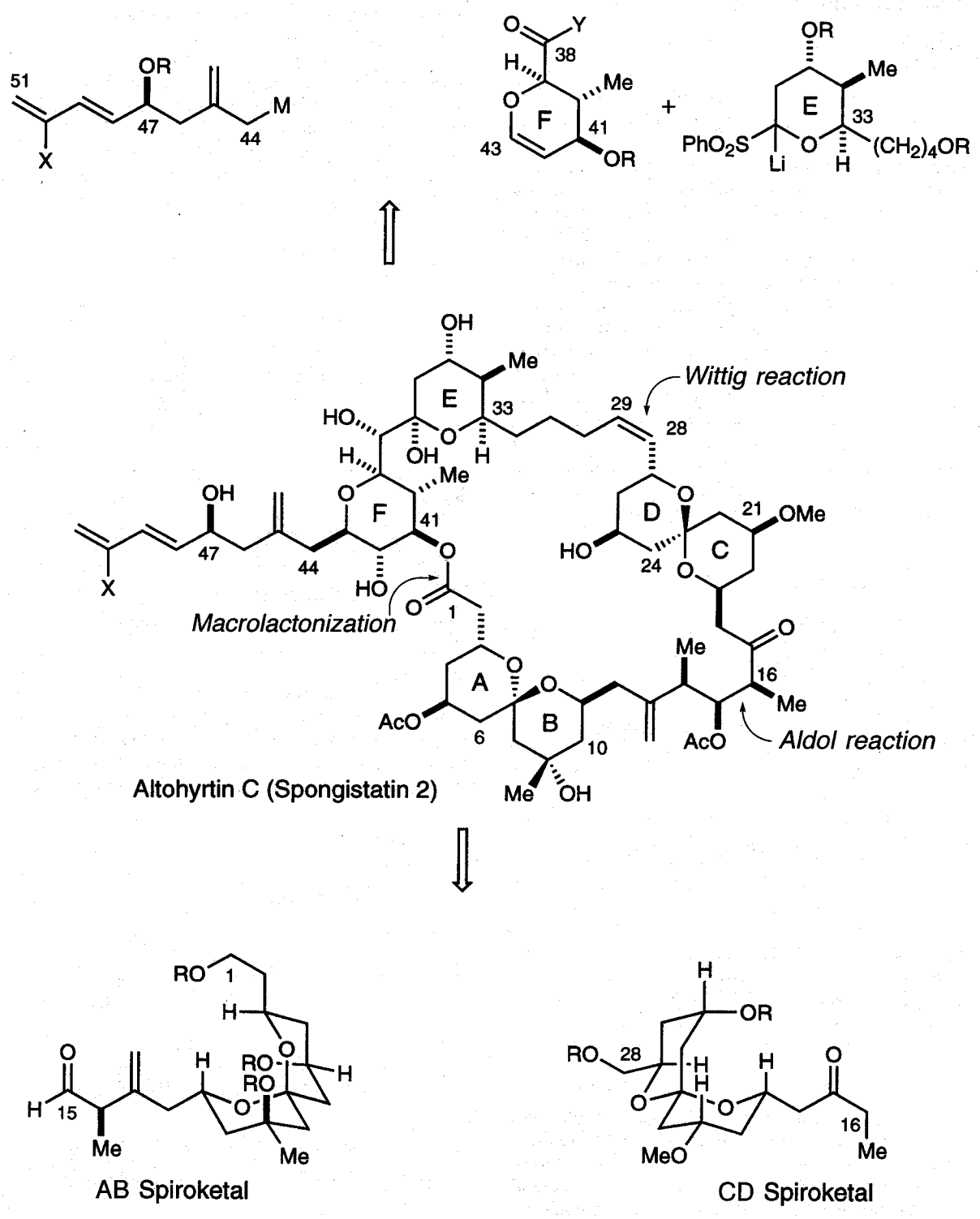


Altohyrtin C (spongistatin 2), whose total synthesis is described in the contributions of Evans et al. on the following pages, is one of a new class of marine natural products isolated at the beginning of the nineties from marine sponges. This class of compounds exhibits excellent antitumor activities.

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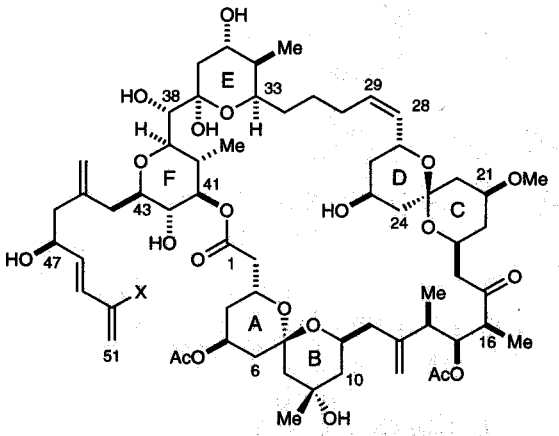
# Enantioselective Synthesis of Altohyrtin C (Spongistatin 2): Synthesis of the AB- and CD-Spiroketal Subunits**

David A. Evans,* Paul J. Coleman, and Luiz Carlos Dias

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

The spongipyran macrolides, a new class of marine natural products, exhibit subnanomolar antitumor activities against a number of human cancer cell lines. Independent bioassay-guided isolation and structure elucidation efforts by the Pettit, Fusetani, and Kitagawa groups have recently identified the structurally related macrolides spongistatins (*Spongia* family),[1] cinachyrolide A (*Cinachyra* family),[2] and the altohyrtins (*Hyrtios* and *Spirastrella* families).[3] The structures of the major constituents in each study, spongistatin 1, cinachyrolide A, and altohyrtin A, were determined on the basis of NMR[4] spectroscopic investigations. While each of these structures has been assigned the same carbon skeleton, the proposed structures differ in the relative stereochemical relationships among the AB and CD spiroketals, rings E and F, and at the $C_{15}$ and $C_{16}$ stereocenters (Figure 1). Since only the Kitagawa altohyrtin structure elucidation included

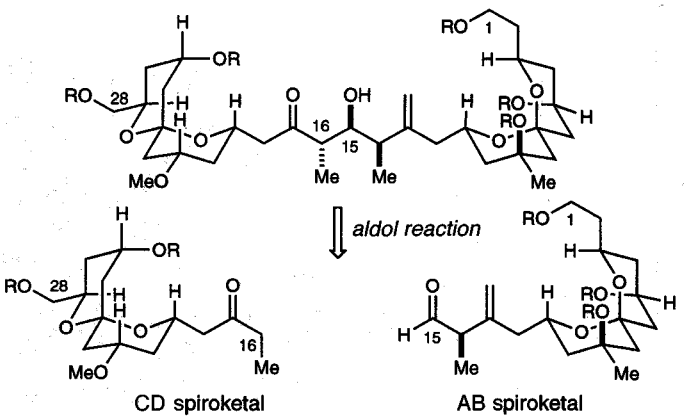


| | X | $IC_{50}$ (KB cell line) |
|---|---|---|
| Altohyrtin A | Cl | 0.01 ng mL$^{-1}$ |
| Altohyrtin B | Br | 0.02 ng mL$^{-1}$ |
| Altohyrtin C | H | 0.40 ng mL$^{-1}$ |

Figure 1. Structures of altohyrtins A–C [3] and their antitumor activities.

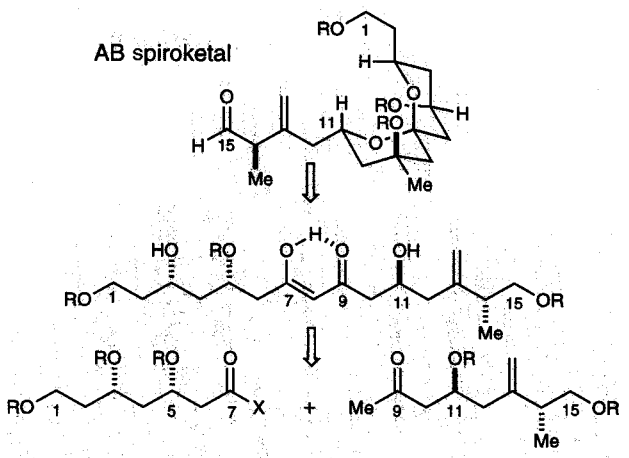
an absolute configuration assignment,[3c,d] it is possible that, because of the lack of an adequate correlation of relative stereochemical assignments between subunits, the stereochemical configurations of some of the indicated skeletal subunits in both spongistatin 1 and cinachyrolide A could be antipodal. This raises the prospect that all three molecules could possess identical stereostructures. On the basis of the preceding discussion, we undertook an enantioselective synthesis of the proposed altohyrtin structure.

The total synthesis of altohyrtin C[3b] described in this and the following two communications verifies the Kitagawa altohyrtin structural assignment, and establishes the identity of altohyrtin C and the independently isolated spongistatin 2.[1b] In this communication, we describe the synthesis of the $C_1-C_{15}$ AB-spiroketal and $C_{16}-C_{28}$ CD-spiroketal altohyrtin subunits, which will be joined through the illustrated aldol fragment coupling reaction (Scheme 1).




Scheme 1. Projected aldol coupling of the altohyrtin AB and CD spiroketals.

The synthesis plan for the $C_1-C_{15}$ AB spiroketal[5] is outlined in Scheme 2. After the illustrated internal deketalization, disconnection of the simplified acyclic precursor at the $C_7-C_8$ bond affords two fragments of similar complexity, the synthesis and assembly of which is now described.




Scheme 2. Retrosynthesis of the AB spiroketal.

Synthesis of $C_1-C_7$ fragment **6** (Scheme 3) began from (*S*) alcohol **1**,[6] prepared from TBS-protected glutaric anhydride.[7] Successive trityl protection and DIBALH reduction afforded aldehyde **2** (81%) along with recovered (*S*)-2-naphthylethanol. Wittig homologation[8] and removal of the silyl protecting group afforded **4**, which was subjected to base-

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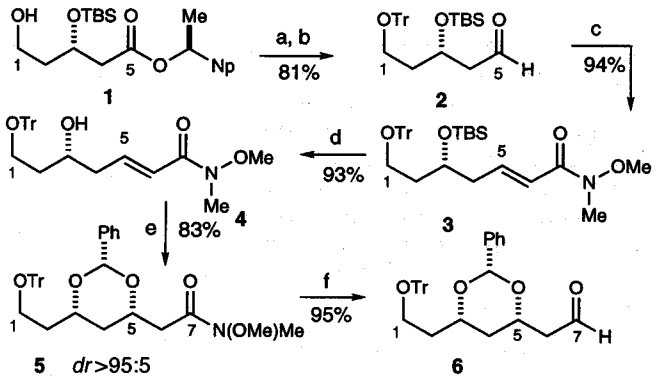
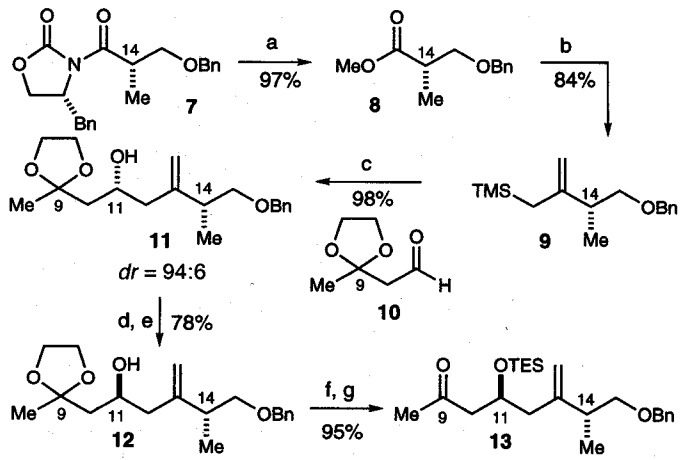


Scheme 3. Synthesis of $C_1-C_7$ fragment **6**. a) TrCl, $Et_3N$, $CH_2Cl_2$; b) DIBALH, toluene, −78°C; c) $Ph_3P$=CHCON(OMe)Me, $CH_2Cl_2$; d) TBAF, THF; e) 1. *t*BuOK, THF, 0°C; 2. PhCHO, 0°C; f) DIBALH, $CH_2Cl_2$, −78°C. (See ref. [4] for abbreviations.)



Scheme 4. Synthesis of $C_8-C_{15}$ fragment **13**. a) $Sm(OTf)_3$ (10 mol%), MeOH; b) 1. $TMSCH_2MgCl$, $CeCl_3$, THF, −78 to +25°C; 2. silica gel, $CH_2Cl_2$, 25°C; c) 1. **9**, $SnCl_4$ (1.1 equiv), $CH_2Cl_2$, −78°C; 2. **10**, $CH_2Cl_2$, 3. $Et_3N$; d) *p*-$NO_2C_6H_4CO_2H$, $PPh_3$, di-*tert*-butyl azodicarboxylate, toluene/THF, 0°C; e) $K_2CO_3$, MeOH; f) PPTS, acetone, reflux; g) TESOTf, 2,6-lutidine, $CH_2Cl_2$, −78°C. (See ref. [4] for abbreviations.)

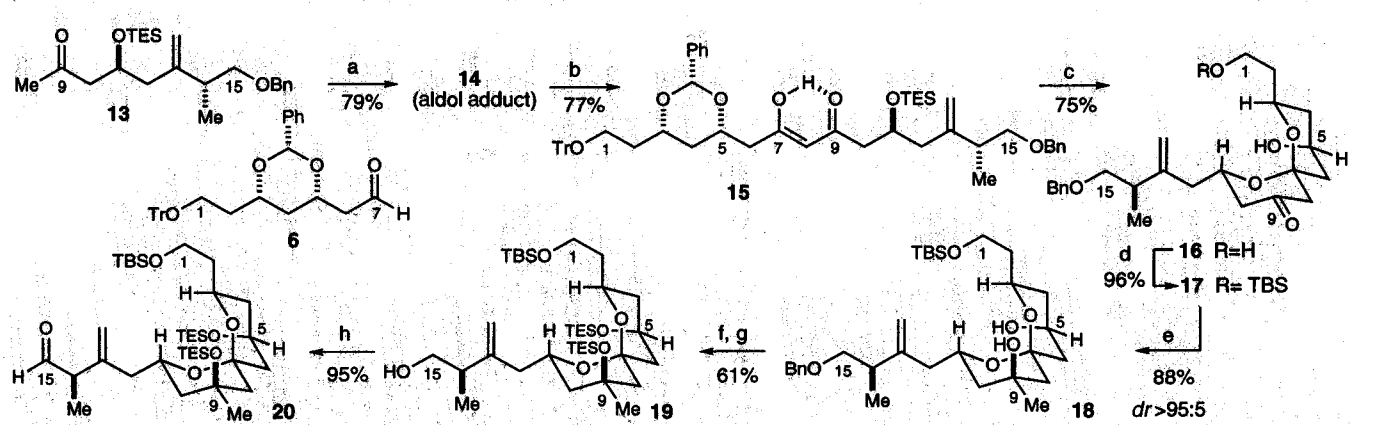
induced, intramolecular heteroconjugate 1,4-addition of the derived benzaldehyde hemiacetal to afford the 1,3-*syn* acetal **5** (83%, *dr* > 95:5).[9] DIBALH reduction provided aldehyde **6** in 56% overall yield for the six-step sequence.

The synthesis of the $C_8-C_{15}$ fragment began with the chiral synthon **8**, readily derived from the oxazolidinone-mediated titanium enolate alkylation product **7** (Scheme 4).[10] Transformation of methyl ester **8** to the derived allylsilane **9** was achieved with (trimethylsilylmethyl)magnesium chloride and cerium(III) chloride, followed by elimination induced by acidic silica gel.[11] The optimal conditions for the allylsilane addition to aldehyde **10**[12] involved pretreatment of **9** with $SnCl_4$ followed by addition of **10**. This protocol provided **11** in 98% yield (*dr* = 94:6). Mitsunobu inversion of the $C_{11}$ alcohol[13] (79%) and subsequent methanolysis (99%) provided **12** possessing the desired absolute stereochemical relationships at both $C_{11}$ and $C_{14}$. Successive ketal hydrolysis and silyl protection afforded the $C_8-C_{15}$ methyl ketone fragment **13** in 53% overall yield for the seven-step sequence.

Union of the $C_1-C_7$ and $C_8-C_{15}$ fragments was initiated by treatment of methyl ketone **13** with dibutylboron triflate and $iPr_2NEt$[14] followed by addition of aldehyde **6** to provide aldol adduct **14** (79%) as a 1:1 mixture of $C_7$ diastereomers (Scheme 5). Oxidation of this mixture with chromium trioxide/pyridine/Celite[15] gave β-diketone **15** in 77% yield along with 12% recovered **14**. Multiple deprotection and spiroketalization of this substrate was achieved by treatment with $HF/H_2O/CH_3CN$. As anticipated, the only spiroketal diastereomer obtained (75%) from this transformation was the thermodynamically favored anomer **16**.[16]

With the AB-spiroketal framework in hand, the construction of the stereocenter at the tertiary atom $C_9$ was achieved by treatment of **17** with methyllithium/cerium trichloride in THF to provide axial alcohol **18** as a single diastereomer (Scheme 5; 86%; *dr* => 95:5).[17] Silyl protection was followed by debenzylation (LDBB)[4,18] to afford the primary alcohol **19** in 61% yield (two steps). Oxidation (Dess–Martin periodinane, pyridine, 95%) to aldehyde **20** proceeded without epimerization of the $C_{14}$ stereocenter. This oxidant is unique in its ability to execute this transformation without conjugating the proximal olefin. Aldehyde **20**, which is too labile for chromatographic purification, must be used immediately in the critical aldol coupling to the CD spiroketal.[19]

If the CD-spiroketal fragment is assembled from an acyclic precursor, the possibility exists for the formation of two diastereomeric structures, designated as $CD_1$ and $CD_2$ (Figure 2). Unlike the "axial–axial" AB spiroketal (analogous to $CD_2$, Figure 2), the CD spiroketal is disposed in an "axial–equatorial" configuration ($CD_1$, Figure 2), which is disfavored in isolated systems on stereoelectronic and steric grounds.[20] While the stabilization of diastereomer $CD_1$ in the altohyrtin



Scheme 5. Construction of the AB spiroketal **20**. a) 1. $Bu_2BOTf$, $iPr_2NEt$, $CH_2Cl_2$, −78°C; 2. **6**, $CH_2Cl_2$, −78°C; b) $CrO_3$, pyridine, Celite, $CH_2Cl_2$; c) $HF/CH_3CN/H_2O$; d) TBSCl, imidazole, $CH_2Cl_2$; e) MeLi, $CeCl_3$, THF, −78°C; f) TESOTf, 2,6-lutidine, $CH_2Cl_2$, −78°C; g) LDBB, THF, −78°C; h) Dess–Martin periodinane, pyridine, $CH_2Cl_2$. (See ref. [4] for abbreviations.)

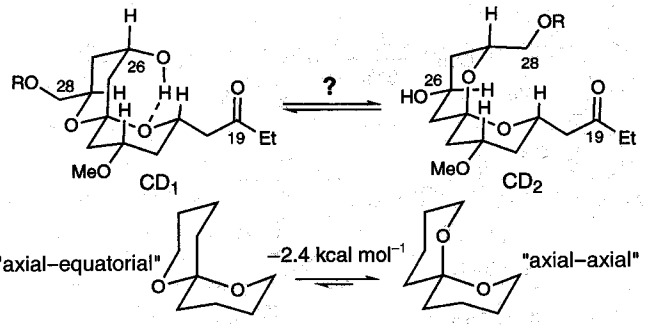


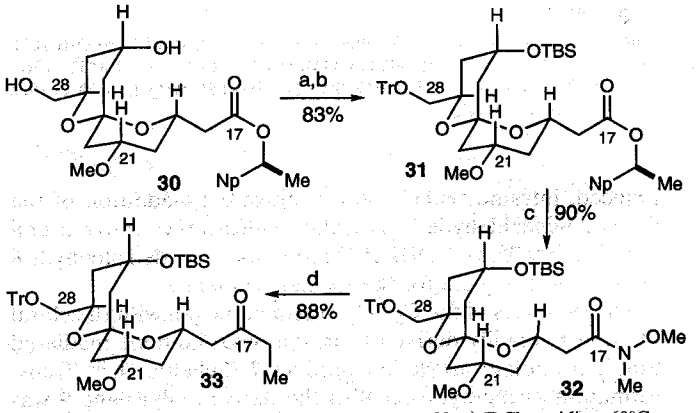

Figure 2. Possible CD-spiroketal configurations.

skeleton may be due to macrocyclic conformational constraints, structural features of the isolated CD system might also aid in enforcing this configuration. In this regard, the potential for an internal hydrogen bond between the $C_{26}$ hydroxyl moiety and the ring-C skeletal oxygen (Figure 2) in spiroketal $CD_1$ was noted.

The synthesis of the CD spiroketal[21] was initiated by the regioselective opening of (*R*)-trityl glycidol[22] (**21**) with divinylcuprate (Scheme 6). The resulting alcohol (**22**) was transformed to methyl ketone **25** by a series of reactions presented in the preceding discussion (cf. Scheme 3). Aldol union of **25**, through its derived boron enolate,[14] with aldehyde **26**[6] afforded the adduct possessing the desired *S* configuration at $C_{21}$ ($dr = 96:4$). Previous work from this laboratory has established that the dominant stereocontrol element in this reaction is the $C_{25}$ alkoxy substituent on the enolate coupling partner and that the trend toward 1,5-*anti* induction is general.[23,24]

Several conventional refunctionalization steps were next carried out prior to spirocyclization. Methylation[25] of aldol adduct **27** afforded spirocyclization substrate **28**. The subsequent deprotection of the four oxygen protecting groups (at $C_{19}$, $C_{25}$, $C_{27}$, and $C_{28}$) and concomitant spirocyclization were achieved upon treatment of **28** with camphorsulfonic acid in a methanol/dichloromethane solution (1/15, 13 h, 25°C).[26] Two separable isomeric spiroketal products **29** and **30** (ratio 6:1) were isolated in 70% yield. A by-product that incorporated a second methyl ether at $C_{25}$ was also identified (18%).[27] Diagnostic NOE experiments provided unequivocal stereochemical assignments for both spiroketal diastereomers.[28] The major isomer **29** possesses the undesired spirane ring fusion ($CD_2$, Figure 2). Equilibration[29] with three equivalents of $Mg(O_2CCF_3)_2$ in $CF_3CO_2H/CH_2Cl_2$ gave a 2.2:1 mixture of isomers **30** and **29**. We believe that the derived magnesium complexes of the two spiroketals are the species undergoing equilibration, thus altering the equilibrium ratio of spiroketal diastereomers.[30] Other conditions afforded higher ratios but lower yields of the isolated spiroketal ($ZnCl_2$, $CH_2Cl_2$, 22°C; **30**:**29** = 4.3:1).

Transformation of **30** to the desired CD-spiroketal ethyl ketone **33** (Scheme 7) was achieved by selective protection of the $C_{28}$ hydroxyl group of **30** as its trityl ether, TBS-silylation




Scheme 7. Synthesis of CD-spiroketal ethyl ketone **33**. a) TrCl, pyridine, 60°C; b) TBSOTf, 2,6-lutidine; c) MeO(Me)NH·HCl, EtMgBr, THF, −10°C; d) EtMgBr, THF, 0°C. (See ref. [4] for abbreviations.)

at $C_{25}$, and transformation of the $C_{17}$ ester functionality to an ethyl ketone through its corresponding Weinreb amide **32**.[31] Attempted transamidation of ester **31** under Lewis acidic conditions (MeONHMe·HCl, $AlMe_3$)[32] afforded none of the desired amide and led to appreciable epimerization of the spiroketal stereocenter.

The described syntheses of the AB- and CD-spiroketal subunits provide efficient routes to significant quantities of these portions of the spongipyran architecture. Realization of the aldol coupling of these fragments and further elaboration to altohyrtin C are discussed in a subsequent communication.[19]

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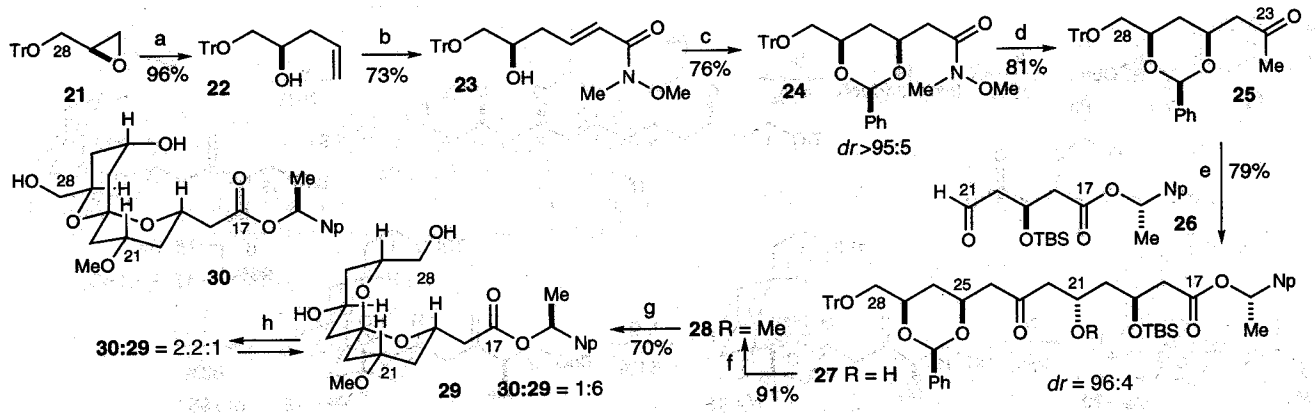


Scheme 6. Synthesis of CD spiroketal **30**. a) Vinylmagnesium bromide, CuI, THF, −78°C; b) $O_3$, $CH_2Cl_2$, $Ph_3P$, −78°C, then $Ph_3P$=CHCON(OMe)Me; c) *t*BuOK, PhCHO, 0°C; d) MeLi, THF, −78°C; e) $Bu_2BOTf$, *i*$Pr_2NEt$, $Et_2O$, −110°C, then **26**; f) $Me_3OBF_4$, 2,6-di-*tert*-butyl-4-methylpyridine; g) CSA, $MeOH/CH_2Cl_2$; h) 3 equiv of $Mg(O_2CCF_3)_2/CF_3CO_2H$, $CH_2Cl_2$: **30** (53%), recovered **29** (24%). (See ref. [4] for abbreviations.)

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**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; Np = 2-naphthyl; TBAF = tetrabutylammonium fluoride; Tr = trityl = triphenylmethyl; Tf = trifluoromethanesulfonyl; Bn = benzyl; PPTS = pyridinium *p*-toluenesulfonate; CSA = camphorsulfonic acid; LDBB = di-*tert*-butylbiphenyllithium.

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[16] The configuration of **16** was determined by NOESY experiments performed on the corresponding $C_5$ acetate.

[17] Similar alkylmetal additions to AB spiroketones have been documented; see reference 5.

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[22] (*R*)-Trityl glycidol was prepared in 95% *ee* by Sharpless asymmetric epoxidation of allyl alcohol and in situ tritylation. Recrystallization provided the enantiomerically enriched compound: H. S. Hendrickson, E. K. Hendrickson, *Chemistry and Physics of Lipids*, **1990**, *53*, 115–120.

[23] Under these reaction conditions, aldehyde **26** has no preferred diastereoface. Coupling of methyl ketone **25** with the antipode of **26** under the same reaction conditions also gives a 1,5-*anti* product.

[24] The diastereoselectivity for this methyl ketone aldol coupling is 9.6:1 at −78°C. At −110°C, the diastereoselectivity increases to 22:1. a) D. A. Evans, P. J. Coleman, B. Cote, *J. Org. Chem.* **1997**, *62*, 788–789; b) I. Paterson, K. R. Gibson, R. M. Oballa, *Tetrahedron Lett.* **1996**, *37*, 8585–8588.

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[28] Stereochemical assignments were supported by NOE experiments (1D and 2D) and $^1$H NMR measurements. An NOE enhancement between $H_{19}$ and $H_{27}$ was observed in the axial–equatorial isomer **30**. The NMR signal for $H_{25}$ was illuminating as well: **29**: $\delta = 3.9$ (m, $J(H_{25}, H_{26ax}) = 11$ Hz); **30**: $\delta = 3.9$ ppm (t, $J = 3.2$ Hz).

[29] Due to the sensitivity of spiroketal substrate **29** to acidic media, equilibration experiments were kept short (1–3 h). In dichloromethane/CSA, **29** equilibrated to a 1:1 (29:30) mixture of spiroisomers after 3 h.

[30] Presumably, the $C_{25}$ hydroxyl is assisting in the equilibration to afford **30** by participating in an internal chelate with the metal cation and proximally positioned anomeric oxygen. For related cases see a) D. R. Williams, P. A. Jass, R. D. Gaston, *Tetrahedron Lett.* **1993**, *34*, 3231–3234; b) M. J. Kurth, E. G. Brown, E. Hendra, H. Hope, *J. Org. Chem.* **1985**, *50*, 1115–1117; c) S. L. Schreiber, T. L. Sommer, K. Satake, *Tetrahedron Lett.* **1985**, *26*, 17–20.

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# Enantioselective Synthesis of Altohyrtin C (Spongistatin 2): Synthesis of the EF-Bis(pyran) Subunit**

David A. Evans,* B. Wesley Trotter, Bernard Côté, and Paul J. Coleman

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

Concurrent with the syntheses of the AB- and CD-spiroketal subunits of the altohyrtin skeleton,[1] the synthesis of the altohyrtin $C_{29}$–$C_{51}$ EF-bis(pyran) fragment was addressed. The principal subunits for this portion of the altohyrtin skeleton are illustrated in Figure 1. The retrosynthetic proposal focuses on the incorporation of the $C_{44}$–$C_{51}$ side chains (X = H, Cl, Br) as allylmetal nucleophiles into the illustrated F-ring epoxide at a late stage in the synthesis. In turn, this bis(pyran) is assembled through acylation of the illustrated E-ring sulfonyl anion with an F-ring[2] carboxylic

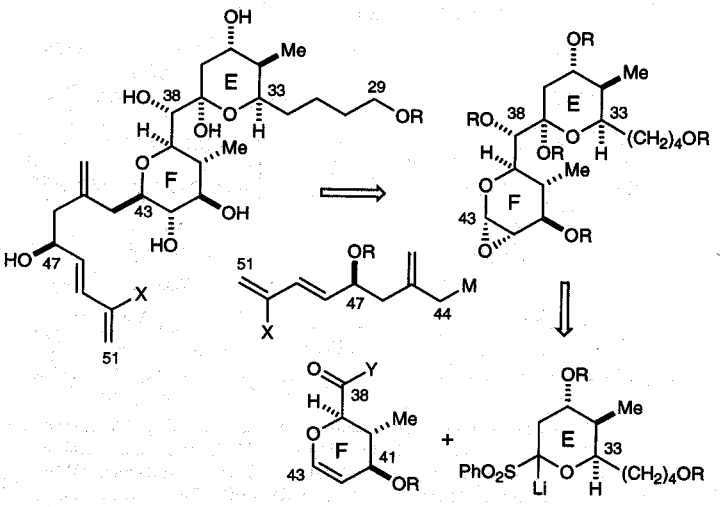


Figure 1. Retrosynthesis of the EF-bis(pyran) subunit.

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