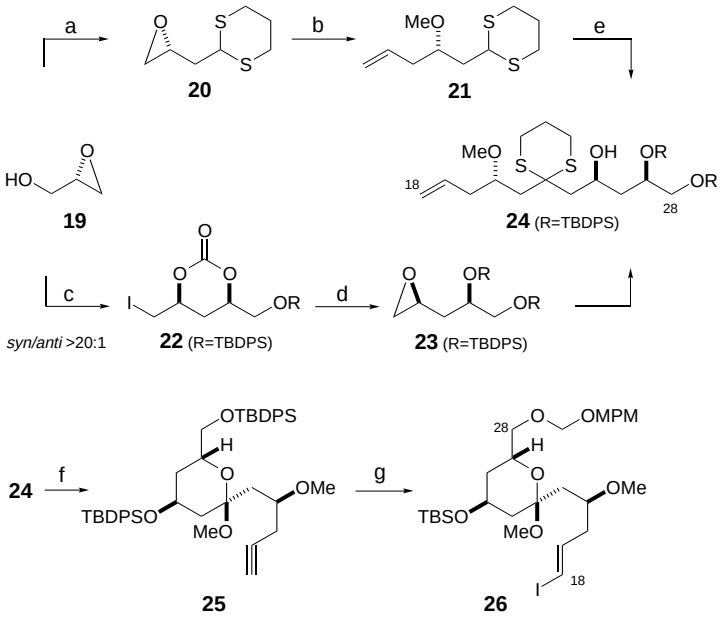
cyanocuprate[17] derived from **13**, to yield the diol. After cleavage of the silyl protecting groups, **14** was subjected to NIS-induced dithiane deprotection to form the single spiroketal **15** in good overall yield. Based on literature precedent,[18] we anticipated spiroketal formation to be stereoselective in the desired sense; indeed, NOE experiments (NOE = nuclear Overhauser enhancement) confirmed this configuration at the spirocenter. By routine synthetic operations the protecting groups of alcohols in **15** were then adjusted resulting in tetraol **16**. The protecting groups at the C1 and C17 primary alcohols were differentiated, and the C9 tertiary alcohol was left unprotected. Since the requisite C5 and C15 acetates were compatible with the remaining synthetic operations, they were installed at this juncture.[19] The C15 acetyl group was found to migrate readily to the C17 primary alcohol once the TBS protecting group was removed. Therefore, the C17 alcohol generated from **17** was immediately subjected without purification to Dess–Martin oxidation[20] to furnish aldehyde **18**.

Scheme 3 summarizes the synthesis of the *trans* vinyl iodide **26**.[21] The key reactions used in this sequence were fundamentally the same as those described for the synthesis of the C1–C17 segment. However, several comments are in order.



Scheme 3. Synthesis of the C18–C28 fragment: a) Et_3N, TBSCl, DMAP, CH_2Cl_2, 90%; 1,3-dithiane, *n*BuLi, THF, −20°C, then DMPU, then epoxide, THF, −78 → −20°C, 83%; TBAF, THF, quant.; NaH, THF, 0°C, Ts-im, 0°C, 79%; b) CuCN, vinyllithium, −78°C, then **20**, THF, −20 → 0°C, 85%; NaH, MeI, THF, 0°C, 90%; c) Et_3N, TBDPSCl, DMAP, CH_2Cl_2, 90%; CuCN, vinyllithium, −78°C, then epoxide, Et_2O, −30 → 0°C, 92%; *n*BuLi, Et_2O, BOC–ON, THF, −78 → 20°C, 96%; IBr, PhMe, −78 → 0°C, 78%; d) K_2CO_3, MeOH, 78%; imidazole, TBDPSCl, CH_2Cl_2, 91%; e) *t*BuONa, *n*BuLi, pentane, 0 → 20°C, then −78°C, **21**, THF, −78°C, then **23**, THF, −78 → −20°C, 54% and 44% recovered **23**; f) TBAF, THF, 0°C, 92%; Et_3N, TBDPSCl, DMAP, CH_2Cl_2, 72%; NIS, $CaCO_3$, MeOH, 0°C, 78%; imidazole, TBDPSCl, CH_2Cl_2, 86%; NMO, OsO_4, acetone/H_2O; $NaIO_4$, MeOH/(pH 7 phosphate buffer), 0 → 20°C; DAMP, *t*BuOK, THF, −78°C, then aldehyde, THF, −78°C, 79% over 3 steps; g) nBu_3SnH, AIBN, toluene, 105°C, 67%; $CaCO_3$, NIS, THF, quant.; TBAF, THF, 92%; iPr_2NEt, $MPMOCH_2Cl$,[36] CH_2Cl_2, 98%; TBAF, THF, quant.; imidazole, TBSCl, CH_2Cl_2, 99%.

First, while ring-opening of **20** was accomplished with the anion of TMS-acetylene allowing earlier incorporation of the alkyne moiety, clean lithiation of the resultant dithiane proved difficult. Second, deprotection of the dithiane group (step f) resulted in a single methyl ketal, whose configuration was tentatively assigned as indicated but was not established experimentally. Third, the hydrostannylation of **25**, followed by NIS treatment, yielded mainly the expected product, along with a small amount of its regio- and stereoisomers. Finally, the C25 TBDPS protecting group was required for efficient synthesis of **25** but the final deprotection to form altohyrtin A (**1**) necessitated substitution to the more labile TBS protecting group.

The completion of the synthesis of **32** is illustrated in Scheme 4. The Ni^{II}/Cr^{II}-mediated coupling[12] of **26** with **18** proceeded smoothly to yield the two expected allylic alcohols, which were oxidized to α,β-unsaturated ketone **27**. After hydrolysis to the C23 hemiketal, the crucial intramolecular Michael cyclization was effected with Triton-B to furnish spiroketal **28** with concomitant deprotection of the C1 methoxyacetate.[22] Out of four possible products, only one diastereomer was isolated. ROESY data on the C1 TBS ether of **28** clearly demonstrated the C19 stereocenter to be desired but the C23 spirostereocenter to be undesired.[23, 24] In light of recent work by Heathcock,[7b] the stereochemical outcome at this spirocenter was not surprising. This stereocenter was configurationally stable under acidic conditions with a protected C25 alcohol, but was expected to epimerize readily if the C25 alcohol was deprotected.[7b] Indeed, deprotection of **28** with HF · py in CH_3CN provided a separable 1:1 mixture of desired C23 diastereomer **30** and undesired **29**, which could be recycled efficiently under acidic conditions (HF · py/CH_3CN or CSA/CH_2Cl_2). Reprotection of the C1 and C25 alcohols with TBSOTf proceeded without compromising the integrity of C23 spiroketal stereocenter.

NMR (NOE) data on the C1 TBS-ether of **31** clearly demonstrated the desired configurations at C19 and C23.[23,24] Selective deprotection of the C1 TBS group, followed by TPAP[25] oxidation, $NaClO_2$[26] oxidation, TBDPSCl protection,[27] and finally cleavage of the C28 protecting group with DDQ[28] furnished the desired product. Interestingly, a small amount of the C23 epimeric spiroketal was isolated during the DDQ deprotection step. Finally, Dess–Martin oxidation of the C28 primary alcohol furnished **32**, the ABCD unit of the target.

Using the methods disclosed in the following communication, we completed the total synthesis of the C23 epimer of altohyrtin A from intermediate **28** with the hope that the C23 stereocenter might be equilibrated to the natural configuration. Although both altohyrtin A and its C23 epimer were relatively stable under acidic conditions (HF · py/THF, CSA/CH_2Cl_2, or HCl/$CHCl_3$), there was no evidence of inversion at the C23 stereocenter.[29] This experiment demonstrated that the macrolactone prevents epimerization at the C23 position, suggesting that the correct C23 configuration must be installed prior to macrolactonization.

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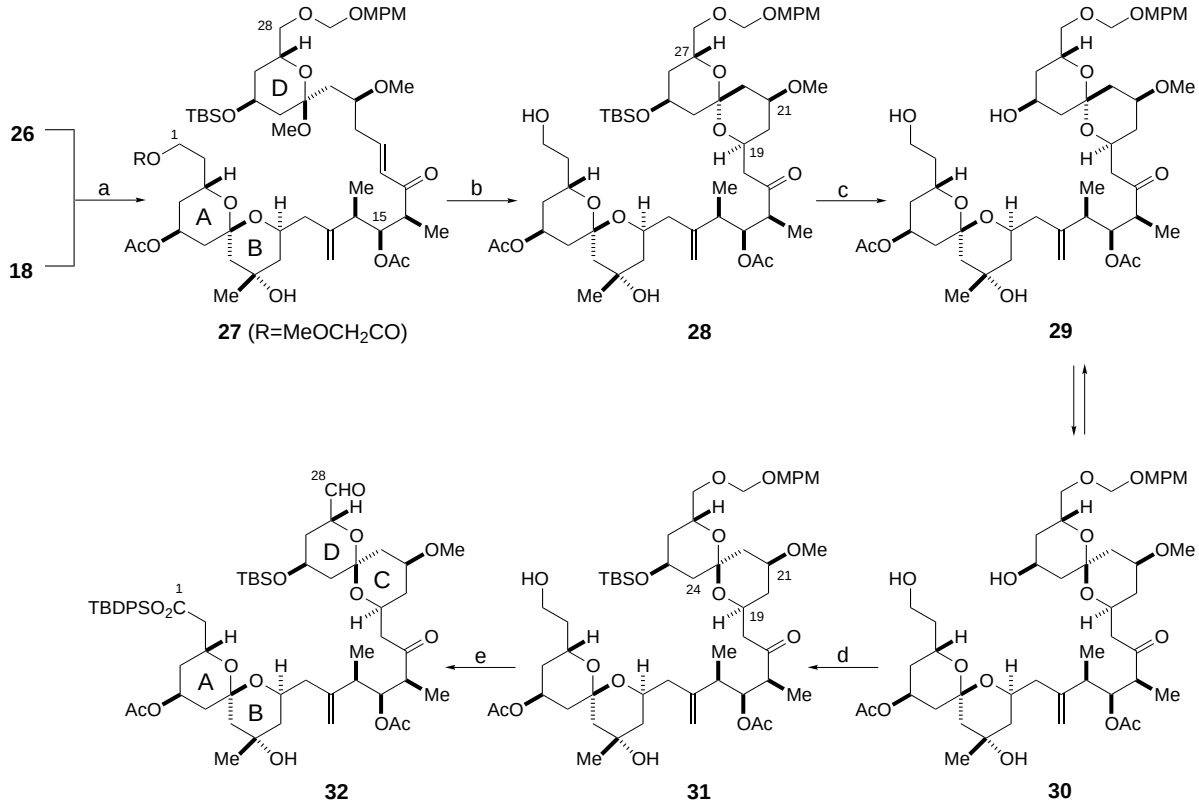

Scheme 4. Synthesis of the C1 – C28 fragment: a) $NiCl_2/CrCl_2$, (–)-bispyridinyl ligand,[12c] THF, 86 %; Dess – Martin periodinane, py, CH_2Cl_2, 83 %; b) PPTS, acetone/H_2O; Triton-B, MeOH/ MeOAc, 0 °C, 50 % over 2 steps; c) HF · py, CH_3CN, 25 % (an additional 25 % was obtained by equilibration of the C23 epimer **29** with CSA/CH_2Cl_2); d) 2,6-lutidine, TBSOTf, –78 °C, 79 %; HF · py/py/THF, 82 %; e) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2; $NaClO_2$, NaH_2PO_4, *t*BuOH/2-methyl-2-butene, 83 % over 2 steps; Et_3N, TBDPSCl, CH_2Cl_2, 82 %; DDQ, CH_2Cl_2/H_2O, 53 %; Dess – Martin periodinane, py, CH_2Cl_2, 81 %.

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

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[13] Satisfactory spectroscopic data (^1H and ^{13}C NMR, MS, and others) were obtained for all new compounds.

[14] Abbreviations used: AIBN = 2,2′-azobisisobutyronitrile; BOC-ON = 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile; CSA = 10-camphorsulfonic acid; DAMP = dimethyl(diazomethyl)phosphonate; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; diketene acetone adduct = 2,2,6-trimethyl-4*H*-1,3-dioxan-4-one; DMAP = 4-dimethylaminopyridine; DMDO = dimethyldioxirane; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone; HMPA = hexamethylphosphoramide; HF · py = hydrogen fluoride pyridine complex; *B*-I-9-BBN = *B*-iodo-9-borabicyclo[3.3.1]nonane; LDA = lithium diisopropylamide; MPM = *para*-methoxybenzyl; MsCl = methanesulfonyl

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chloride; NCS = *N*-chlorosuccinimide; NIS = *N*-iodosuccinimide; NMO = *N*-methylmorpholine *N*-oxide; Piv = pivaloyl; PPTS = pyridinium *p*-toluenesulphonate; TBAF = tetrabutylammonium fluoride; TBAI = tetrabutylammonium iodide; TBDPS = *tert*-butyldiphenylsilyl; TBS = *tert*-butyldimethylsilyl; Tf = triflate; TIPS = triisopropylsilyl; TPAP = tetrapropylammonium perruthenate; Ts-im = *para*-toluenesulphonyl imidazole; Ts_2O = *para*-toluenesulfonic anhydride.

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[21] The *cis* vinyl iodide corresponding to **26** might be suitable for the following key Michael cyclization, though this was not tested.

[22] The yields (50% to 80%) for the hydrolysis and subsequent Michael addition depended on the protecting group arrangement. A substrate bearing TBS groups on the C5, C9, and C15 alcohols and TBDPS on the C25 alcohol gave the best result. One of the by-products isolated in the case of **27** was the α,β-unsaturated ketone resulting from elimination of the C15 acetate.

[23] These experiments were performed by Dr. Yuan Wang at Eisai Research Institute, Andover, Massachussetts.

[24] For the C1 TBS ether of **28**, distinct NOEs between the C19 and C21 protons and between the C27 and C22(eq) protons were observed. For the C1 TBS ether of **31**, distinct NOEs between the C19 and C21 protons and between the C19 and C24(eq) protons were observed.

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Total Synthesis of Altohyrtin A (Spongistatin 1): Part 2**

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In the preceding communication we reported the synthesis of the ABCD unit of altohyrtin A.[1] We will now present the synthesis of the EF unit and the completion of a total synthesis of altohyrtin A.

The first step in the retrosynthetic analysis of EF fragment **B** was the C37 – C38 bond disconnection. In the synthetic direction, it was expected that this bond formation could be realized by nucleophilic addition of glycal carbanion **F** to C38 aldehyde **G**, followed by acid-catalyzed methanolysis of the resultant glycal. Fragment **G** was then disconnected into carbanion **I** and glycal epoxide **H**, which should be available from the corresponding glycal **J**.[2] We were particularly interested in this disconnection strategy because of the obvious structural similarity between **F** and **J**; **F** and **J** might be synthesized with similar chemistry or even via a common intermediate. These glycals could be prepared from the corresponding acyclic precursors **F′** and **J′**, which contain a typical polypropionate/acetate arrangement of functional groups. Among the many synthetic methods known for the preparation of polypropionates/acetates, the chemistry developed by Roush et al.[3] and by Brown et al.[4] were chosen. The proposed carbanion **I**, or its synthetic precursor, contained the novel chlorodiene functionality which, to the best of our knowledge, had never been synthesized before. It was anticipated that the chlorodiene moiety could be incorporated by the addition of an organometallic species, derived from 2,3-dichloropropene, to aldehyde **L**, followed by dehydration.

As illustrated in Scheme 1, the E-ring building block was synthesized by utilizing sequential crotyl- and allyl-boronate chemistry.[5, 6] While both the Brown and Roush methods gave the desired adducts, the Brown methodology was superior in terms of stereoselectivity. After protection of the C35 alcohol of **5** and cleavage of the C33 benzyl protecting group, **6** was transformed into glycal **7** by means of a β-ketoester to facilitate the thermally induced elimination. Finally, glycal **7** was converted into iodoglycal **8** with the method developed by Freisen;[7] the TIPS protecting groups at C29 and C35 were required for clean lithiation of the glycal. Alternatively, **6** was

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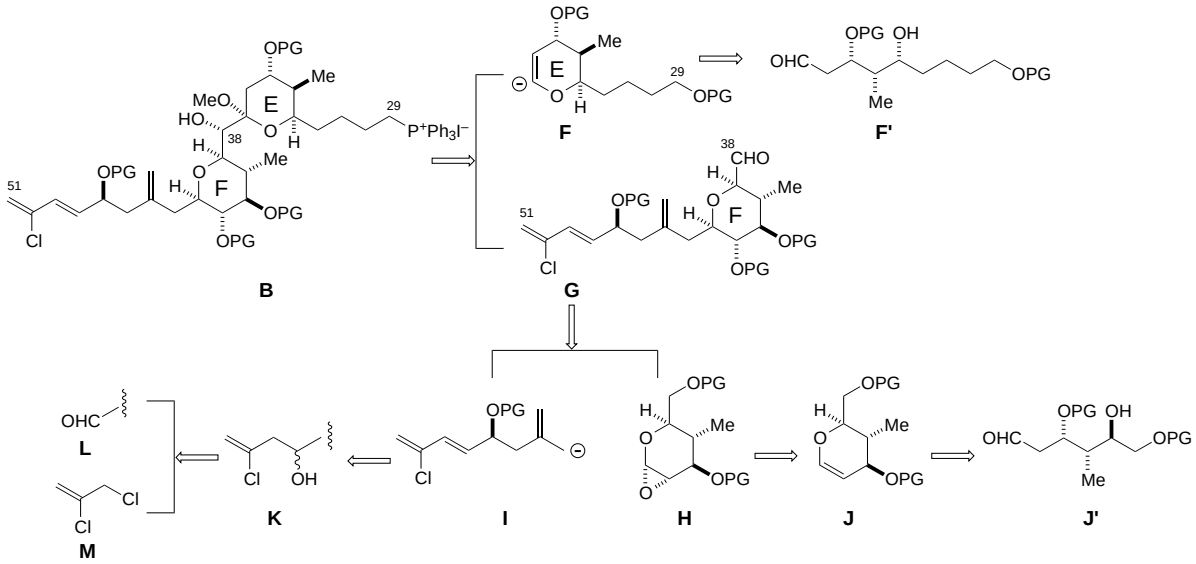
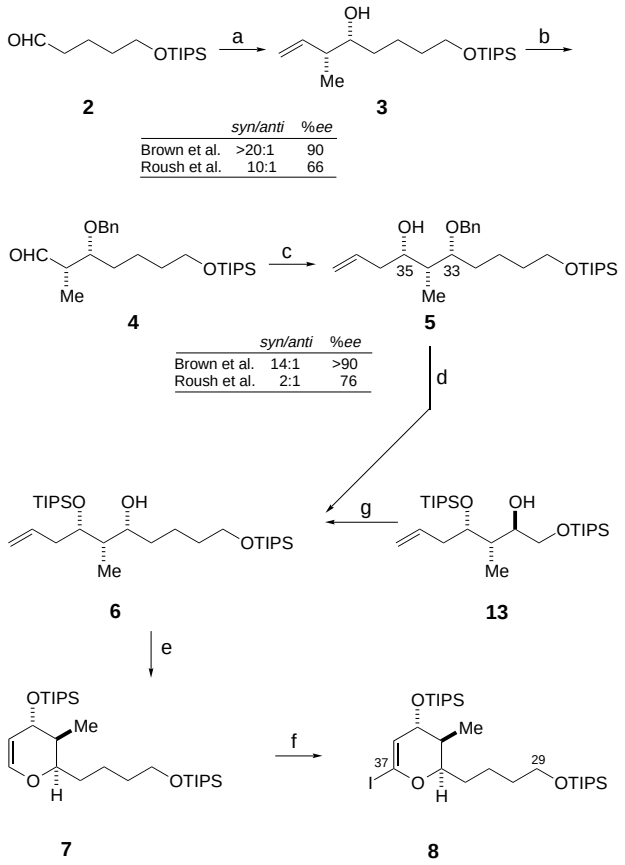


Figure. 1. Retrosynthesis of the C29 – C51 fragment (EF unit). PG = protecting group.



Scheme 1. Synthesis of the C29 – C37 fragment: a) (−)-Ipc$_2$-(*Z*)-crotyl boronate,[4b] THF, −78°C, 65%; b) NaH, BnBr, TBAI, THF, 0→20°C, 97%; NMO, OsO_4, THF/H_2O; $NaIO_4$, MeOH/H_2O, 0→20°C; c) (−)-Ipc$_2$-allyl boronate,[4a] PhMe, −78°C, 64% over 3 steps; d) 2,6-lutidine, TIPSOTf, CH_2Cl_2, 0→20°C; Li/NH_3, THF, −78°C, 81% over 2 steps; e) NMO, OsO_4, THF/H_2O; $NaIO_4$, MeOH/H_2O, 0→20°C; Et_3N, diketene acetone adduct, hexanes, 70°C; 125°C, 0.2 Torr, 54% over 4 steps; f) *t*BuLi, THF, −78→−30°C, then Bu_3SnCl, −78→20°C; K_2CO_3, NIS, THF, 0°C, 75% over 2 steps; g) Et_3N, MsCl, Et_2O; HF·py/py/THF, 61% over 2 steps (an additional 15% was obtained by recycling the bis-silylated starting material once); KOH, MeOH, 92%; sulfone,[30] *n*BuLi, −78→20°C, 87%; Li/NH_3, THF, −78°C, 85%.

also obtained from intermediate **13**, used in the F-ring synthesis (Scheme 2).

The same methods were used to construct the F-ring building block **14**. The TIPS protecting groups for the C38 and C41 alcohol in glycal **14** enhanced the stereoselectivity of epoxidation with DMDO;[2] only epoxide **15** was detected by ^{1}H NMR.

The synthesis of C44 – C48 segment **18** is also included in Scheme 2.[8] The C45 – C46 bond was formed by cuprate coupling between α-bromoacrolein diethyl ketal **16**[9] and (*R*)-TBS-glycidol **17** to afford the homoallylic alcohol. Acid treatment in acetone allowed concomitant deprotection of the TBS ether, formation of the acetonide, and hydrolysis of the acetal to form the α,β-unsaturated aldehyde, which was transformed into the allylstannane **18** in three steps.

Simple alkyl cuprate addition to a glycal epoxide was first reported by this group.[10] The present case required the addition of a highly functionalized allylic derivative. Although methallyl cuprates readily added to **15**, allyl cuprates bearing the C47 and C48 functionalities exhibited greatly diminished reactivity towards epoxide **15**. Among a variety of allylstannanes prepared and tested, only acetonide allylstannane **18** gave satisfactory results. While an excess of **18** was required to drive the reaction to completion, it was readily recovered from the crude reaction mixture. In this fashion, **19** was obtained in good yield with high stereoselectivity. As noted previously,[1] the C41 and C42 alcohols were masked with identical protecting groups followed by manipulation at C47 and C48 to allow for oxidation to aldehyde **21**.

Although no methodology existed to install the chlorodiene, it was known that allylindium species prepared from allylic halides react with aldehydes under mild conditions.[11] Coupling of the allylindium reagent derived from 2,3-dichloropropene[12] with aldehyde **21** cleanly afforded the two homoallylic alcohols, which were then dehydrated with Martin's sulfurane[13] to afford exclusively the *trans*-chlorodiene in high overall yield. Cleavage of the C38 TBS protecting group, followed by Swern oxidation of the primary alcohol, furnished aldehyde **22**.

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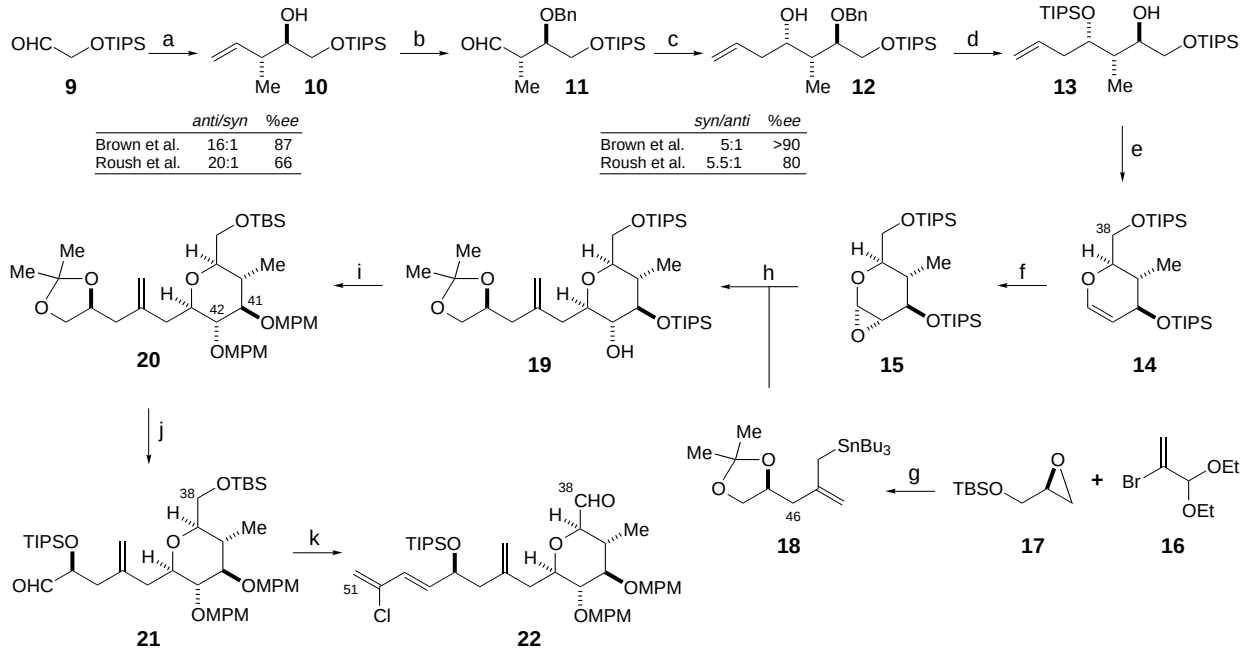

Scheme 2. Synthesis of the C38–C51 fragment: a) (*S*,*S*)-diisopropyl-(*E*)-crotyl boronate,[3b] PhMe, −78°C, 80%; b) NaH, BnBr, TBAI, THF, 0→20°C, 84%; NMO, OsO_4, THF/H_2O; $NaIO_4$, MeOH/H_2O, 0→20°C; c) (*R*,*R*)-diisopropyl-allyl boronate,[3a] PhMe, −78°C, 74% over 3 steps; d) 2,6-lutidine, TIPSOTf, CH_2Cl_2, 0→20°C; Li/NH_3, THF, −78°C, 80% over 2 steps; e) NMO, OsO_4, THF/H_2O; $NaIO_4$, MeOH/H_2O, 0→20°C; Et_3N, diketene acetone adduct, hexanes, 70°C; 125°C, 0.2 Torr, 61% over 4 steps; f) DMDO,[31] CH_2Cl_2/acetone, −10°C, quant.; g) **16**, *n*BuLi, Et_2O, −78°C, then CuI, Et_2O, −78°C, then **17**, −78→20°C, 65%; TsOH·H_2O, acetone, 64%; $CeCl_3 \cdot H_2O$, CH_2Cl_2/MeOH, then −78°C, $NaBH_4$, 83%; Ph_3P, NCS, CH_2Cl_2, 0°C, 95%; Bu_3SnLi,[32] THF, −78°C, 81%; h) $Me_2Cu(CN)Li_2$, **18**, 0°C, then **15**, −43→−15°C, 70%;[33] i) TBAF, THF, quant.; TBSCl, DMAP, CH_2Cl_2/Et_3N, 91%; KH, MPMCl, DMF/THF, 0→20°C, 81%; j) $ZnBr_2$, H_2O, CH_2Cl_2, 56% and an additonal 5% on resubmission of recovered starting material; PivCl, DMAP, CH_2Cl_2/py, 80%; 2,6-lutidine, TIPSOTf, CH_2Cl_2, 91%; LAH, THF, −78°C, 61% and an additonal 6% on resubmission of recovered starting material; oxalyl chloride, DMSO, CH_2Cl_2, −78°C, Et_3N, −78→0°C, 95%; k) In, 2,3-dichloropropene, NaI, DMF, then **21**; Martin's sulfurane, CH_2Cl_2, 85% over 2 steps; HF·py/py/THF, 76% and an additonal 10% on resubmission of recovered starting material; oxalyl chloride, DMSO, CH_2Cl_2, −78°C, 10 min, alcohol, Et_3N, −78→0°C, 89%.

The crucial coupling of the E- and F-ring building blocks (Scheme 3) was envisioned to arise from the addition of an E-ring nucleophile to the highly functionalized aldehyde **22**. Studies on model compounds suggested the importance of a chelation-controlled addition to obtain the desired configuration at C38.[14] Thus, the novel Grignard reagent was prepared by treatment of **8** with *tert*-butyllithium, followed by addition of magnesium dibromide, and was coupled with aldehyde **22** to furnish the desired alcohol **23** in excellent yield and with high stereoselectivity.[15] Attempts to form the methyl ketal directly from glycal **23** by addition of acidic methanol resulted in undesired Ferrier-type rearrangements. However, a two step procedure involving iodomethanolysis[16] and reductive dehalogenation gave a satisfactory result. Addition of bromobenzene allowed for selective reduction of the alkyl iodide in the presence of the chlorodiene. The configuration of the C38 alcohol was established by modified Mosher ester analysis on the methyl ketal of **23**.[17, 18] The TIPS protecting groups at C29, C35, C47 were switched to the more labile TBS groups at this stage.[19] After selective cleavage of the primary C29 TBS group, **24** was converted into phosphonium salt **25**. The methyl ketal present at C37 was prone to elimination to form the corresponding glycal under thermal and acidic conditions. This side reaction was significantly suppressed by addition of methanol.

As shown in Scheme 4, **25** and **32** (synthesis described in the preceding communication) were coupled by utilizing a titration protocol[20] for Wittig olefination to afford the *cis*-olefin **26** ($J_{H28,H29} = 10.0$ Hz). DDQ cleavage[21] of the C41 and C42 MPM protecting groups occurred with concomitant, but incomplete, hydrolysis of the methyl ketal. Fluoride induced removal of the silyl ester and macrolactonization under the Yamaguchi conditions[22] proceeded smoothly to furnish the desired macrolactone **27**. As anticipated,[1] macrolactonization occurred selectively at the C41 alcohol.[23] At this stage the unhydrolyzed C37 methyl ketal could be separated from the lactol.[24] Finally, cleavage of the three TBS protecting groups in **27** furnished synthetic altohyrtin A (or spongistatin 1; **1**).[25] The synthetic material was found to be identical (^{1}H NMR in [D_6]DMSO and CD_3CN, MS, $[\alpha]_D$, TLC) with the authentic sample kindly provided by Professor Motomasa Kobayashi at Osaka University. In addition, the synthetic and natural materials exhibited the same biological activity.[26,27] It is exciting and intriguing to note that the C23 epimer of alothyrtin A[1] also exhibits potent cytotoxicty.[26, 27]

In summary, this synthesis has firmly established the relative and absolute configuration proposed for altohyrtin A by the Kitagawa group. To the best of our knowledge, there has been no direct comparison of altohyrtin A and spongistatin 1. However, comparison of the ^{1}H NMR spectra for both authentic and synthetic altohyrtin A with the spectrum (CD_3CN) of spongistatin 1 deposited in the supplementary material by Pettit[28] presents a convincing case that they are indeed the same compound. Thus, this work resolves the

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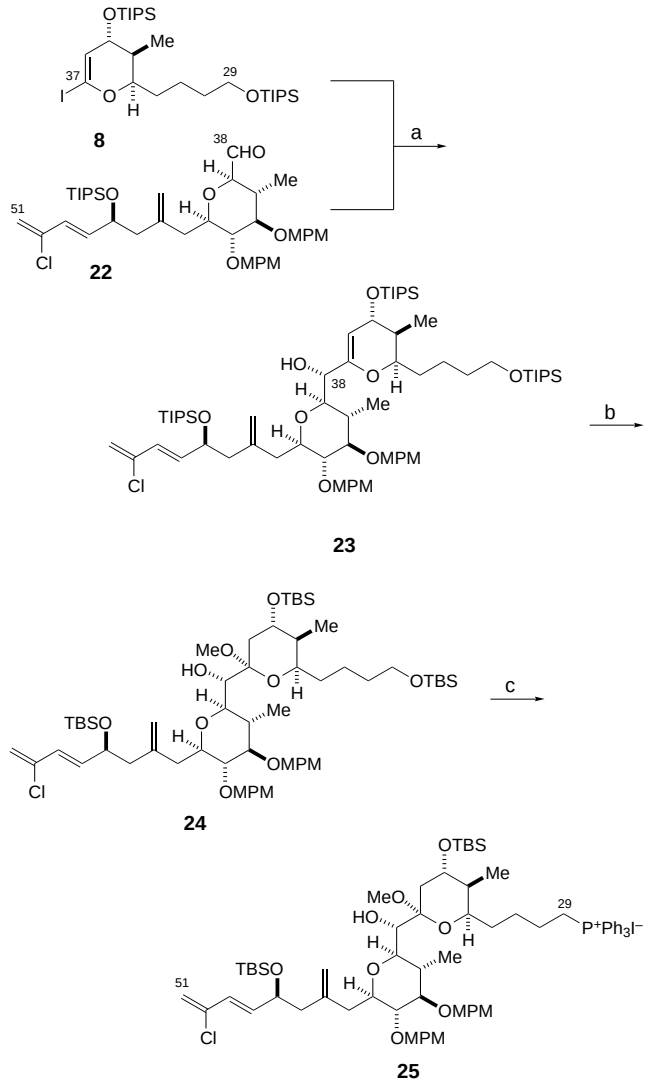
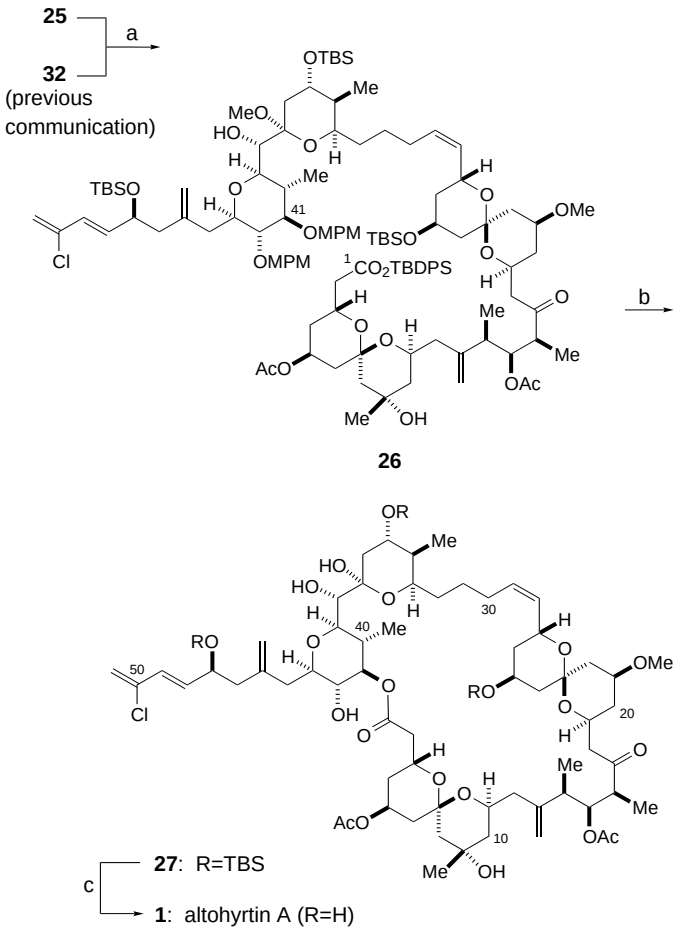


Scheme 3. Synthesis of the C29–C51 fragment: a) **8**, *t*BuLi, Et_2O, −78°C, then $MgBr_2$, **22**, −78 → −50°C, 78%; b) NIS, $CaCO_3$, MeOH/THF/CH_3CN/HC$(OMe)_3$, 0 → 20°C, 81%; Bu_3SnH, AIBN, THF/PhBr, 80°C, 54% and an additional 16% on resubmission of recovered starting material; TBAF, THF, 76%; imidazole, TBSCl, DMF, 75%; c) HF · py/py/THF/MeOH, 78%; Ts_2O, DMAP, CH_2Cl_2/*i*Pr_2NEt, 75%; NaI, acetone/*i*Pr_2NEt, 85%; Ph_3P, CH_3CN/MeOH, 80°C, 75% and an additonal 10% on resubmission of recovered starting material.



Scheme 4. Synthesis of altohyrtin A (spongistatin 1): a) LDA, THF/HMPA, −5°C, 40%; b) DDQ, CH_2Cl_2/H_2O, 60% as a 3:2 mixture of hemiketal and methyl ketal; KF, MeOH; Et_3N, 2,4,6-trichlorobenzoyl chloride, PhMe, then DMAP, 50% as a 3:2 mixture of hemiketal and methyl ketal; c) HF · py/py/THF, 20–30%.[25]

discrepancies in the configuration between altohyrtin A and spongistatin 1, and we further speculate that configuration of all the members in the spongipyran class of natural products is represented by structure **1**.[29]

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