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A Second-Generation Synthesis of the C1−C28 Portion of the Altohyrtins (Spongistatins)

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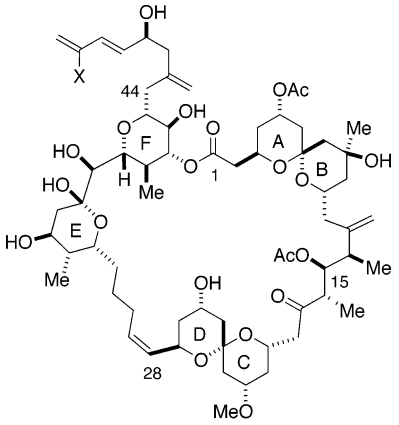
Abstract: A practical second-generation synthesis of an advanced intermediate in our total synthesis of altohyrtin C (spongistatin 2) has been developed. A new approach to the C1−C15 (AB) portion features a vinyllithium addition to an aldehyde followed by a palladium-catalyzed allylic reduction to install the troublesome C13−C15 segment. Our general approach to the C16−C28 (CD) spiroketal has been retained, but some improvements have been made. Most notably, the kinetically controlled CD-spiroketalization reaction now proceeds in high yield with excellent diastereoselection. This new strategy uses the anti-aldol coupling used in our first-generation synthesis to join AB and CD fragments. A total of 9.6 g of intermediate **57** has been produced using this improved route.

In 1993, the groups of Pettit, Kitagawa, and Fusetani independently reported the isolation and characterization of a group of remarkably active antitumor compounds from marine sponges. Pettit reported the isolation of spongistatin 1 from a *Spongia* sp. in the Indian Ocean,[1] Kitagawa described the isolation of altohyrtin A from the Okinawan sponge *Hyrtios altum*,[2] and Fusetani reported the isolation of cinachyrolide A off the coast of the Japanese island Hachijo-jima from a sponge of the genus *Cinachyra*.[3] In addition to these initial reports, a number of additional compounds in this family were reported by Pettit[4] and Kitagawa.[5] In 1994, on the basis of Mosher's ester and circular dichroism analysis, Kitagawa and co-workers established the absolute and relative configurations of the altohyrtins.[6] The antitumor activity of this family of molecules compounds has been described as "probably the best to date in the NCI's evaluation programs."[7] Altohyrtin A (spongistatin 1), the most active member, has an average IC_{50} of 0.13 nM against the NCI's panel of 60 cancer cell lines and is even more active against certain cell lines in the panel.[8] The altohyrtins act by inhibiting tubulin polymerization and seem to bind at a unique site on the tubulin dimer.[8]



1: R = Cl (altohyrtin A; spongistatin 1)
2: R = H (altohyrtin C; spongistatin 2)

The altohyrtins have attracted the attention of a number of other research groups, and so far there have been five total syntheses.[9−13] In addition, a number of other groups have reported efforts toward the total synthesis of the altohyrtins.[14] The syntheses reported to date have been "traditional", in the sense that they have contributed a great deal to our understand-

(1) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. *J. Org. Chem.* **1993**, *58*, 1302.
(2) Kobayashi, M.; Aoki, S.; Sakai, H.; Kawazon, K.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Tetrahedron Lett.* **1993**, *34*, 1993.
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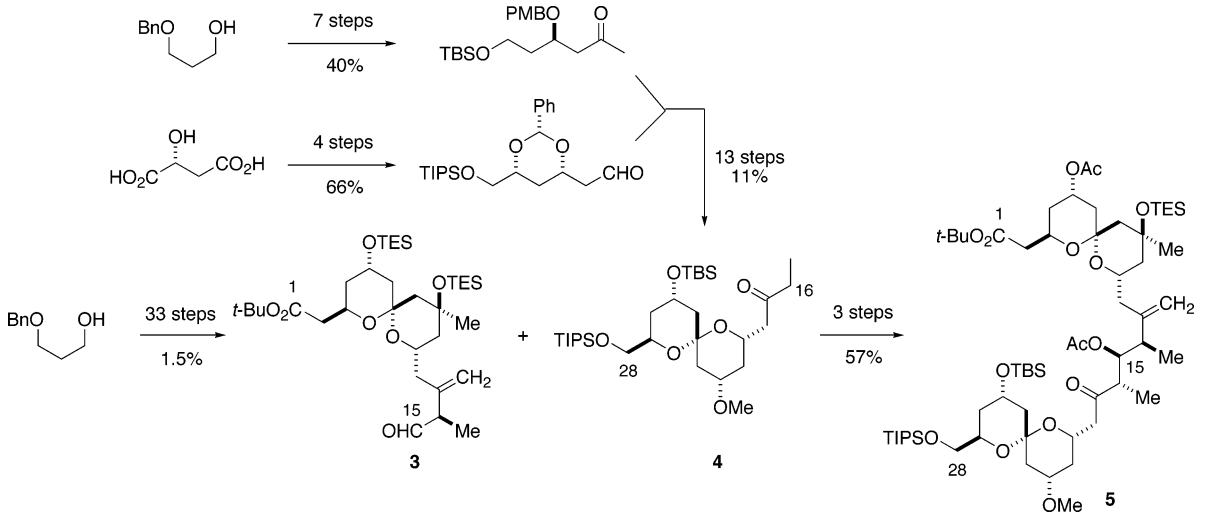
(5) Kobayashi, M.; Aoki, S.; Sakai, H.; Kawazon, K.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1993**, *41*, 989.
(6) Kobayashi, M.; Aoki, S.; Kitagawa, I. *Tetrahedron Lett.* **1994**, *35*, 1243.
(7) Pettit, G. R. *J. Nat. Prod.* **1996**, *59*, 812−821.
(8) Bai, R.; Taylor, G. F.; Cichacz, Z. A.; Herald, C. L.; Kepler, J. A.; Pettit, G. R.; Hamel, E. *Biochemistry* **1995**, *34*, 9714.
(9) (a) Evans, D. A.; Coleman, P. J.; Dias, L. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2738−2741. (b) Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2741−2741. (c) Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J.; Dias, L. C.; Tyler, A. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2744−2747. (d) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671−8726.
(10) (a) Guo, J.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 187−192. (b) Hayward, M. M.; Roth, R. M.; Duffy, K. J.; Dalko, P. I.; Stevens, K. L.; Guo, J.; Kishi, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 192−196.

10.1021/ja030316h CCC: $25.00

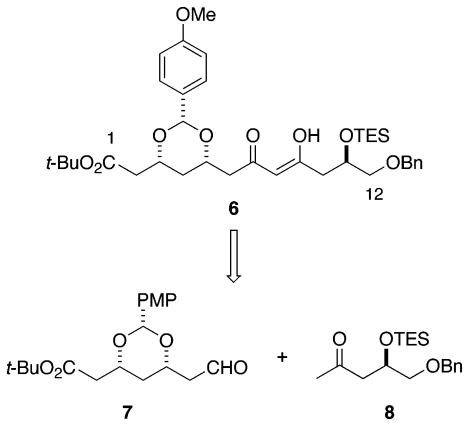
Scheme 1



ing of organic synthesis and, in particular, to the unique synthetic challenges presented by the altohyrtin skeleton, but they have not provided significantly more altohyrtin than has been isolated from the natural source—none of the previous syntheses has provided more than 4 mg of final product. It is our goal to develop a total synthesis that is sufficiently efficient that we can prepare multigram quantities of altohyrtin C (spongistatin 2).

We have previously reported first-generation syntheses of the C1−C28 and C29−C44 building blocks (Scheme 1).[15,16] Our synthesis of the C1−C28 segment **5** required 60 total steps, a longest linear sequence of 36 steps, and gave an overall yield for this sequence of 0.86% (somewhat higher if one includes recycling at several stages). The synthesis permitted us to prepare several hundred milligrams of **5**, but needed significant improvement if we are to prepare gram quantities of altohyrtins. In this and the following Article, we report a second-generation synthesis of the C1−C28 segment that has yielded almost 10 grams of the intermediate and the incorporation of this building block in a total synthesis of altohyrtin C (spongistatin 2).

One of the problems in our first-generation synthesis was the long linear synthesis of compound **3**, representing C1−C15. Furthermore, nine of these 33 steps, proceeding in only 41% overall yield, were required to add C14 and C15 and install the methylene group at C13. Thus, one goal of our second-generation synthesis was to develop a convergent synthesis of the A/B spiroketal moiety, and another was to develop a better way of incorporating C13−C15. Indeed, we had already developed such a convergent route for the synthesis of the C/D spiroketal **4** (see Scheme 1). Another goal that we had in mind in developing a revised synthesis of C1−C28 was to make the synthetic approaches to the A/B and C/D spiroketal subunits as similar as possible, so that we can start with identical or enantiomeric starting materials and minimize the number of chemically different operations. To meet these objectives, we identified compound **6** as our target and envisioned this spiroketal precursor as arising from unification of aldehyde **7** with methyl ketone **8** in a manner similar to that used for the synthesis of the C/D spiroketal in our first-generation synthesis.



The improved route to intermediate **7** starts with (*S*)-malic acid (Scheme 2) and utilizes a sequence similar to that

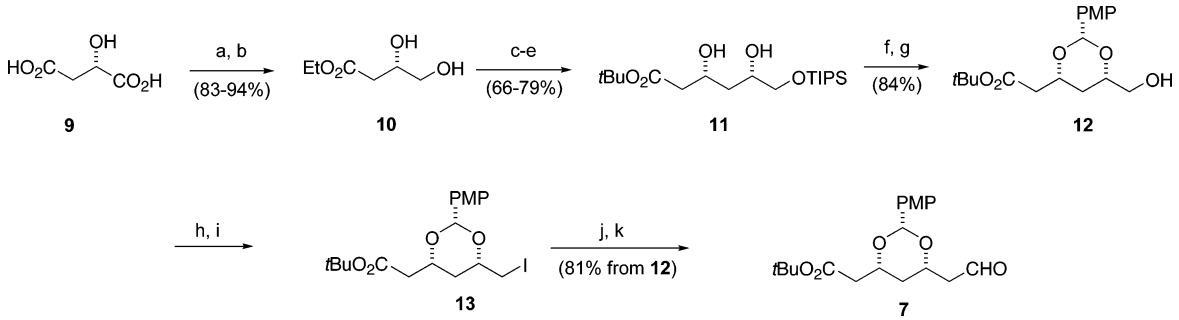
(11) (a) Smith, A. B., III; Doughty, V. A.; Lin, Q.; Zhuang, L.; McBriar, M. D.; Boldi, A. M.; Moser, W. H.; Murase, N.; Nakayama, K.; Sobukawa, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 191. (b) Smith, A. B., III; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Kerns, J. K.; Brook, C. S.; Murase, N.; Nakayama, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 196. (c) Smith, A. B., III; Doughty, V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett.* **2002**, *4*, 783.

(12) (a) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581. (b) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585. (c) Paterson, I.; Keown, L. E. *Tetrahedron Lett.* **1997**, *38*, 5727. (d) Paterson, I.; Oballa, R. M. *Tetrahedron Lett.* **1997**, *38*, 8241. (e) Paterson, I.; Wallace, D. J.; Gibson, K. R. *Tetrahedron Lett.* **1997**, *38*, 8911. (f) Paterson, I.; Chen, D. Y.-K.; Coster, M. J.; Aceña, J. L.; Bach, J.; Gibson, K. R.; Keown, L. E.; Oballa, R. M.; Trieselmann, T.; Wallace, D. J.; Hodgson, A. P.; Norcross, R. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4055−4060.

(13) (a) Crimmins, M. T.; Washburn, D. G. *Tetrahedron Lett.* **1998**, *39*, 7487. (b) Crimmins, M. T.; Katz, J. D.; McAtee, L. C.; Tabet, E. A.; Kirincich, S. J. *Org. Lett.* **2001**, *3*, 949−952. (c) Crimmins, M. T.; Katz, J. D. *Org. Lett.* **2000**, *2*, 957−960. (d) Crimmins, M. T.; Katz, J. D.; Washburn, D. G.; Allwein, S. P.; McAtee, L. F. *J. Am. Chem. Soc.* **2002**, *124*, 5661−5663.

(14) For leading references to synthetic approaches from other laboratories, see the list in ref 16, plus the following: (a) Zuev, D.; Paquette, L. A. *Org. Lett.* **2000**, *2*, 679−682. (b) Terauchi, T.; Nakata, M. *Tetrahedron Lett.* **1998**, *39*, 3795−3798. (c) Lemaire-Audoire, S.; Vogel, P. *Tetrahedron Lett.* **1998**, *39*, 1345−1348. (d) Lemaire-Audoire, S.; Vogel, P. *J. Org. Chem.* **2000**, *65*, 3346−3356. (e) Zemribo, R.; Mead, K. T. *Tetrahedron Lett.* **1998**, *39*, 3895−3898. (f) Fernandez-Megia, E.; Gourlaouen, N.; Ley, S. V.; Rowlands, G. J. *Synlett* **1998**, 991−994. (g) Micalizio, G. C.; Pinchuk, A. N.; Roush, W. R. *J. Org. Chem.* **2000**, *65*, 8730−8736. (h) Anderson, J. C.; McDermott, B. P. *Tetrahedron Lett.* **1999**, *40*, 7135−7138. (i) Samadi, M.; Munoz-Letelier, C.; Poigny, S.; Guyot, M. *Tetrahedron Lett.* **2000**, *41*, 3349−3353. (j) Terauchi, T.; Terauchi, T.; Sato, I.; Tsukada, T.; Kanoh, N.; Nakata, M. *Tetrahedron Lett.* **2000**, *41*, 2649−2653. (k) Kary, P. D.; Roberts, S. M. *Tetrahedron: Asymmetry* **1999**, *10*, 217−219. (l) Kim, H.; Hoffmann, M. R. *Eur. J. Org. Chem.* **2000**, 2195−2201. (m) Barrett, A. G. M.; Braddock, D. C.; de Koning, P. D.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 375−380.

Scheme 2 [a]



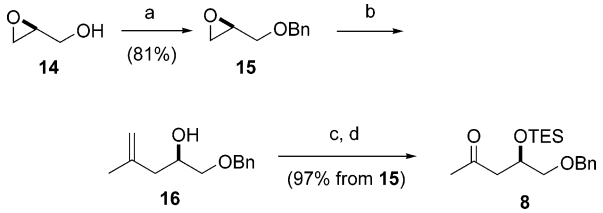
[a] (a) EtOH, $SOCl_2$; (b) BMS, $NaBH_4$, THF; (c) TIPSCl, imidazole, DMF; (d) *tert*-butylthio acetate, THF; (e) Et_2BOMe, $NaBH_4$, THF, MeOH; (f) 4-MeOPhCH(OMe)$_2$, PPTS, CH_2Cl_2; (g) TBAF, THF; (h) 4-ClPhSO$_2$Cl, Et_3N, CH_2Cl_2; (i) NaI, $NaHCO_3$, Na_2SO_3, MEK; (j) vinylmagnesium bromide, Li_2CuCl_4, THF; (k) O_3, MeOH, CH_2Cl_2, Bu_3P.

previously employed in the synthesis of the CD spiroketal.[17] Diethyl (*S*)-malate, formed by esterification with thionyl chloride in EtOH, was regioselectively reduced with borane−dimethyl sulfide complex and catalytic sodium borohydride[18] to produce diol **10** in 83−94% yield. Diol **10** was protected as the primary TIPS ether immediately after purification to avoid lactonization, and the resulting compound was converted to the β-keto ester by a mixed Claisen condensation with the lithium enolate of *tert*-butyl acetate. The C3 ketone carbonyl was stereoselectively reduced to 1,3-syn diol **11** by a chelation-controlled reduction with diethyl methoxy borane and sodium borohydride.[19] Treatment of diol **11** with anisaldehyde dimethyl acetal and PPTS afforded the *p*-methoxybenzylidine acetal which was desilylated to alcohol **12**. Alcohol **12** was homologated to aldehyde **7** by a four-step sequence involving formation of the *p*-chlorobenzenesulfonate,[20] which was displaced with NaI in methyl ethyl ketone to obtain iodide **13**. The iodide was displaced by the cuprate derived from vinylmagnesium bromide and catalytic Li_2CuCl_4, and the resulting alkene was carefully ozonized (Sudan III dye indicator) to give aldehyde **7**.[21]

Ketone **8** was prepared by the efficient four-step sequence shown in Scheme 3. When (*S*)-glycidol benzyl ether (**15**)[22] was treated with isopropenylmagnesium bromide and Li_2CuCl_4, the epoxide was smoothly opened by the vinyl cuprate to give homoallylic alcohol **16**. This material was treated with TESCl and imidazole to protect the hydroxyl group, and the alkene was ozonized to give ketone **8** in 97% yield from epoxy ether **15**.

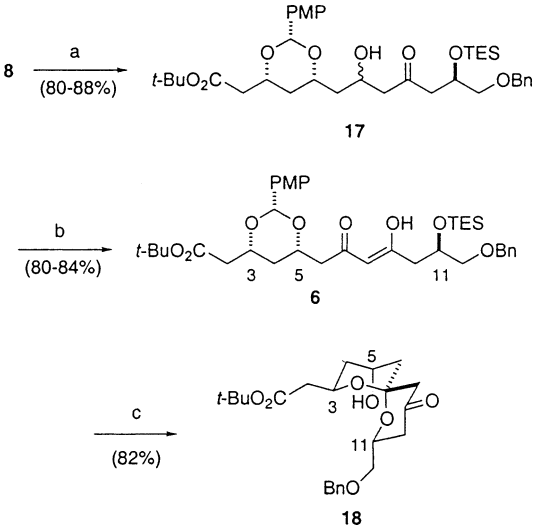
Spiroketalization precursor **6** was prepared as shown in Scheme 4. The lithium enolate of ketone **8** reacted with aldehyde **7** to give a mixture of aldol diastereomers (**17**) in 80−88% yield. These aldols were oxidized with the Dess−Martin reagent to give diketone **6**, which was isolated as its enolic form in 80−84% yield. The Dess−Martin oxidation reaction deserves special comment. A survey of a variety of oxidizing reagents was explored.[23] Standard Dess−Martin conditions (periodinane, CH_2Cl_2)[24] led to irreproducible yields (30−80%).[25] In the course of optimizing the reaction conditions, we noticed that higher yields resulted when a heavy precipitate formed as the reaction progressed. We hypothesized that this was an iodine-III species

Scheme 3 [a]



[a] (a) NaH, BnBr, DMF; (b) isopropenylmagnesium bromide, Li_2CuCl_4, THF; (c) TESCl, imidazole, DMF; (d) (i) O_3, $NaHCO_3$, MeOH, CH_2Cl_2; (ii) DMS.

Scheme 4 [a]



[a] (a) LDA, then **7**; (b) Dess−Martin, 1 equiv of H_2O, THF, CH_2Cl_2; (c) 10:10:1 THF:CH_3CN:12 N HCl.

(15) (a) Claffey, M. M.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 7646−7647. (b) Hayes, C. J.; Heathcock, C. H. *J. Org. Chem.* **1997**, *62*, 2678−2679. (c) Claffey, M. M.; Hayes, C. J.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8267−8274.

(16) Wallace, G. A.; Scott, R. W.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 4145−4152.

(17) The enantiomer of **9** was used, see ref 15.

(18) Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067.

(19) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.

(20) It was necessary to use the *p*-chlorosulfonate instead of the more common tosylate because the *p*-anisilidine acetal was hydrolyzed under the reaction conditions with longer reaction times necessary to displace the tosylate even in the presence of $NaHCO_3$ and Na_2SO_3.

(21) Use of tributylphosphine as the reducing agent minimized methanolysis of the acetal in this step.

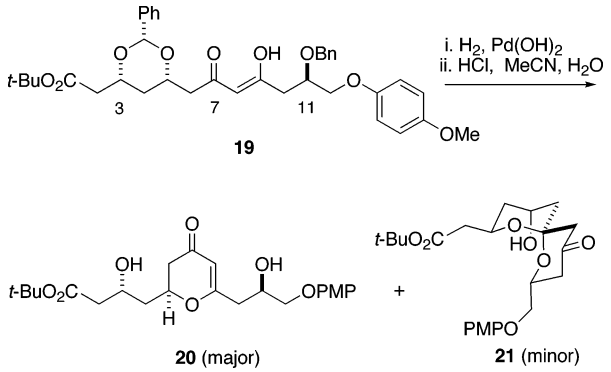
(22) Tse, B. *J. Am. Chem. Soc.* **1996**, *118*, 7094. Compound **15** is also commercially available from the Aldrich Chemical Co.

(23) Oxidizing reagents surveyed include Moffat−Swern; CrO_3, pyridine; IBX; PDC; TPAP, NMO; Dess−Martin, pyridine.

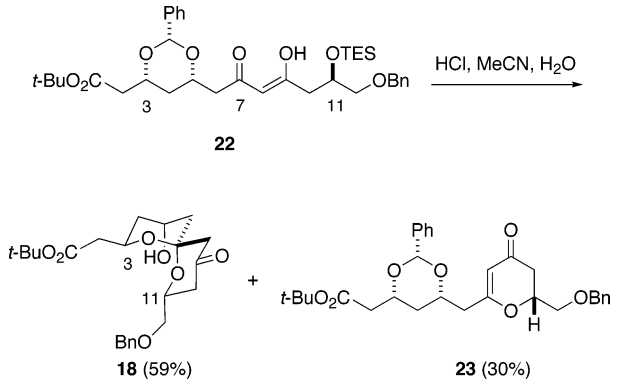
(24) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4155.

(25) Problems with oxidation of aldol products under Dess−Martin conditions have been noted previously: Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

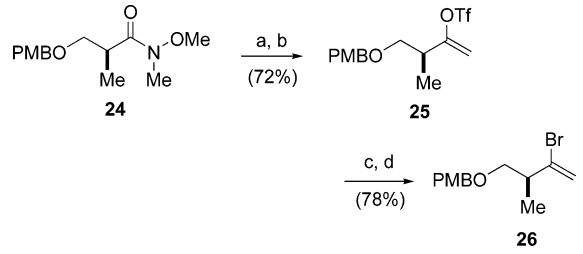
Scheme 5



Scheme 6



Scheme 7 [a]



[a] (a) MeLi, Et_2O; (b) LiHMDS, 4-chloro-2-aminopyridyl triflimide, THF; (c) Bu_3SnH, LDA, CuCN, THF; (d) NBS, CH_2Cl_2.

and that, if it were to remain in solution, it might have a deleterious effect by oxidizing the diketone product.[26] When the oxidation was carried out in 1:1 THF:CH_2Cl_2 with 1 equiv of water, the amount of precipitate was maximized, and we were able to obtain reproducibly excellent yields of the enolic diketone **6**. This observation is in contrast to the report of Meyer and Schreiber, who advise the use of Dess−Martin periodinane in methylene chloride under strictly *anhydrous* conditions for the oxidation of β-hydroxy esters to β-keto esters.[27] These authors report that water accelerates Dess−Martin oxidations and increases the amount of tricarbonyl compound, whereas our conditions decelerate the oxidation and result in less tricarbonyl compound.

Treatment of **6** with HCl in THF−CH_3CN gave spiroketal **18** in 82% yield. As expected, only one diastereomer (*R* configuration at the anomeric position) was produced in the spiroketalization reaction because the most stable chair−chair conformation of this diastereomer has both carbon substituents equatorial and both oxygens axial with respect to the other ring, thus profiting from a "double anomeric effect".[28]

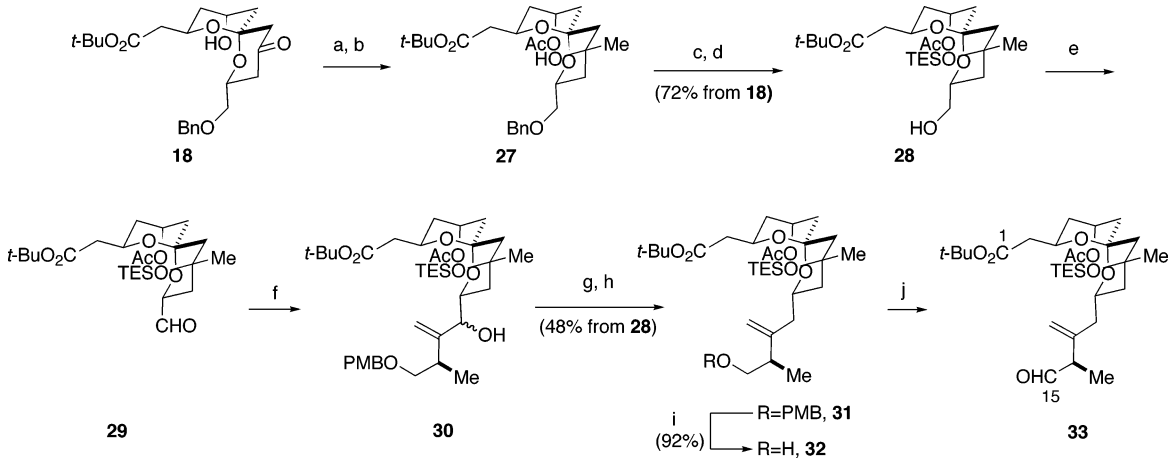
Success in the spiroketalization reaction depends strongly on the correct choice of protecting groups for the C3,C5 diol and C11 hydroxy group. In preliminary investigations, we explored the use of a simple benzylidine group to protect the C3 and C5 syn diol. As shown in Scheme 5, this derivative (**19**)[29] was protected by a benzyl at C11, so that all three OH groups (C3, C5, and C11) could be revealed at one time, prior to the spiroketalization. After catalytic hydrogenolysis of the benzyl ethers, the resulting triol was treated with HCl in aqueous acetonitrile to get a mixture of dihydropyrone **20** and spiroketal **21**. Attempts to convert **20** into the desired product by longer treatment under acidic conditions sufficed only to destroy **20**, probably by dehydration of the C11 alcohol and by hydrolysis of the *tert*-butyl ester. The best isolated yield of spiroketal **21** was 32%.

We also investigated compound **22**,[27] in which the C11 hydroxy group is protected as a triethylsilyl ether (Scheme 6). In this case, both the TES and the benzylidine groups can be removed by treatment with acid, so we were able to use a benzyl group for the C12 primary alcohol, rather than the much less convenient *p*-methoxyphenyl group. However, treatment of **22** with 5:5:1 THF, acetonitrile, and 6 N HCl gave 59% yield of the desired spiroketal **18**, accompanied by 30% yield of the dihydropyrone **23**. Further treatment of **23** with aqueous acid did result in formation of more **18**, but also resulted in some decomposition, apparently due to hydrolysis of the *tert*-butyl ester and dehydration of one or more of the secondary alcohols. It was this result that prompted us to use a more acid-labile benzylidine group for protection of the C3,C5 diol.

One way in which we hoped to improve on our first-generation synthesis was the method for adding the "orphan" stereocenter at C14. Because this stereocenter is not part of a rigid ring, as are those in the spiroketal moiety, it must be introduced by absolute stereocontrol using a chiral reagent or by using a "chiral pool" building block. In our previous synthesis, we introduced this center by use of an Evans asymmetric aldol reaction. This necessitated a number of steps to change a C13 hydroxy group into the required methylene group and contributed greatly to the long linear sequence of steps required to synthesize the full C1−C15 building block. In our revised approach, we elected to use a chiral building block that would carry both the necessary C13 methylene group and the C14 stereocenter. Such a starting material is (*S*)-2-methyl-3-hydroxypropanoic acid, which has previously been converted into Weinreb amide **24** by Paterson and co-workers.[30] As shown in Scheme 7, this material is converted to a methyl ketone which is deprotonated by LiHMDS and the resulting enolate treated with 4-chloro-2-aminopyridyl triflimide to obtain vinyl triflate **25**. The triflate was converted to the vinylstannane by a copper-mediated coupling reaction, and this stannane was readily converted to vinyl bromide **26** upon treatment with NBS.

(26) The oxidation of diketones by iodine-III species is a well-known process, see for a review: Moriarty, R. M.; Prakash, O. *Org. React.* **1999**, *54*, 273. We have also isolated the triketone product in a similar system: Claffey, M. M.; Heathcock, C. H., unpublished results.
(27) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549−7552.
(28) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauvé, G.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105.
(29) See the Supporting Information for the reactions used and yields obtained in the preparation of **19** and **22**.
(30) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535.

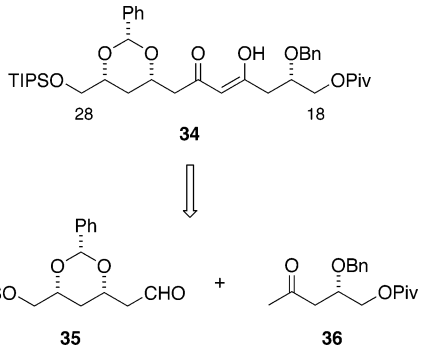
Scheme 8 [a]



[a] (a) MeLi, $CeCl_3$, THF; (b) Ac_2O, DMAP, CH_2Cl_2; (c) TESOTf, 2,6-lutidine, CH_2Cl_2; (d) H_2, $Pd(OH)_2$, THF; (e) Moffat−Swern; (f) bromide **26** plus 2 equiv of *t*-BuLi, Et_2O, then **29**; (g) *N*-formylbenzotriazole, DMAP, CH_2Cl_2; (h) $Pd_2(dba)_3$, Bu_3P, NH_4CO_2H, cyclohexane; (i) DDQ, CH_2Cl_2, H_2O; (j) Dess−Martin, CH_2Cl_2.

The remainder of the C1−C15 synthesis is summarized in Scheme 8. We first converted the ketone of **18** to the tertiary alcohol by the addition of methyllithium in the presence of $CeCl_3$. The secondary alcohol of the resulting diol was selectively protected with acetic anhydride and DMAP to give diester **27**. The tertiary alcohol was protected with TESOTf, and the benzyl ether was removed by hydrogenolysis to give alcohol **28** in 72% yield over the four steps from **18**. Alcohol **18** could be converted to aldehyde **29** under Moffat−Swern conditions.[31] Bromide **26** (prepared as shown in Scheme 7) was lithiated with *tert*-butyllithium and the resulting vinyllithium reagent was treated with aldehyde **29** to obtain alcohol **30** as a 1:1 mixture of diastereomers. The alcohol was formylated by Katritzky's method,[32] and the resulting allylic formate was reduced by Tsuji's method,[33] using $Pd(PBu_3)_4$ in the presence of ammonium formate to give the reduction product **31** in 48% yield from alcohol **28** as the only observed regioisomer.[34] The PMB protecting group in **31** could be removed under standard conditions with DDQ[35] to give alcohol **32** in 92% yield. This alcohol was oxidized with Dess−Martin reagent to give aldehyde **33**. This compound is quite prone to double bond isomerization and is used in the aldol coupling without purification. The conversion of alcohol **28** into alcohol **32** proceeds in 44% overall yield, as compared to 41% overall yield for a similar conversion in our first-generation synthesis. However, the new route only requires five steps rather than nine steps, resulting in significant savings in reagent costs. Most importantly, it avoids the technically challenging Tebbe methylenation that was used to install the C13 methylene group in our original route.

Now that after we had developed a more efficient synthesis of the AB spiroketal, we turned our attention to improving our first-generation synthesis of the CD spiroketal moiety, ketone **4** (see Scheme 1). Our revised retrosynthetic plan is summarized below:

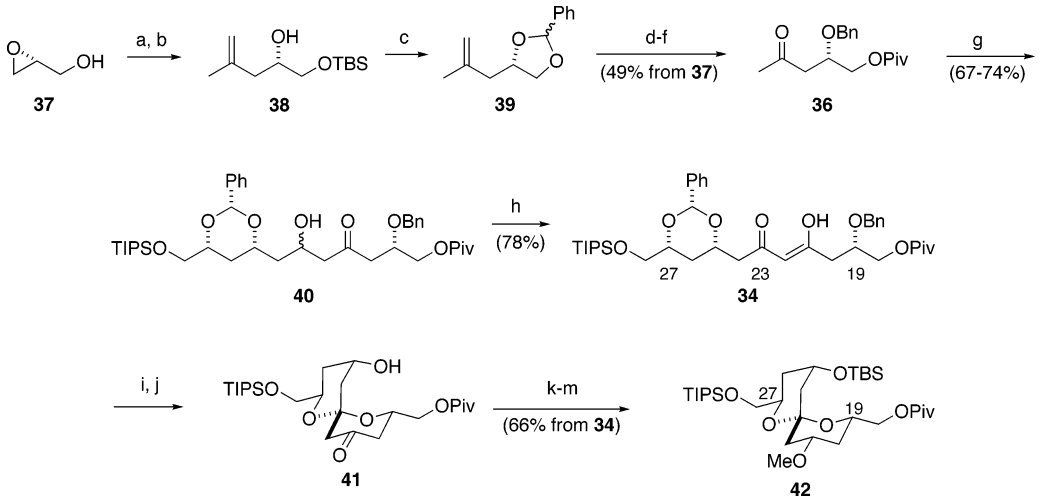


In this plan, we have made two significant changes from our first-generation synthesis of the C16−C28 segment. First, compound **34** has one less carbon in the chain than the spiroketalization substrate previously employed. Second, we have chosen a pivaloyl ester as the terminal protecting group instead of the TBS ether used in the first-generation synthesis, mainly because our previous experience with TBS ethers has shown that they are somewhat labile to the hydrogenolysis conditions necessary to remove the benzyl and benzylidine groups. In addition, we thought that the similar steric environment of the two terminal positions in **34** might make it difficult to selectively remove a TBS protecting group in the presence of a TIPS protecting group.[36] To assemble the spiroketalization precursor **34**, we needed aldehyde **35** and ketone **36**. Aldehyde **35** was prepared as we have previously described.[15c]

We started the synthesis of ketone **36** with (*R*)-glycidol (**37**), as shown in Scheme 9. Protection of the alcohol and opening of the epoxide with isopropenylmagnesium bromide in the presence of catalytic Li_2CuCl_4 gave secondary alcohol **38**.[37] Benzylidine acetal **39** was prepared by treating monoether **38** with benzaldehyde dimethyl acetal and camphorsulfonic acid. Reduction of **39** with diisobutylaluminum hydride resulted in regioselective cleavage of the benzylidine group, leading to the primary alcohol, which was protected as the pivaloyl ester.

(31) Tidwell, T. T. *Org. React.* **1990**, *39*, 297−572.
(32) Katritzky, A. R.; Chang, H. X.; Yang, B. *Synthesis* **1995**, 503.
(33) (a) Tsuji, J.; Yamakawa, T. *Tetrahedron Lett.* **1979**, *7*, 613. (b) Tsuji, J.; Shimizu, I.; Minami, I. *Chem. Lett.* **1984**, 1017.
(34) Care had to be taken to avoid overreduction to the alkane; TLC analysis with 30% ethyl acetate in benzene separates the alkene from the overreduced product.
(35) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.
(36) Recall that our first-generation spiroketalization substrate had one more carbon in the chain, making the TBS ether in that case significantly less sterically hindered.
(37) Migration of the pivaloyl protecting group to the secondary alcohol was observed during the epoxide opening when the more direct route from glycidol pivalate was attempted.

Scheme 9 [a]

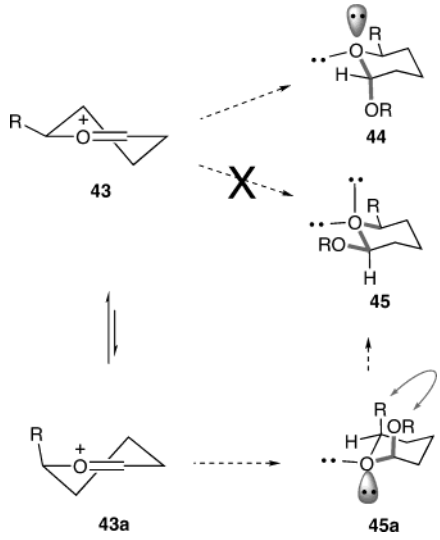


[a] (a) TBSCl, imidazole, DMF; (b) isopropenylmagnesium bromide, Li_2CuCl_4, THF; (c) $PhCH(OMe)_2$, CSA, cat. MeOH, DMF; (d) DIBAL, CH_2Cl_2; (e) PivCl, Et_3N, DMAP, CH_2Cl_2; (f) OsO_4, $NaIO_4$, THF, H_2O; (g) LDA, then **35**; (h) Dess−Martin, H_2O, CH_2Cl_2, THF; (i) H_2, $Pd(OH)_2$, THF; (j) $ZnBr_2$, CH_2Cl_2; (k) TBSOTF, 2,6-lutidine, CH_2Cl_2; (l) $NaBH_4$, $CeCl_3$, MeOH; (m) Cs_2CO_3, NaH, MeI.

Cleavage of the double bond under Johnson−Lemieux conditions[38] delivered ketone **36** in 49% yield from (*R*)-glycidol without purification of any of the intermediates. Ketone **36** was coupled to aldehyde **35** by a lithium enolate aldol reaction to give hydroxy ketone **40** as a mixture of diastereomers. This mixture was oxidized with the Dess−Martin conditions developed for the AB spiroketal (vide supra) to give the diketone, which exists completely in the enolic form **34**, in 78% yield.

The benzyl ether and benzylidine acetal were cleaved by hydrogenolysis, and the resulting crude triol was treated with anhydrous $ZnBr_2$ in methylene chloride. Remarkably, *R* spiroketal **41** was produced in greater than 80% yield as the only observed diastereomer! This was quite a welcome result, because the similar spiroketalization in our first-generation synthesis[15c] had delivered the *R* and *S* spiroketals as a 7:1 mixture in a total yield of about 60%. Without further purification, compound **41** was silylated with *tert*-butyldimethylsilyl triflate. In their altohyrtin synthesis, Crimmins and co-workers found that a similar ketone can be reduced selectively to the desired equatorial alcohol with hydride reducing reagents.[39] A quick survey of such reducing agents revealed that ketone **41** is selectively reduced under Luche conditions, giving the desired equatorial isomer exclusively. This alcohol was then methylated with MeI, Cs_2CO_3, and NaH to give compound **58**.[40] The five-step sequence that converts diketone **34** to spiroketal **42** in 66% yield is a significant improvement over the similar sequence used in the first-generation synthesis, which gave a comparable intermediate in only 29% yield.

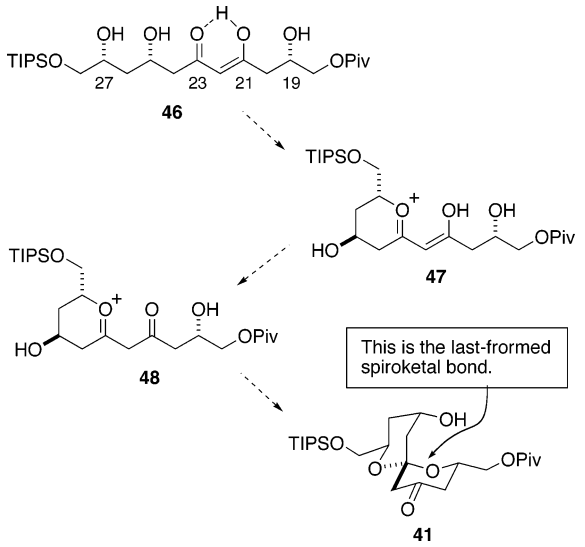
The remarkable stereoselectivity observed in the C/D spiroketalization reaction deserves comment. Previous studies[15b] have shown that the *R* and *S* spiroketals are of comparable stability and that extended treatment of the *R* spiroketal results in isomerization to the *S* configuration. Therefore, the high stereoselectivity observed in the conversion of **34** to **41** is clearly a kinetic result. Yet why should the *R* spiroketal be the kinetic product of ketalization? To understand this result, it is first necessary to realize that the stereochemistry of nucleophilic additions to cyclic oxocarbenium ions is subject to the same stereoelectronic effect[41] that operates in additions to cyclic enones[42] and imines.[43] That is, when an alcohol adds to oxocarbenium ion **43**, the kinetic product for stereoelectronic reasons should be **44** in which the new C−O bond is anticoplanar with one of the oxygen lone pairs, not **45**, in which the new bond is gauche to both lone pairs. Thus, if the conformation is as shown in the following example, the newly formed ketal bond will be trans to the substituent at C5:



Of course, the alternative half-chair conformation of oxocarbenium ion **43** (shown above as **43a**) could undergo axial

(38) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
(39) Crimmins, M. T.; Katz, J. D. *Org. Lett.* **2000**, *2*, 957. They used L-Selectride for their reduction.
(40) These unusual conditions were originally developed in a trial reaction where Cs_2CO_3 and MeI did not effect the desired reaction so NaH was added to the reaction mixture.
(41) Deslongchamps, P. Stereoelectronic Effects in Organic Chemistry. In *Organic Chemistry Series*; Baldwin, J. E., Ed.; Pergamon Press: Oxford, 1989; Vol. 1.
(42) (a) Corey, E. J. *Experentia* **1953**, *9*, 329. (b) Corey, E. J. *J. Am. Chem. Soc.* **1954**, *76*, 175. (c) Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 6229.
(43) (a) Stevens, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 102. (b) Stevens, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 103.

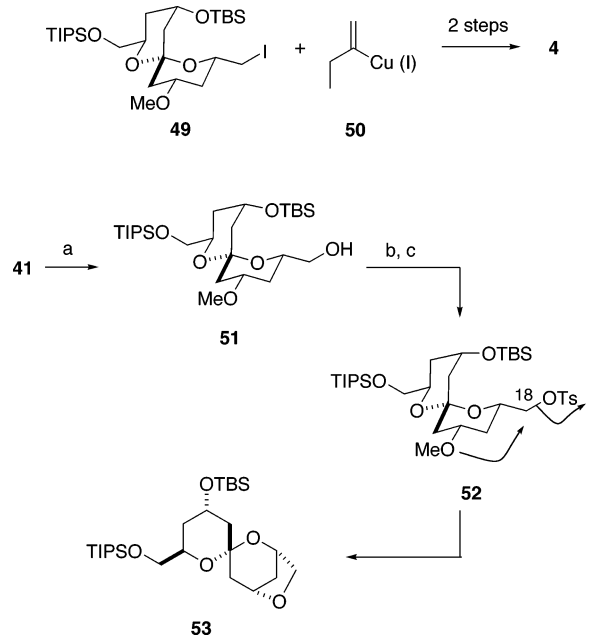
Scheme 10



addition of the alkoxy group, leading to conformer **45a**, which would eventually isomerize to the cis isomer **45**. This possibility is disfavored both by the fact that conformer **43a** is probably somewhat disfavored, relative to **43**, and by the steric hindrance that would result from interaction of the incoming axial OR group with the R group.[44] Another possibility for the observed kinetic stereoselectivity in the spiroketalization process, suggested by a reviewer, is that the zinc cation templates the *R* configuration at the spiroketal center by chelation to the C25 axial hydroxyl, the spiroketal O, and one of the C17 pivalolyoxy oxygens, along the lines suggested by Evans.[9c] However, the stereoselectivity observed in the present case is much greater than that seen by Evans, who used zinc chloride in methylene chloride to equilibrate a 1:6 ratio of *R* and *S* spiroketals (obtained by protic acid spiroketalization) to a 4.3:1 ratio.

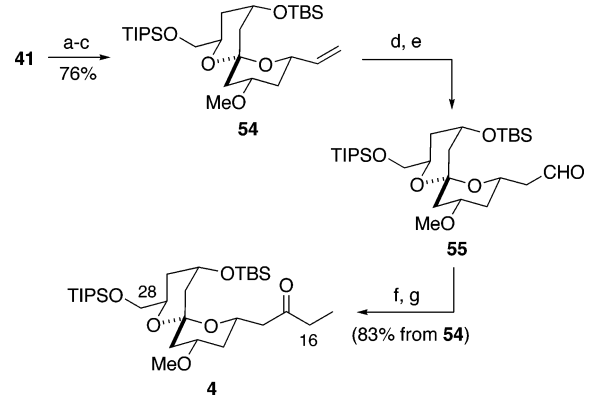
Because we have chosen a spiroketalization substrate with a carbonyl group at C21 (altohyrtin numbering), and because the 1,3-diketone exists completely in the intramolecularly hydrogen-bonded form illustrated in Scheme 10, the first ketal bond to form involves the C27 hydroxy group, leading to postulated intermediate oxocarbenium ion **47**. After ketonization of the enol in **47**, postulated intermediate **48**, now freed of its constraints, can undergo addition of the C19 hydroxy group. The stereoelectronic principle now ensures that the C19 hydroxy group will add trans to the C27 substituent, thus delivering the *R*-configured spiroketal.[45] We think that the higher stereoselectivity observed in the present case, relative to the very similar one employed in our first-generation synthesis, is due to slower equilibration of the kinetic product in the current case, possibly because the deletion of one carbon in this case has brought the pivaloyloxy group closer to the oxocarbenium ion, thus retarding subsequent ketal isomerization.[46]

Scheme 11 [a]



[a] (a) DIBAL, CH_2Cl_2; (b) TsCl, Et_3N, CH_2Cl_2; (c) NaI, MEK, reflux.

Scheme 12 [a]



[a] (a) DIBAL, CH_2Cl_2; (b) Moffat−Swern; (c) Ph_3PCH_2, THF; (d) (i) 9-BBN; (ii) H_2O_2, NaOH; (e) Dess−Martin, CH_2Cl_2; (f) EtMgBr, THF; (g) Dess−Martin, CH_2Cl_2.

Now that the difficult transformations were behind us, we were ready to convert compound **42** to ethyl ketone **4**. Our original plan for carrying out this transformation is shown in Scheme 11. In a manner similar to our conversion of iodide **13** to aldehyde **7** (see Scheme 2), we planned to couple iodide **49** with a vinyl cuprate **50** to obtain an alkene that could be oxidatively cleaved to give ketone **4**. To this end, the pivaloyl protecting group in **41** was removed by reduction with diisobutylaluminum hydride, and the resulting primary alcohol was converted to the tosylate with tosyl chloride and Et_3N. Unfortunately, all attempts to convert this sulfonate to the necessary iodide failed because the oxygen of the methyl ether readily displaces the leaving group at C18 to give the tricyclic ether **53**.

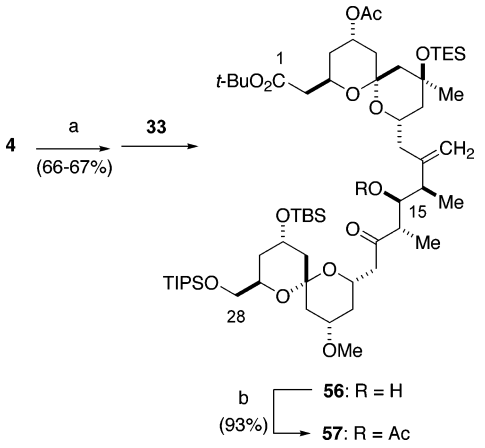
To avoid this problem, a more circuitous route to ketone **4** was employed (Scheme 12). After the pivaloyl group was removed by reduction with diisobutylaluminum hydride, the resulting alcohol was oxidized under Moffat−Swern conditions, and the aldehyde was subjected to Wittig methylenation to obtain alkene **54** in 76% yield from **41**. This alkene was

(44) For a similar example and detailed analysis of the situation, see: Pothier, N.; Goldstein, S.; Deslongchamps, P. *Helv. Chim. Acta* **1992**, *75*, 604−620.

(45) The same stereoelectronic preference operates in the formation of the A/B spiroketal **18** (Scheme 4). In that case, axial addition of the C11 hydroxy group should give the observed *S* spiroketal because addition should be trans to the substituent at C3, which in this case has the *R* configuration.

(46) For examples in which proximal heteroatom substituents stabilize glycosides with respect to acid-catalyzed hydrolysis, see: (a) Roush, W. R.; Lin, X.-F. *J. Am. Chem. Soc.* **1995**, *117*, 2236. (b) Overend, W. G.; Rees, C. W.; Sequeira, J. S. *J. Chem. Soc.* **1962**, 3429. (c) Buncel, E.; Bradley, P. R. *Can. J. Chem.* **1967**, *45*, 515.

Scheme 13 [a]



[a] (a) (*c*-hex)$_2$BCl, Et$_3$N, hexanes; (b) Ac$_2$O, DMAP, CH$_2$Cl$_2$.

converted to the terminal alcohol by hydroboration with 9-BBN followed by oxidation under standard conditions. Oxidation of the resulting alcohol with Dess−Martin periodinane gave aldehyde **55**. Addition of ethylmagnesium bromide gave a mixture of secondary alcohol diastereomers that were oxidized under Dess−Martin conditions to give our ketone **4** in 83% yield from alkene **54**. Ketone **4** was prepared in 9.0% overall yield for the 21 linear steps starting from (*R*)-malic acid.

Now that we had our requisite aldehyde **33** and ketone **4**, we were ready to carry out the critical anti-aldol reaction. This reaction is now well precedented and proceeded without event as shown in Scheme 13. Ethyl ketone **4** was converted into the (*E*)-enolate by reaction with (*c*-hex)$_2$BCl and triethylamine. Aldehyde **33** was added to the resulting (*E*)-enolate to give 67% yield of the desired anti-aldol product **56**, which was readily acetylated with acetic anhydride and DMAP to give diacetate **57** in 93% yield. The spectroscopic properties of this compound were identical to those produced by our first-generation synthesis. As in our previous report,[15c] the major aldol product is accompanied by a small amount (about 7%) of an isomeric aldol resulting from enolization of ketone **4** at C4 rather than C2. Both Evans[9d] and Patterson[12f] reported a 9:1 ratio of aldols in a similar coupling of a C1−15 aldehyde with the dicyclohexylboron enolate of a C16−29 ketone in which the substrates differed by remote protecting groups. These groups both refer to a "9:1 diastereomeric ratio" in the aldol reaction, but neither provided definitive evidence that the minor aldol was a diastereomer rather than a regioisomer.

The revised synthetic route described in this Article requires a total of 62 steps, with a longest linear sequence of 35 steps. We have prepared a total of 9.6 g of compound **57** by this route. The total synthesis of altohyrtin C (spongistatin 2) is described in the accompanying paper.

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

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