Synthesis of the C1−C28 Portion of Spongistatin 1 (Altohyrtin A)

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A synthetic approach was developed to the C1−C28 subunit of spongistatin 1 (altohyrtin A, **65**). The key step was the coupling of the AB and CD spiroketal moieties via an *anti*-aldol reaction of aldehyde **62** and ethyl ketone **57**. The development of a method for the construction of the AB spiroketal fragment is described and included the desymmetrization of C_2-symmetric diketone **10** and the differentiation of the two primary alcohols of **16**. Further elaboration of this advanced intermediate to the desired aldehyde **62** included an Evans' *syn*-aldol reaction and Tebbe olefination. The synthesis of the CD spiroketal fragment **56** involved the ketalization of a triol−dione, generated in situ by deprotection of **45**, to provide a favorable ratio (6−7:1) of spiroketal isomers **46** and **47**, respectively. The overall protecting group strategy, involving many selective manipulations of silyl protecting groups, was successfully developed to provide the desired C1−C28 subunit of spongistatin 1 (altohyrtin A) (**65**).

In 1993 and 1994, a series of novel, marine-derived, macrocyclic lactones with closely related structures, including the spongistatins,[1] cinachyrolide A,[2] and the altohyrtins,[3] were reported. The altohyrtin/cinachyrolide/spongistatin macrocyclic lactones are tremendously cytotoxic to various tumor lines and are therefore of interest as potential cancer therapeutic agents. Spongistatin 1 itself has been characterized as "probably the best to date in the NCI's evaluation programs",[4] exhibiting 50% growth inhibition against a range of tumor lines at concentrations in the range of 10^{-10}−10^{-12} mol/L! In addition, spongistatin 1 showed potent activity against a subset of highly chemoresistant tumor types.[4] Spongistatin appears to inhibit microtubule assembly by binding to tubulin at the vinca alkaloid binding site.[5] The compound also has potent antifungal properties, inhibiting the growth of many fungi, including strains resistant to amphotericin B, ketoconazole, and flucytosine.[6]

These exquisitely active marine natural products provide a good example of the power of Nature to point us in the direction of organic structures of potential use in chemotherapy. The problem is that they are available from Nature in only minute amounts and there is currently no practical way to farm sponges to obtain larger quantities of the metabolites. However, because of their exceedingly high potency, it has been estimated that a full clinical trial could be carried out with only a few grams of material. We believe that, even despite their great complexity, it is within the realm of feasibility that organic synthesis could provide several-gram quantities of the spongistatins, and it is the goal of the current project to develop an efficient total synthesis to provide several grams of the natural product.

The unique structural complexity and stereochemical diversity of these macrolides attracted the attention of several research groups.[7] To date, two groups have published complete total syntheses. Evans and co-workers reported the first total synthesis of a member of this family of natural products and demonstrated that spongistatin 2 and altohyrtin C are identical (**2**).[8] Further confirmation that the altohyrtin and spongistatin families were identical came from the publication of Kishi's total synthesis of altohyrtin A which proved to be identical to spongistatin 1 (**1**).[9]

At the inception of our synthetic efforts, the quandary surrounding the relationship of the spongistatins, altohyrtins, and cinachyrolides led us to focus on altohyrtin A (**1**), since it was the only structure whose absolute and relative configuration was supported by adequate data. Our strategy was designed around a macrolactonization as the final key step. Further disconnection of the C28−C29 double bond revealed two similarly complex fragments, which were to be joined using a Wittig reaction. The C1−C28 subunit, containing both spiroketal moieties, was envisioned as arising from an *anti*-aldol

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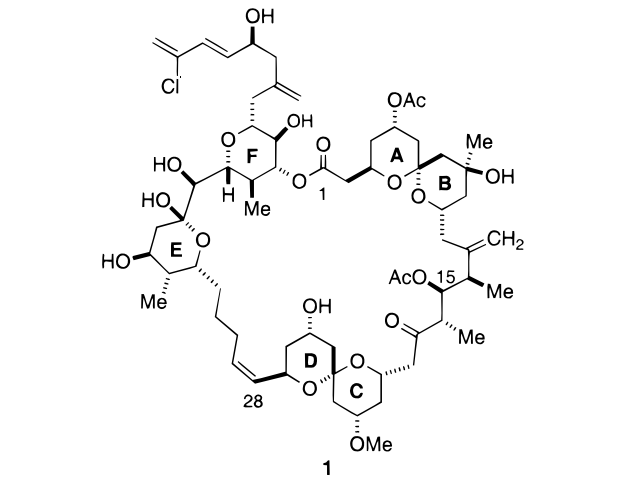

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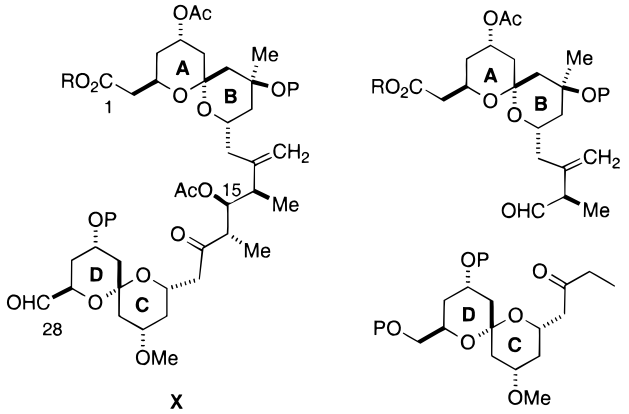


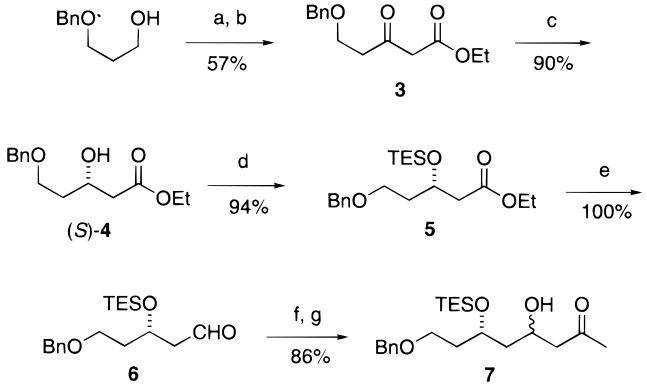
X

reaction that would establish the relative configuration of the C15 and C16 stereocenters.

In order to exploit the methodology developed for the model system,[10] a key intermediate in the synthesis of the AB spiroketal subunit would be a C_2-symmetric diketone (e.g., compound **10**, Scheme 2), which would be desymmetrized and further elaborated to the C1−C15 altohyrtin A system. Unraveling and disassembling the diketone revealed keto-ester **3** as a starting material. Following a literature procedure,[11] ethyl acetoacetate was treated with NaH followed by *n*-BuLi and the resulting dianion was alkylated with benzyloxymethyl chloride (BOMCl)[12] to provide keto-ester **3** in moderate yield. However, we developed a new route to generate ester **3** more efficiently and with greater purity. Swern−Moffatt oxidation[13] of 3-(benzyloxy)-1-propanol provided the crude aldehyde, which was extended to *β*-keto-ester **3** by treatment with ethyl diazoacetate in the presence of catalytic $SnCl_2$ in CH_2Cl_2.[14] This more practical sequence furnished keto-ester **3** in 57% overall yield.

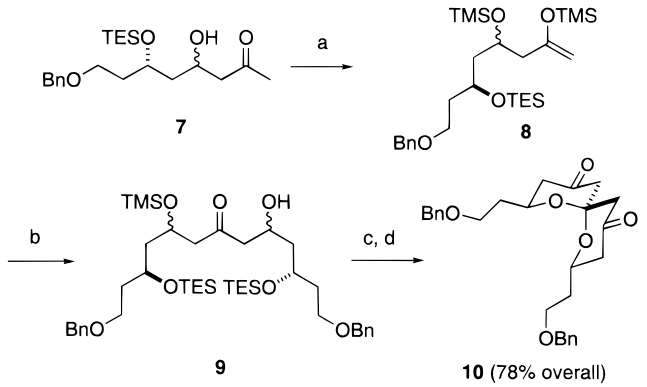
Hydrogenation of keto-ester **3** was performed using a modified protocol of Noyori and co-workers[15] to provide

Scheme 1



a. Swern-Moffatt. b. N_2CHCO_2Et, $SnCl_2$. c. Noyori hydrogenation. d. TESCl, imidazole. e. diisobutylaluminum hydride. f. acetone dimethylhydrazone, *n*-BuLi, $CeCl_3$. g. *m*-CPBA, THF.

Scheme 2



a. TMSOTf, Hünig's base. b. **6**, BF_3•Et_2O. c. HF, CH_3CN, H_2O. d. Dess-Martin periodinane.

hydroxy ester (*S*)-**4** (91% ee). The resulting alcohol was protected as silyl ether **5** in 94% yield by treatment with triethylsilyl chloride and imidazole in dimethylformamide. Subsequent reduction with diisobutylaluminum hydride quantitatively generated crude aldehyde **6**, which was sufficiently pure to use in the next reaction. The two-step elongation, involving the condensation of the aldehyde with acetone dimethylhydrazone followed by hydrazone cleavage, afforded the hydroxy ketone **7** in 86% yield.

Extension of the chain through an aldol coupling was most efficiently accomplished by treatment of methyl ketone **7** with 2.5 equiv of trimethylsilyl triflate and Hünig's base in CH_2Cl_2 to simultaneously protect the alcohol and generate the silyl enol ether **8**. A Mukiayama aldol reaction, catalyzed by BF_3•Et_2O, was performed with the silyl enol ether and aldehyde **6**. The resulting aldol product **9** was treated with aqueous HF in CH_3CN to cleave the silicon protecting groups and promote acid-catalyzed ketalization. The resulting mixture of spiroketal diols was then oxidized with Dess−Martin periodinane to afford diketone **10** in 78% yield over the four steps with a single purification.

With an efficient route to diketone **10**, we faced two major challenges, desymmetrization and differentiation of the two hydroxyethyl side chains. With utilization of the methodology developed with the model system, diketone **10** was treated with LDA in a mixture of THF

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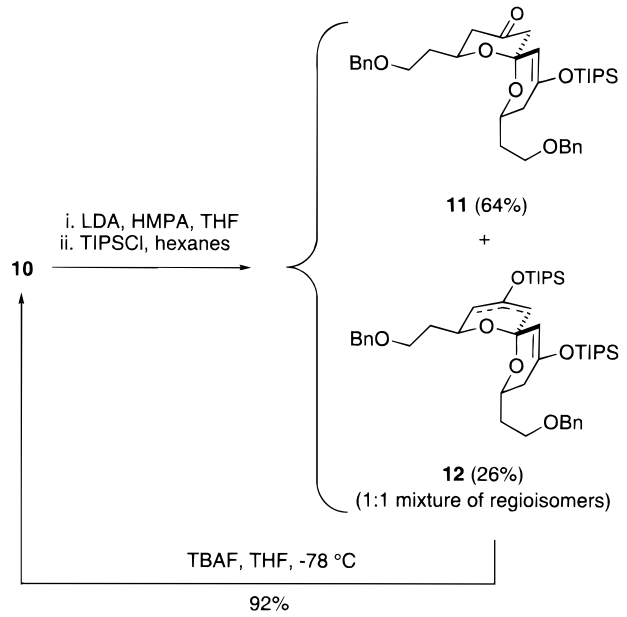
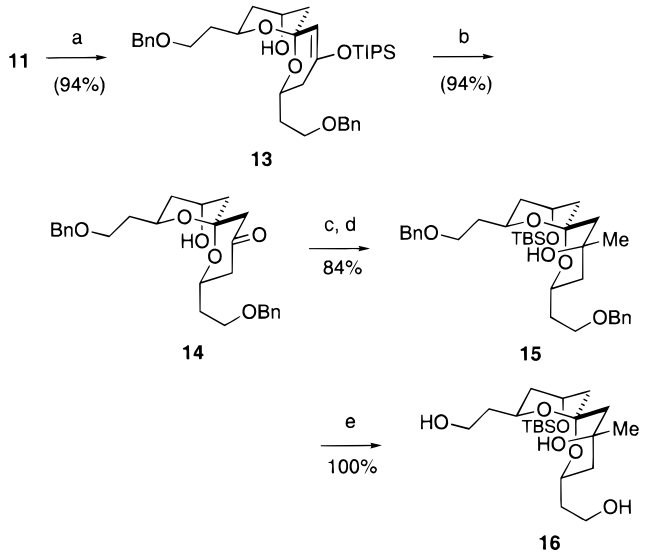
Scheme 3



Scheme 4

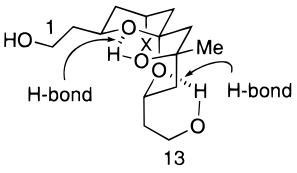


a. L-Selectride, THF. b. TBAF•3H_2O, THF. c. MeLi (4 equiv.), $CeCl_3$, THF. d. TBSOTf, Et_3N, CH_2Cl_2. e. H_2, $Pd(OH)_2$/C, EtOAc.

and HMPA and the resulting enolate was trapped with triisopropylsilyl chloride to provide the desired mono(silyl enol) ether **11** (64%) accompanied by the bis(silyl enol) ether **12** (26%) and recovered starting material (8%). Despite the moderate yield, the good mass recovery and the potential to recycle material made this transformation practical. Treatment of the bis(silyl enol) ether with TBAF·3H_2O at low temperature regenerated the diketone **10** in 92% yield. Therefore, with one recycle operation, the mono(silyl enol) ether **11** was obtained in 84% yield (Scheme 3).

Functionalization of the spiroketal rings was performed without complications. Reduction of ketone **11** was performed with L-Selectride to give solely the axial alcohol **13**. The silyl enol ether was smoothly cleaved with TBAF·3H_2O in THF at −78 °C to provide the desymmetrized spiroketal **14** in 94% yield. Addition of the methylcerium reagent to ketone **14** occurs in a highly stereoselective manner, providing the axial tertiary alcohol (**15**), which was selectively silylated on the less hindered hydroxy group by reaction with TBSOTf and Et_3N in CH_2Cl_2 at −78 °C to provide silyl ether **15** in 84% yield for the two steps. Subsequent hydrogenation of the benzyl ethers afforded the desired triol **16** (Scheme 4).

At this point we were faced with the second major challenge: differentiation of the two hydroxyethyl side chains. The one subtle difference between the two alcohols is the capability of the C13 alcohol to form an intramolecular hydrogen bond with an ether oxygen of the spiroketal:



13

16: X = OTBS

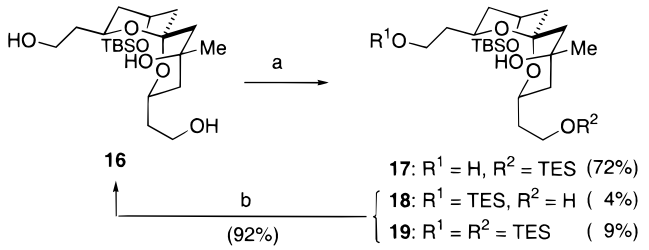
The other primary alcohol at C1 is less able to form a similar intramolecular hydrogen bond because the corresponding ether oxygen of the spiroketal is hydrogen bonded to the axial tertiary hydroxy group. On the basis of this hypothesis, we thought the two primary hydroxy groups might have different reactivity.

Initial efforts to differentiate the side chains were performed on the analogous C5-acetate derivative and included treatments with either benzoyl chloride or TESCl in CH_2Cl_2 in the presence of DMAP and Et_3N. Modest selectivity was observed with the major isomers resulting from reaction at the C1 alcohol. This selectivity indicated that the C1 alcohol was sterically less encumbered than the C13 alcohol in agreement with the prediction that the C13 alcohol participated in intramolecular hydrogen bonding.

We speculated that a greater difference in reactivity of the two primary hydroxy groups might be observed by generation of the monoanion. Although two primary alkoxides can form, the C13 alkoxide should predominate in the equilibrium because the associated cation can be chelated by the proximal spiroketal oxygen. Reaction of the monoalkoxide with a silyl halide should lead to reaction predominately at the C13 hydroxy group. In the event, treatment of **16** with 1 equiv of LDA in THF, followed by addition of triethylsilyl chloride, afforded the expected silyl ether **17** as the major regioisomer in 72% yield, accompanied by 4% of isomer **18**, 9% of the bis-silylated product **19**, and 12% of recovered starting material. Treatment of the two undesired products, **18** and **19**, with TBAF·3H_2O in THF gave 92% yield of triol **16**, thus providing the desired product **17** in a net yield of 89% for the silylation and one recycle of the recovered starting material and undesired silylation products (Scheme 5).

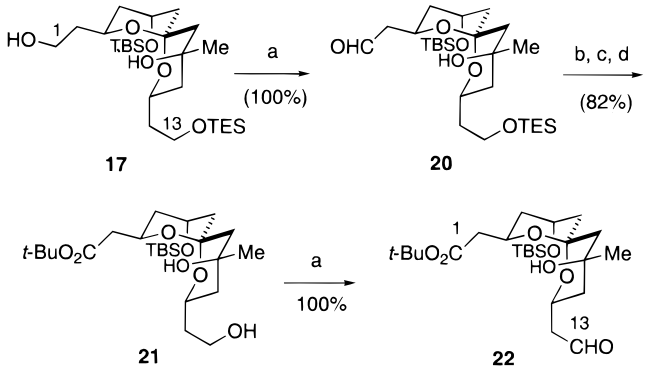
Alcohol **17** was oxidized with Dess−Martin periodinane to aldehyde **20**. Homonuclear decoupling experiments with aldehyde **20** confirmed its structure, thus firmly establishing the regiochemistry of the silylation reaction shown in Scheme 5. The primary triethylsilyl ether was cleaved with aqueous camphorsulfonic acid in THF. Further oxidation of the aldehyde at C1 with sodium

Scheme 5



a. i. LDA, THF; ii. TESCl. b. TBAF•3H_2O, THF.

Scheme 6



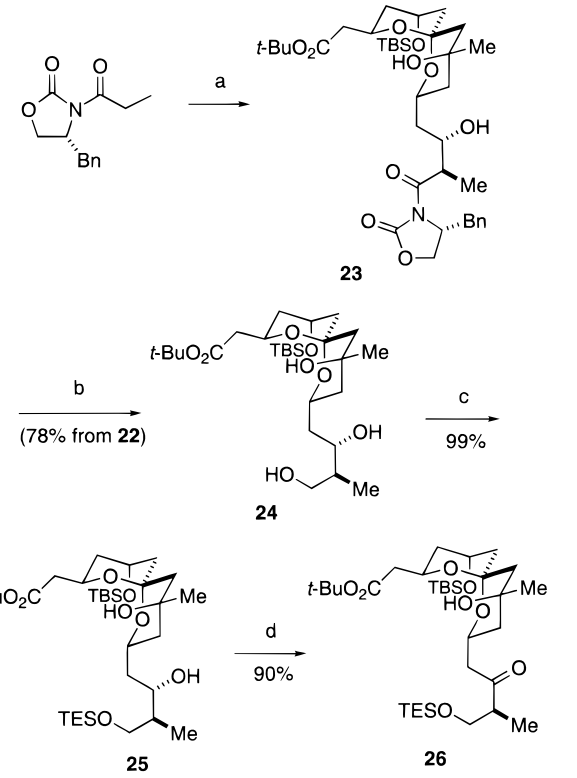
a. Dess-Martin periodinane. b. CSA, THF, H_2O. c. $NaClO_2$. d. *i*-PrN=C(O-*t*-Bu)NH-*i*-Pr

chlorite[16] provided the corresponding acid, which was converted to the *tert*-butyl ester using excess *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea[17] in CH_2Cl_2. The optimized conditions resulted in an 82% yield of *tert*-butyl ester **21** for the four steps with only a single purification necessary. The side chain manipulations were completed with the oxidation of alcohol **21** with Dess−Martin periodinane to afford aldehyde **22** in excellent yield (Scheme 6).

Our next task was installation of the linker between the AB and CD spiroketals. As shown in Scheme 7, the requisite two-carbon extension and methyl substituent were appended diastereoselectively to the aldehyde **22** by employing Evans' *syn*-aldol methodology.[18] The crude aldol product **23** was reduced with $LiBH_4$ in EtOH and THF to cleave the chiral auxiliary to provide the primary alcohol **24** in 78% yield for the two steps. The selective protection of the primary alcohol occurred without incident to give silyl ether **25** in nearly quantitative yield. Subsequent oxidation with Dess−Martin periodinane provided ketone **26**.

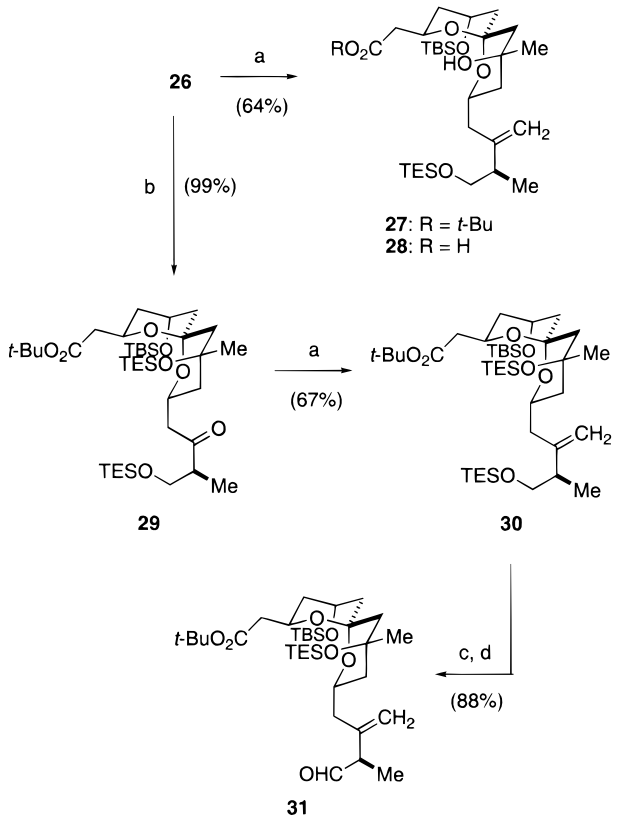
Although several methylenation protocols were employed to convert ketone **26** into the corresponding olefin, the Tebbe reagent[19] proved to be the preferred method for this transformation. As shown in Scheme 8, treatment of ketone **26** with Tebbe reagent in THF provided olefin **27** in 64% yield, accompanied by acid **28** and recovered

Scheme 7



a. i. Bu_2BOTf, Et_3N; ii. **22**. b. $LiBH_4$, EtOH, THF. c. TESCl, Et_3N, CH_2Cl_2. d. Dess-Martin periodinane.

Scheme 8



a. Tebbe reagent, THF. b. TESOTf, 2,6-lutidine, CH_2Cl_2, –48 °C. c. CSA/THF/ H_2O. d. Dess-Martin periodinane.

starting material. The formation of this side product was circumvented by protection of the tertiary alcohol prior

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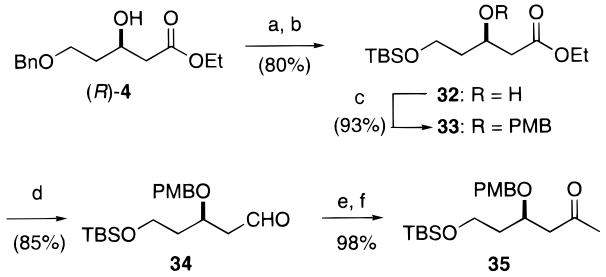
Scheme 9



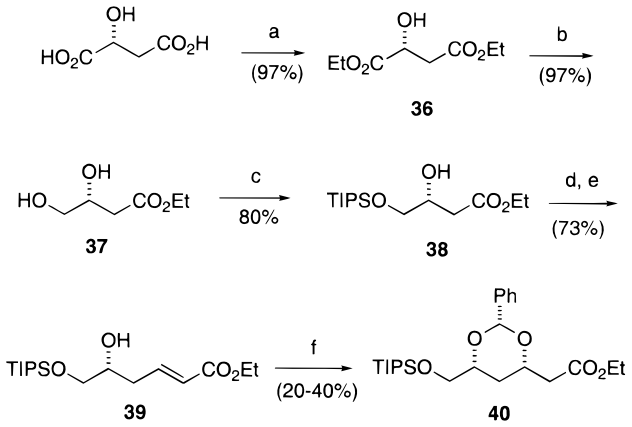
a. H_2, Pd/C, EtOH. b. TBSCl, THF, imidazole, 0 °C.
c. PMBOC=NHCCl$_3$, BF_3•OEt_2, CH_2Cl_2.. d. DIBALH, CH_2Cl_2.
e. MeMgBr, Et_2O. f. Dess-Martin periodinane.

to the olefination. Thus, treatent of **26** with triethylsilyl triflate and 2,6-lutidine in CH_2Cl_2 gave the bis-TES ether **29** in nearly quantitative yield. The ketone was converted to the corresponding 1,1-disubstituted olefin by utilizing the Tebbe reagent. The protection of the alcohol prior to Tebbe reaction proved to be advantageous, since the formation of the acid side product was eliminated and olefin **30** was isolated in 67% yield along with 33% recovered ketone **29**. Selective desilylation of **30** with aqueous camphorsulfonic acid in THF and subsequent Dess−Martin oxidation provided the target aldehyde **31** in 88% yield for the two steps. At this point, the requisite AB spiroketal fragment was synthesized and ready for the key *anti*-aldol coupling with the ethyl ketone of the CD spiroketal subunit.

A model system was investigated to explore the ketalization of the CD spiroketal,[20] and the methodology developed was subsequently applied to the synthesis of the C16−C28 subunit of altohyrtin A. The construction of the ketalization precursor began with the hydroxy ester (*R*)-**4**, the enantiomer of hydroxy ester (*S*)-**4** used in the synthesis of the AB-spiroketal fragment. The benzyl ether of (*R*)-**4** was removed and replaced with a *tert*-butyldimethylsilyl ether by hydrogenation with Pd/C in EtOH followed by treatment of the crude diol with TBSCl and imidazole in THF at 0 °C to provide TBS ether **32** in 80% yield for the two steps. Treatment of **32** with (*p*-methoxybenzyl)trichloroacetimidate[21] in the presence of catalytic BF_3•OEt_2 afforded the *p*-methoxybenzyl ether **33**, which was reduced by diisobutylaluminum hydride to obtain aldehyde **34**. Addition of methylmagnesium bromide in ether at 0 °C, followed by oxidation of the resulting diastereomeric mixture of alcohols with Dess−Martin periodinane, provided methyl ketone **35** (Scheme 9).

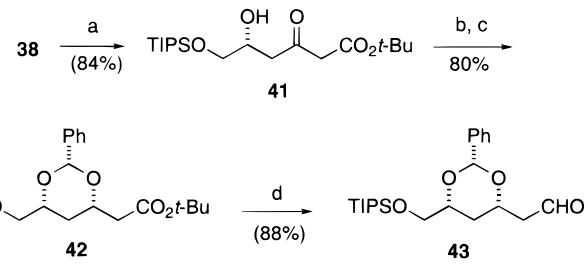
The aldehyde necessary to perform an aldol reaction with methyl ketone **35** was derived initially from D-malic acid. Esterification was accomplished by reaction with thionyl chloride in absolute ethanol, providing diethyl malate (**36**), which was reduced to diol **37** using borane dimethyl sulfide complex and catalytic sodium borohydride.[22] Selective silylation of the resulting diol with triisopropylsilyl triflate and 2,6-lutidine in CH_2Cl_2 generated the TIPS ether **38** in 80% yield. Reduction of ester **38** with diisobutylaluminum hydride followed by reaction

Scheme 10



a. EtOH, $SOCl_2$. b. BH_3•DMS, $NaBH_4$. c. TIPSOTf, 2,6-lutidine.
d. DIBALH, CH_2Cl_2. e. Ph_3P=$CHCO_2Et$. f. PhCHO, KHMDS, THF.

Scheme 11



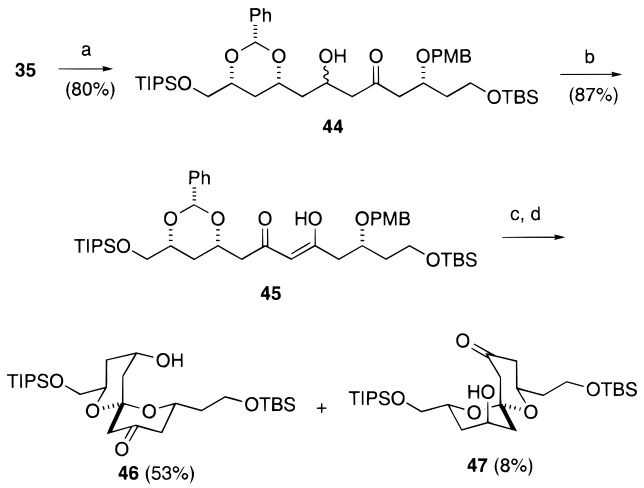
a. LDA, H_3CCO_2*t*-Bu (4 equiv). b Et_2BOMe, $NaBH_4$, MeOH, THF.
c. $PhCH(OMe)_2$, PPTS, CH_2Cl_2. d. DIBALH, toluene.

with ethyl triphenylphosphoranylidine acetate afforded the desired (*E*)-α,*β*-unsaturated ester **39**, accompanied by 7% of the *Z* isomer. Installation of the benzylidene acetal was performed as in our model study, in which it worked reasonably well to give the desired model dioxane derivative in 73% yield.[20] Unfortunately, this protocol did not translate well to the requisite acetal **40**, which was isolated in only 20−40% yield (Scheme 10). Many efforts to optimize this procedure failed to furnish a practical, isolated yield of product. As a result, a new route to the aldehyde was required.

As shown in Scheme 11, a precedented [23] mixed Claisen condensation of the lithium enolate of *tert*-butyl acetate with ester **38** provided *β*-keto ester **41**. Although this reaction was complicated by competitive enolization of the starting ester, we found that by forming the enolate at −78 °C and adding it to a solution of ester **38** in THF at 0 °C, followed by warming to room temperature, the desired *β*-keto ester **41** was obtained in 84% yield. The ketone carbonyl group was stereoselectively reduced with Et_2BOMe and $NaBH_4$ in THF/MeOH,[24] and the resulting *syn*-1,3-diol was converted into the benzylidine acetal by reaction with benzaldehyde dimethyl acetal in the presence of pyridinium *p*-toluenesulfonate (PPTS) in refluxing CH_2Cl_2; acetal **42** was obtained in a yield of 80% for the two-step process. Reduction of **42** with diisobutylaluminum hydride provided the desired aldehyde **43** in 88% yield.

(20) Hayes, C. J.; Heathcock, C. H. *J. Org. Chem.* **1997**, *62*, 2678−2679.
(21) Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738−3740.
(22) Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067−4086.
(23) Wess, G.; Kesseler, K.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Jendralla, H.; Bock, K.; Holzstein, G.; Kleine, H.; Schnierer, M. *Tetrahedron Lett.* **1990**, *31*, 2545−2548.
(24) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155−158.

Scheme 12

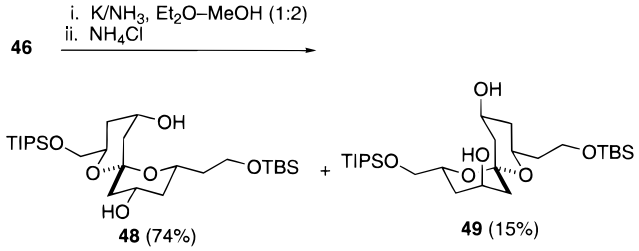


a. i. LDA, THF. ii. **43**. b. Dess-Martin periodinane. c. H_2, $Pd(OH)_2/C$, EtOAc. d. $ZnBr_2$, CH_2Cl_2, −78 → 0 °C.

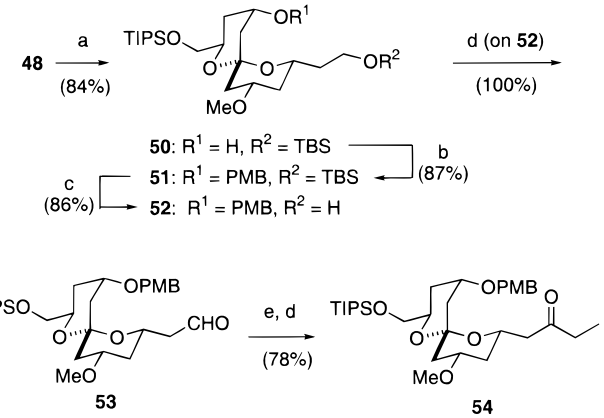
Methyl ketone **35** was treated with LDA followed by the addition of aldehyde **43** to provide the aldol product **44** in 80% yield. Careful oxidation with Dess−Martin periodinane resulted in the formation of **45**,[25] the ketalization precursor, in 87% yield. Following the precedent set in the ketalization of the model system, the dione was anticipated to ketalize with an acceptable degree of selectivity, generating the dispiroketal. However, initial attempts to deprotect **45** and promote acid-catalyzed spiroketalization met with only minimal success. Hydrogenation of the dione with Pearlman's catalyst in EtOAc removed both the benzylidene acetal and the PMB ether. The subsequent acid-catalyzed ketalization proved to be challenging and was investigated by subjecting the crude hydrogenation product to a series of protic acid conditions, keeping in mind the acid-labile silicon protecting groups on the terminal hydroxyl groups. Treatment of the triol−dione with acetic acid and aqueous HCl in $CHCl_3$ displayed encouraging results. Using this two-step sequence, two spiroketals (**46** and **47**) were isolated in yields of 64% and 6%, respectively. However, these results were not reproducible on various batches of the ketalization precursor with yields ranging from 26 to 64%. After the screening of a variety of other protic acids and solvents, the best conditions for the ketalization were PPTS in CH_2Cl_2 to provide 46% yield of the desired spiroketal. Our attention then shifted to Lewis-acid-catalyzed ketalizations. Several relatively strong Lewis acids [$Ti(Oi\text{-}Pr)_4$, Me_2AlCl, $BF_3{\cdot}OEt_2$] resulted solely in decomposition, while weaker Lewis acids [$MgBr_2$, $Mg(O_2CCF_3)$, $ZnCl_2$] proved to be impractically slow. Moderate success was achieved with 1.2 equiv of anhydrous $ZnBr_2$ in CH_2Cl_2 for 30 min warming from −78 to 0 °C. The desired isomer was isolated in 53% yield accompanied by 8% of the minor isomer possessing the opposite configuration at the spiroketal carbon (Scheme 12). The low mass recovery was attributed to cleavage of the terminal silicon protecting groups under the acidic conditions. Despite the moderate yield for this ketalization sequence, the 6−7:1 ratio of spiroketal products (**46**:**47**) is impressive. Molecular mechanics calculations (which indicate no clear thermodynamic preference for one spiroketal configuration) and control equilibrations (which gave an approximate equimolar mixture of **46** and **47**) prove that the observed product ratio is kinetic.

(25) Compound **45** is seen by NMR spectroscopy to exist completely in an enolic form, either that shown or the isomer in which the OH and C═O groups are reversed.

Scheme 13



Scheme 14



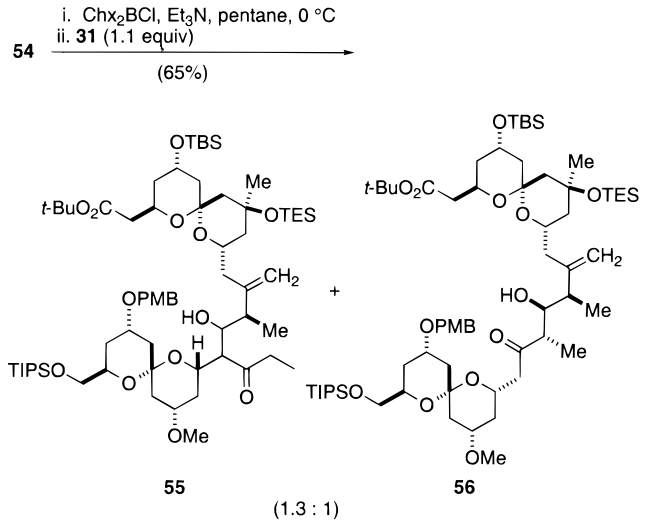
a. $Me_3O{\bullet}BF_4$, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 0 °C. b. i. KHMDS, THF; ii. PMBCl. c. H_2SiF_6, *t*-BuOH, CH_3CN, 0 °C. d. Dess-Martin periodinane. e. EtMgBr, Et_2O, 0 °C

Elaboration of the spiroketal to the target CD-spiroketal subunit began by dissolving metal reduction of the ketone **46** to obtain diol **48** (Scheme 13). The reduction was performed by adding the ketone in 1:2 $Et_2O{\cdot}MeOH$ to the K/NH_3 slurry and quenching with solid NH_4Cl to provide 74% of **48** along with 15% of the minor isomer **49**. This byproduct obviously results from isomerization of the spiroketal center, at some stage in the process. However, we have thus far not been able to eliminate its formation in this reduction. The assigned configuration was based on analysis of its ^1H NMR spectrum and confirmed by the observation that it is also produced by reduction of compound **47**, the minor isomer of the spiroketalization.

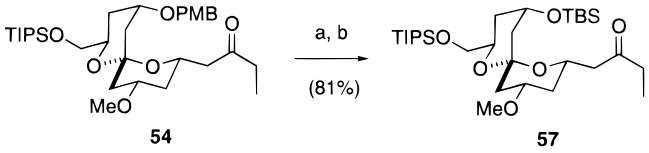
As shown in Scheme 14, the equatorial hydroxy group of diol **48** was selectively methylated by reaction with excess Meerwein's salt ($Me_3O{\cdot}BF_4$) and 2,6-di-*tert*-butyl-4-methylpyridine in CH_2Cl_2 at 0 °C, affording methyl ether **50** in 84% yield. NOESY experiments on compound **50** showed unequivocally that the spiroketal center has the desired (*R*)-configuration. The axial hydroxy group was protected as a PMB ether by deprotonation with KHMDS in THF followed by alkylation with PMBCl to provide **51** in 87% yield.

The fully protected spiroketal was then transformed to the key ethyl ketone necessary for the *anti*-aldol coupling of the two spiroketal fragments. We first attempted to selectively deprotect the TBS ether by treatment with $TBAF{\cdot}3H_2O$ in THF at −10 °C, but to our surprise, the TIPS ether was removed preferentially

Scheme 15



Scheme 16



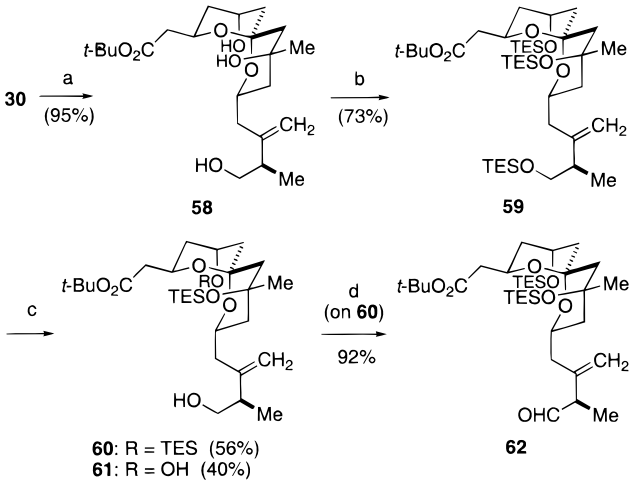
a. H_2, $Pd(OH)_2$/C, EtOAc. b. TBSOTf, 2,6-lutidine, CH_2Cl_2.

under these conditions. However, use of aqueous CSA in THF gave the desired alcohol **52** with good selectivity and in 78% yield. Optimum conditions were found in which **51** was treated with fluorosilic acid (H_2SiF_6) in *t*-BuOH and CH_3CN at 0 °C to provide **52** in 86% yield. The synthesis of ethyl ketone **54** was completed by a three-step conversion of the primary alcohol into the ethyl ketone. Dess−Martin periodinane oxidation yielded aldehyde **53**, which was treated with EtMgBr in ether at 0 °C. The temperature of this reaction is crucial to effect complete conversion of the starting material, since addition at low temperature (−78 °C) resulted in substantial amounts of recovered aldehyde. The resulting diastereomeric mixture of secondary alcohols was oxidized with Dess−Martin periodinane to afford the ethyl ketone **54** in 78% yield for the three steps with one final purification.

We were now ready to examine the major *anti*-aldol union of the two spiroketal subunits. With utilization of the methodology developed by Brown and co-workers,[26] treatment of the ketone **54** with a mixture of dicyclohexylboron chloride and triethylamine in pentane at 0 °C was followed by addition at −78 °C of 1.1 equiv of aldehyde **31**. After 3.5 h the reaction was quenched and worked-up to provide two aldol products (65%), recovered ketone **54** (27%), and recovered aldehyde **31** (44%). HPLC separation of the aldol products revealed a 1.3:1 ratio of products. The slightly favored, less-polar isomer **55** proved to be a product resulting from reaction of the aldehyde with the boron enolate possessing the wrong regiochemistry. The more-polar isomer was the desired *anti*-aldol product **56** (Scheme 15).

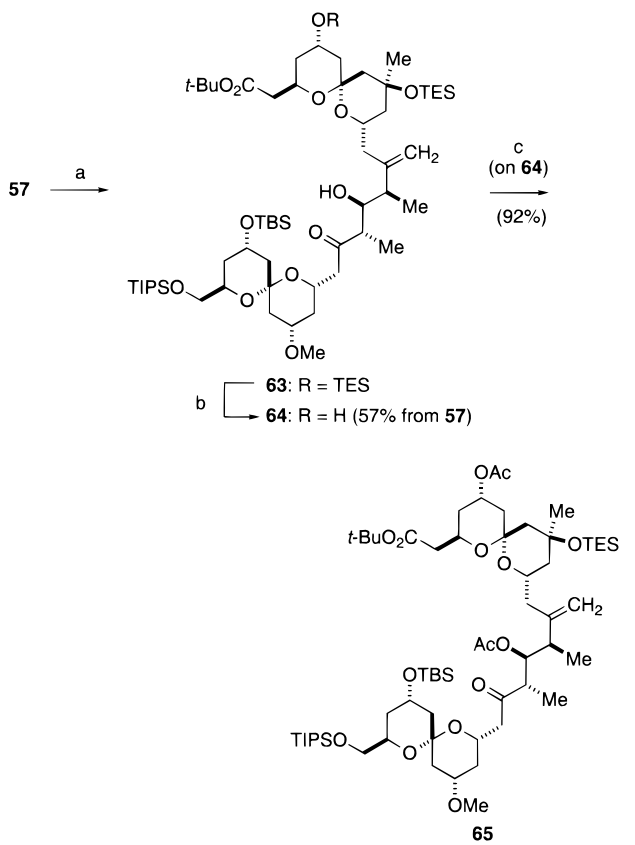
Concurrent with our early aldol couplings, Evans and co-workers published their total synthesis of altohyrtin C,[8] which was based partly on the same key *anti*-aldol disconnection. The Evans *anti*-aldol reaction was very similar to ours, differing mainly in the protecting groups; in their case the C25 secondary alcohol was protected as a TBS ether and the C28 primary alcohol as a trityl group. We suspected that the different regiochemical outcome of our aldol reaction was due to the C25 PMB group. To test this hypothesis, the PMB group was removed by hydrogenolysis and subsequent silylation with TBS-triflate to provide ethyl ketone **57** in 81% yield (Scheme 16).

Scheme 17



a. H_2SiF_6, *t*-BuOH, CH_3CN. b. TESOTf, 2,6-lutidine, CH_2Cl_2.
c. CSA, THF, H_2O. d. Dess-Martin periodinane.

Scheme 18



a. i. Chx_2BCl, Et_3N, pentane, 0 °C; ii. **62** (1.8 equiv). b. HF•pyridine, THF, 0 °C. c. Ac_2O, DMAP, pyridine.

(26) Ganesan, K.; Brown, H. C. *J. Org. Chem.* **1993**, *58*, 7162−7169.

Because of this change, it was also necessary to change the protecting groups in aldehyde **31**, since the secondary alcohol at C5 must be orthogonal to the one at C25. To accomplish this change with material available, we retreated to compound **30** (see Scheme 8). Global desilylation occurred in almost quantitative yield when this material was treated with H_2SiF_6 in *t*-BuOH/CH_3CN (Scheme 17). Reprotection with triethylsilyl triflate provided the tris(silyl ether) **59** in 73% yield. Selective deprotection of the primary TES ether by reaction with aqueous camphorsulfonic acid in THF at 0 °C did not proceed smoothly and provided an unoptimized 56% yield of the desired alcohol **60** along with 40% of diol **61**. Alcohol **60** was oxidized with Dess−Martin periodinane to provide the TES-protected aldehyde **62** in 92% yield.

Investigation of the *anti*-aldol reaction with the newly protected substrates **57** and **62** (1.18 equiv) afforded the desired aldol product in approximately 70% yield, along with recovered aldehyde (35%) and another diastereomer (ca. 9%). Since the aldol product **63** was contaminated with a small amount of the copolar ketone **57**, a selective deprotection of the TES ether was performed on the mixture with HF·pyridine in THF at 0 °C to provide the desired diol **64** in a combined yield of 57% for the two steps. Acetylation with acetic anhydride and DMAP in pyridine gave diacetate **65** in 92% yield (Scheme 18).

At this point, we have in hand several hundred milligrams of compound **65**, corresponding to the ABCD subunit of spongistatin 1 (altohyrtin A). The final protecting group array has proven feasible for the synthesis of this subunit and is consistent with our plans for the remainder of the synthesis. The protecting group shuffle at the end of the route is obviously not optimal, but this can easily be remedied by installation of the appropriate protecting groups when larger quantities of **56** and **61** are prepared for future development of the synthesis. Investigations on the coupling of **64** to the EF subunit and completion of the total synthesis of spongistatin 1 are currently underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization for all new compounds reported in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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