Article

Multigram Synthesis of the C29–C51 Subunit and Completion of the Total Synthesis of Altohyrtin C (Spongistatin 2)

Clayton H. Heathcock, Mark McLaughlin, Jesus Medina, Jed L. Hubbs, Grier A. Wallace, Robert Scott, Michele M. Claffey, Christopher J. Hayes, and Gregory R. Ott

J. Am. Chem. Soc., **2003**, 125 (42), 12844-12849• DOI: 10.1021/ja030317+ • Publication Date (Web): 27 September 2003

J|A|C|S
ARTICLES
Published on Web 09/27/2003

Multigram Synthesis of the C29−C51 Subunit and Completion of the Total Synthesis of Altohyrtin C (Spongistatin 2)

Clayton H. Heathcock,* Mark McLaughlin, Jesus Medina, Jed L. Hubbs, Grier A. Wallace, Robert Scott, Michele M. Claffey, Christopher J. Hayes, and Gregory R. Ott

Contribution from the Center for New Directions in Organic Synthesis, Department of Chemistry, University of California, Berkeley, California 94720

Received May 27, 2003; E-mail: heathcock@cchem.berkeley.edu

Abstract: A multigram synthesis of the C29−C51 subunit of altohyrtin C (spongistatin 2) has been accomplished. Union of this intermediate with the C1−C28 fragment and further elaboration furnished the natural product. Completion of the C29−C51 subunit began with the aldol coupling of the boron enolate derived from methyl ketone **8** and aldehyde **9**. Acid-catalyzed deprotection/cyclization of the resulting diastereomeric mixture of addition products was conducted in a single operation to afford the E-ring of altohyrtin C. The diastereomer obtained through cyclization of the unwanted aldol product was subjected to an oxidation/reduction sequence to rectify the C35 stereocenter. The C45−C48 segment of the eventual triene side chain was introduced by addition of a functionalized Grignard reagent derived from (*R*)-glycidol to a C44 aldehyde. Palladium-mediated deoxygenation of the resulting allylic alcohol was followed by adjustment of protecting groups to provide reactivity suitable for the later stages of the synthesis. The diene functionality comprising the remainder of the C44−C51 side chain was constructed by addition of an allylzinc reagent to the unmasked C48 aldehyde and subsequent dehydration of the resulting alcohol. Completion of the synthesis of the C29−C51 subunit was achieved through conversion of the protected C29 alcohol into a primary iodide. The synthesis of the C29−C51 iodide required 44 steps with a longest linear sequence of 33 steps. From commercially available tri-*O*-acetyl-D-glucal, the overall yield was 6.8%, and 2 g of the iodide was prepared. The C29−C51 primary iodide was amenable to phosphonium salt formation, and the ensuing Wittig coupling with a C1−C28 intermediate provided a fully functionalized, protected *seco*-acid. Selective deprotection of the required silicon groups afforded an intermediate appropriate for macrolactonization, and, finally, global deprotection furnished altohyrtin C (spongistatin 2). This synthetic approach required 113 steps with a longest linear sequence of 37 steps starting from either tri-*O*-acetyl-D-glucal or (*S*)-malic acid.

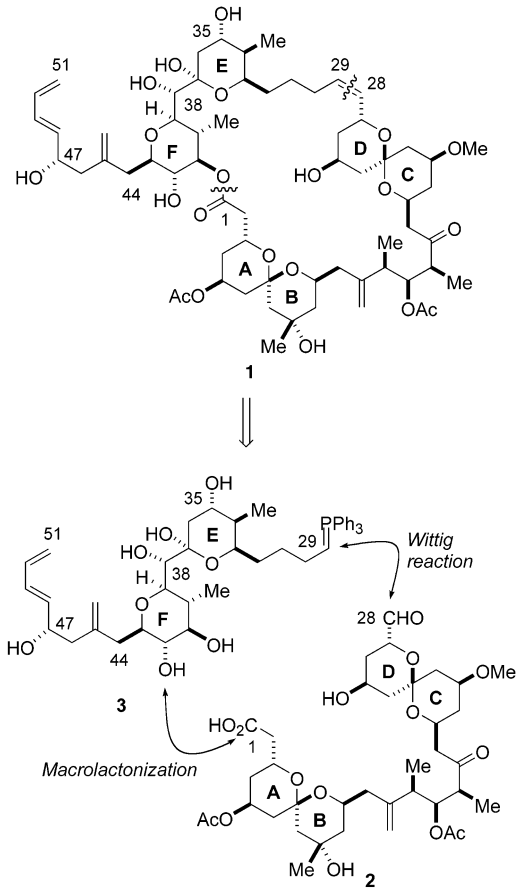
As discussed in the previous Article in this issue,[1] the spoingipyran natural products are potent marine cytotoxins that have potential for use in cancer chemotherapy, and this structurally unique family of compounds has attracted considerable synthetic interest.[2] Our goal is to develop a total synthesis of one of these molecules, altohyrtin C (spongistatin 2, **1**), that is efficient enough to provide multigram quantities of the natural product for in vivo studies as a possible anticancer drug. Our synthetic approach assembles the altohyrtin macrocycle from suitably protected versions of two major building blocks, the C1−C28 unit **2** and the C29−C51 unit **3**. In the preceding Article, we have described a greatly improved process for the C1−C28 fragment of the altohyrtins, leading to almost 10 g of a functional derivative of **2**. In this Article, we report a multigram synthesis of a protected version of the C29−C51 subunit **3**[3] and the method whereby these two advanced intermediates have been fashioned into 0.25 g of altohyrtin C. As in the published syntheses, the synthetic strategy was designed around macrolactonization as the final key step, preceded by a Wittig reaction to form the C28−C29 (*Z*)-alkene bond.

Our revised plan for the C29−C51 unit breaks the target down into four units, the most complex of which is the methyl ketone **4**, which we have previously obtained in 11 steps from commercially available tri-*O*-acetyl-D-glucal.[3] The other projected building blocks are aldehyde **5**, prepared by the use of Evans' oxazolidone chemistry, vinyl bromide **6**, and an allylorganometallic reagent that would be used to append the three terminal carbons of the side chain.

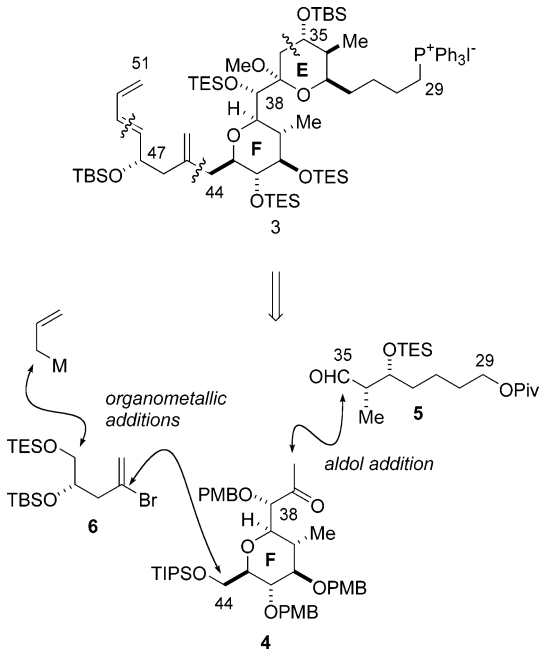
In our previous work,[3] the aldol coupling of methyl ketone **4** with aldehyde **5** was conducted via the lithium enolate. In this work, we discovered that the initial lithium aldolate rapidly reacts with a second equivalent of aldehyde, leading to a complex mixture of 2:1 adducts that could be converted into the desired aldol **7** only by treatment with methanolic K_2CO_3. Although the desired aldol product could be liberated by this

(1) Hubbs, J. L.; Heathcock, C. H. *J. Am. Chem. Soc.* **2003**, *125*, 12836.
(2) A comprehensive reference list for previous synthetic work, presented in ref 1, is omitted here in the interest of conserving journal space.
(3) For our first-generation synthesis of a C29−C44 fragment, see: Wallace, G. A.; Scott, R. W.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 4145.

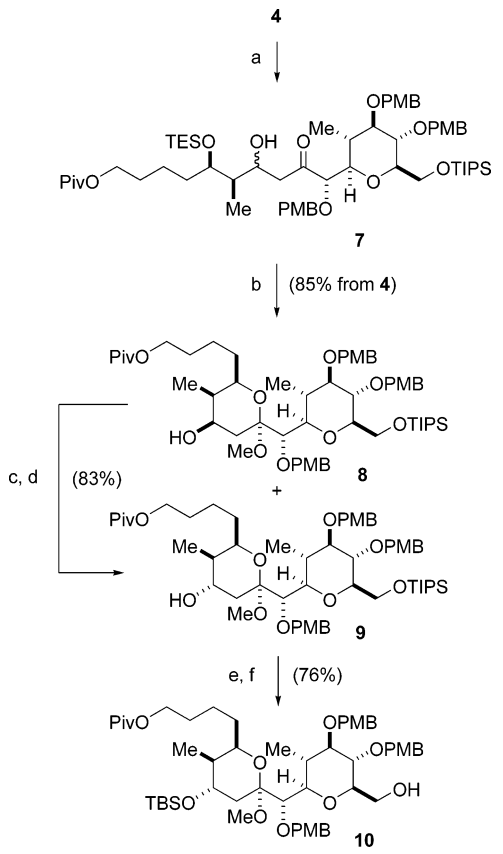
10.1021/ja030317+ CCC: $25.00



method in good yield (88%, 3.4:1.0 mixture of diastereomers at C35, favoring the unwanted epimer), the wasteful nature of this procedure with respect to the aldehyde prompted investigation of an alternative. To this end, generation of the boron enolate of ketone **4** by the action of dicyclohexylboron chloride and triethylamine, followed by the addition of 1.05 equiv of the aldehyde **5**, afforded the aldol **7** directly (Scheme 1). These aldol products were then subjected to catalytic amounts of triphenylphosphine hydrobromide in methanol/tetrahydrofuran



Scheme 1 [a]



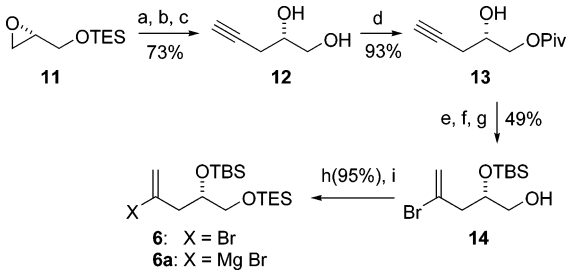
[a] (a) Cy_2BCl, Et_3N, CH_2Cl_2, −78 °C, then aldehyde **5**; (b) $Ph_3P{\cdot}HBr$, MeOH, THF (1:1.1 mixture of **8**:**9**); (c) Dess−Martin periodinane, pyridine, CH_2Cl_2; (d) L-Selectride, THF, −78 °C; (e) KHMDS, TBSCl, THF; (f) TBAF, THF.

to effect deprotection of the triethylsilyl ether and cyclization to the methyl ketals **8** and **9** in a single operation, in 85% overall yield from the methyl ketone **4**. The 1.1:1.0 mixture of diastereomers obtained by this procedure was separable by flash column chromatography, and the undesired epimer was recycled in 83% yield through an oxidation−reduction sequence, which employed the Dess−Martin periodinane[4] and L-Selectride. Having established the method by which the configuration at C35 in the unwanted diastereomer could be rectified, the resulting axial hydroxy group of **9** was protected as a TBS ether, and the primary TIPS ether was selectively removed using TBAF, providing alcohol **10** in 76% yield for the two steps.

With relatively large quantities of alcohol **10** in hand, attention was turned to the synthesis of the vinyl bromide **6** that would form the foundation for what would ultimately become the triene side chain of altohyrtin C. It was envisaged that the C47 stereocenter could be derived from a suitably protected glycidol by regioselective opening of the epoxide with an acetylide anion. Such a reaction, utilizing (*R*)-glycidyl pivaloate and lithium (trimethylsilyl)acetylide, had indeed been previously reported.[5] On a larger scale, however, it was preferable to use (*R*)-glycidol triethylsilyl ether **11** to avoid unwanted side reactions (Scheme 2). The crude product from the epoxide opening was treated sequentially with pyridinium *p*-toluenesulfonate and K_2CO_3 to cleave the TES and TMS groups in 73% overall yield. The

(4) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(5) MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033 and references therein.

Scheme 2 [a]

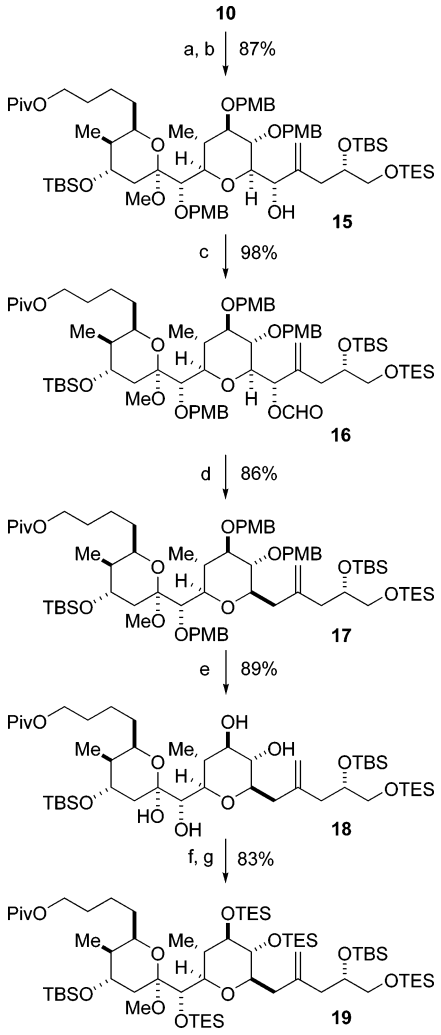


[a] (a) TMSA, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C; (b) PPTS, MeOH/THF; (c) K_2CO_3, MeOH, THF; (d) PivCl, pyridine, CH_2Cl_2; (e) 9-Br-BBN, CH_2Cl_2, 0 °C, then AcOH; (f) TBSCl, imidazole, DMF; (g) DIBAL-H, toluene, −78 °C; (h) TESCl, EtN^iPr_2, DMF; (i) *t*-BuLi, THF, −78 °C, then $MgBr_2{\cdot}OEt_2$.

primary hydroxyl of the resulting alkynediol **12** was then selectively acylated with pivaloyl chloride, and the vinyl bromide was introduced by bromoboration[6] of the alkyne. Subsequent protection of the secondary hydroxyl of **13** as a TBS ether, followed by DIBAL-H mediated cleavage of the pivaloyl group and reprotection of the primary alcohol as a TES ether, provided vinyl bromide **6**.[7] The Grignard reagent **6a**, required for coupling with the EF bis-pyran subunit, was available by successive treatment with *tert*-butyllithium and magnesium bromide etherate.

The union of the bis-pyran subunit **10** with the functionalized Grignard reagent **19** was performed as shown in Scheme 3. Oxidation of the primary alcohol **11** under Moffat−Swern conditions[8] yielded a rather unstable aldehyde, which was used in crude form. Treatment of the oxidation reaction mixture with an excess of Grignard reagent **6a** afforded the desired alcohol **15** in 87% yield as a single diastereomer. Although the configuration of the product alcohol was assumed to be that shown, based on literature precedent[9] for similar additions of vinyl Grignard reagents to aldehydes, the stereochemical outcome of this transformation was ultimately inconsequential because the ensuing synthetic steps would eliminate this stereocenter. Along these lines, formylation using Katritzky's *N*-formylbenzotriazole[10] provided the allylic formate **16** in 98% yield and set the stage for a deoxygenation reaction in which it was required that the exoskeletal position of the alkene was maintained. We sought to accomplish this goal by a modification of the π-allyl reduction method of Tsuji.[11] Through systematic investigation, it was found that less polar solvents in combination with a high ratio of tributylphosphine to palladium (200:1) gave a >20:1 ratio of the desired exoskeletal alkene **17**, relative to the internal alkene isomer. The observed effect of the excess exogenous ligand on the ratio of alkene products suggests that greater steric bulk at the palladium promotes intramolecular

Scheme 3 [a]



[a] (a) (COCl), DMSO, CH_2Cl_2, −78 °C, then EtN^iPr_2; (b) Grignard **6a**, THF, −78 °C; (c) *N*-formylbenzotriazole, EtN^iPr_2, DMAP, CH_2Cl_2; (d) 10 mol % $Pd(PPh_3)_4$, 2000 mol % Bu_3P; ammonium formate, cyclohexane, 80 °C; (e) DDQ, CH_2Cl_2/pH 7 buffer, 89%; (f) $Ph_3P{\cdot}HBr$,MeOH/THF, 0 °C; (g) TESCl, imidazole, DMF.

hydride transfer to the more substituted position, leaving the Pd coordinated to the less substituted double bond. Under the optimized reaction conditions, deoxygenation occurred efficiently to give alkene **17** in 86% yield, together with a minor side product, the ^1H NMR spectrum of which was consistent with loss of the TES protecting group. Treatment of the recovered primary alcohol with TESCl led to an additional 4% of alkene **17** and brought the total yield up to 90%. Thus, the Grignard addition, allylic deoxygenation protocol gives alkene **17** in 77% overall yield for the three steps.

Having demonstrated a successful approach to a C29−C48 fragment **17** of the altohyrtins, effort was then focused on the elaboration of this substrate to include the three carbons atoms that form the end of the triene side chain of altohyrtin C. A concern at this point, however, was the stability of a fully formed diene functionality to the oxidative conditions necessary to effect removal of the three PMB groups at a late stage in the synthesis. Indeed, our studies on model systems[12] had indicated competing

(6) (a) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731. (b) Hara, S.; Satoh, Y.; Ishiguro, H.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 735.

(7) Although this sequence begins and ends with a triethylsilyl protecting group on the primary hydroxyl, an intermediate pivaloyl group was necessary because the acidic conditions of the bromoboration reaction were not compatible with the silyl ether.

(8) For reviews, see: (a) Tidwell, T. T. *Synthesis* **1990**, 857. (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297−572.

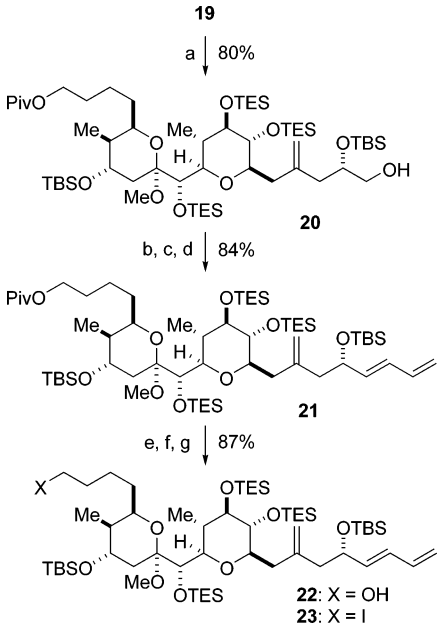
(9) (a) Guo, J.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 187−192. (b) Hayward, M. M.; Roth, R. M.; Duffy, K. J.; Dalko, P. I.; Stevens, K. L.; Guo, J.; Kishi, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 192−196.

(10) Katritzky, A. R.; Chang, H. X.; Yang, B. *Synthesis* **1995**, 503.

(11) (a) Tsuji, J.; Yamakawa, T. *Tetrahedron Lett.* **1979**, *7*, 613. (b) Tsuji, J.; Shimizu, I.; Minami, I. *Chem. Lett.* **1984**, 1017.

(12) Ott, G. R.; Heathcock, C. H. unpublished results. These model studies were carried out on the substrate reported in: Ott, G. R.; Heathcock, C. H. *Org. Lett.* **1999**, *1*, 1475.

Scheme 4 [a]

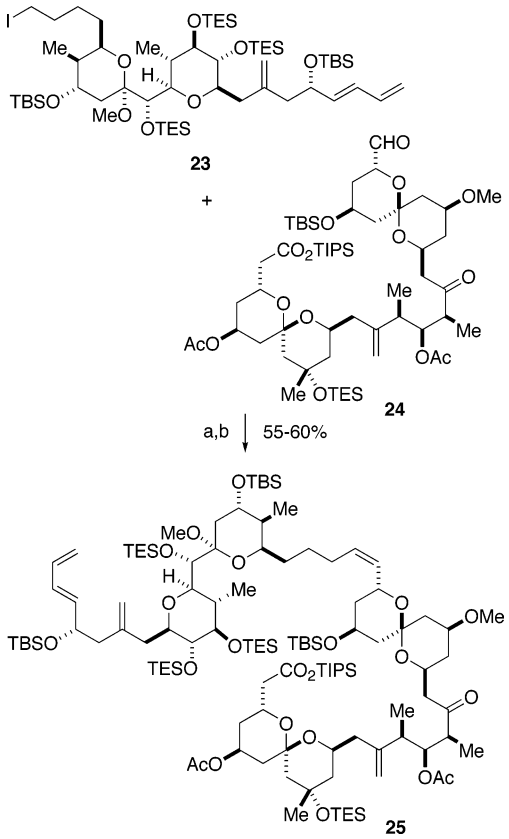


[a] (a) Ph_3P·HBr, MeOH/CH_2Cl_2, 0 °C; (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then EtN^iPr_2; (c) allylMgBr/$ZnCl_2$, Et_2O, −78 °C; (d) Martin's sulfurane, $CHCl_3$; (e) DIBAL-H, toluene, −78 °C; (f) MsCl, Et_3N, CH_2Cl_2, 0 °C; (g) NaI, $NaHCO_3$, Na_2SO_3, acetone, 56 °C.

diene oxidation to a dieneone under the influence of DDQ, and Paterson had reported a similar problem in related systems.[13] On the basis of these observations, we decided to exchange the PMB ethers for TES ethers because this would direct our synthesis toward late-stage persilylated intermediates very similar to those already proven to be viable by other synthetic groups. Thus, before commencing with the installation of the diene functionality, PMB-protected intermediate **17** was treated with 4 equiv of DDQ in dichloromethane/pH 7 buffer to provide triol hemiketal **18** in 89% yield. Under the aqueous reaction conditions, the methyl ketal suffered hydrolysis, a result observed previously by Kishi[9] and Paterson.[13] Treatment of the hemiketal with catalytic acid in methanol simultaneously regenerated the methyl ketal and cleaved the primary TES ether to give a tetraol, which upon exposure to excess TESCl afforded compound **19**.

With an appropriately protected C29−C48 fragment in hand, completion of the diene construction was now possible and began with selective deprotection of the primary TES ether of **19** under mild acidic conditions (Scheme 4). Although the success of this deprotection was extremely sensitive toward acid concentration and reaction time, careful monitoring by TLC allowed us to obtain the desired primary alcohol **20** in 80% yield. Ammonium fluoride in methanol was examined as a potential alternative reagent for this delicate transformation but proved too sluggish and gave lower yields. Oxidation of primary alcohol **20** was conducted using Moffat−Swern conditions, and the crude aldehyde was treated with an excess of allylzinc

Scheme 5 [a]



[a] (a) Ph_3P, MeCN, EtN^iPr_2, 80 °C; (b) MeLi·LiBr, THF, −78 °C, then aldehyde **24**, 55−60% (two steps).

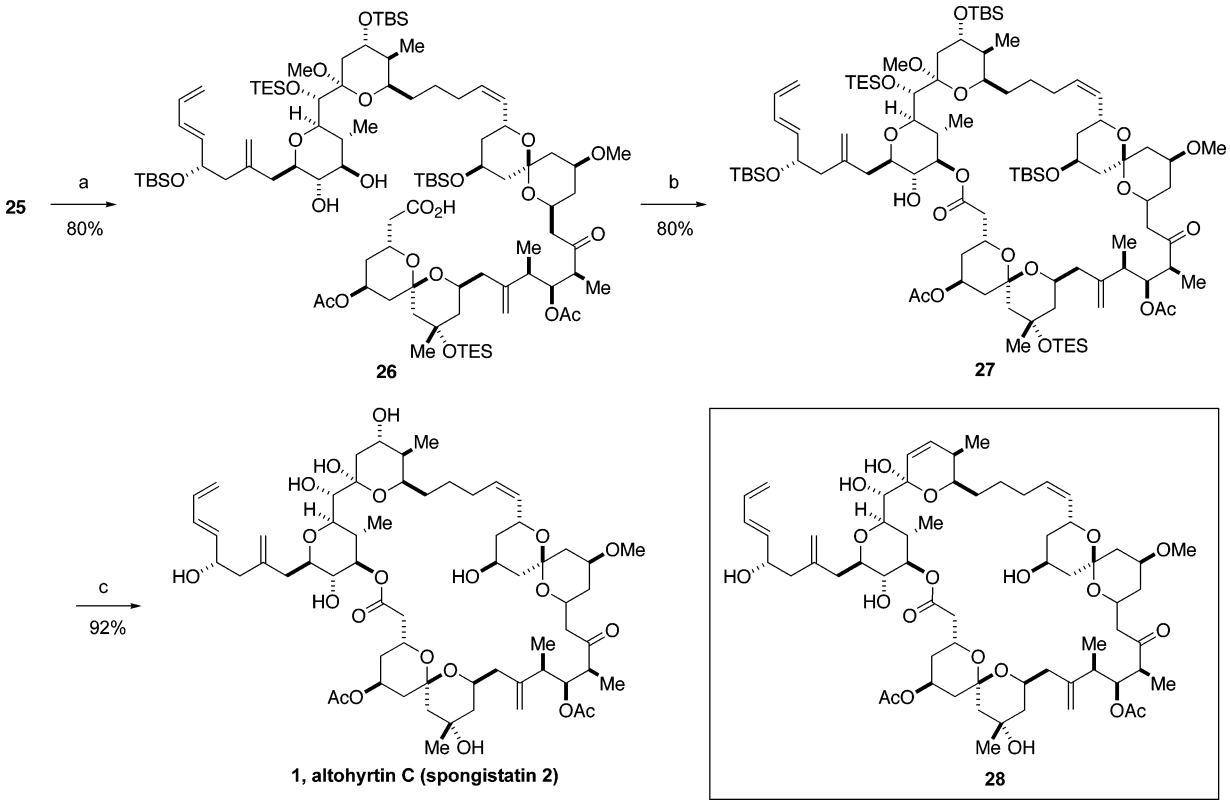
reagent[14] to provide a 2:1 diastereomeric mixture of alcohols. When these alcohols were subjected to Martin's sulfurane,[15] dehydration occurred to give the (*E*)-alkene **21** in 84% overall yield from alcohol **20**. Finally, in preparation for the Wittig coupling with the C1−C28 (ABCD) portion of altohyrtin C, the C29 pivaloyl group was cleaved with DIBAL-H, and the resulting primary alcohol **22** was converted into iodide **23** by mesylation, followed by the modified Finkelstein conditions utilized by Evans.[16]

Conversion of iodide **23** into a phosphonium salt required the use of 3 equiv of triphenylphosphine. Purification of the phosphonium salt was briefly investigated, and, although it was possible to remove the excess triphenylphosphine by flash column chromatography, significant material losses were suffered. Thus, for practical reasons, the phosphonium salt was used crude in the Wittig coupling with C1−C28 aldehyde **24**,[1] a reaction we anticipated might be problematic based on the experience of other synthetic groups. Moderate to low yields for similar Wittig reactions have been observed in all of the other completed spongistatin total syntheses, with the exception of the most recently reported synthesis of altohyrtin C by Crimmins,[17] in which a Wittig reaction between a closely related phosphonium salt and a truncated aldehyde comprising C16−C28 of altohyrtin C occurred in 86% yield when MeLi·LiBr

(13) Paterson, I.; Cowden, C. J.; Rahn, V. S.; Woodrow, M. D. *Synlett* **1998**, 915. In contrast, a similar deprotection of a bis-PMB ether was achieved without difficulty in the syntheses of altohyrtin A by Kishi (ref 13) and by Paterson (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). It appears that the presence of the side-chain halogen retards the oxidation process that we had observed, permitting conventional removal of the PMB groups.

(14) Scarlato, G. R.; DeMattei, J. A.; Chong, L. S.; Ogawa, A. K.; Lin, M. R.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6139.
(15) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327.
(16) 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.
(17) Crimmins, M. T.; Katz, J. D.; Washburn, D. G.; Allwein, S. P.; McAtee, L. F. *J. Am. Chem. Soc.* **2002**, *124*, 5661.

Scheme 6 [a]



[a] (a) TBAF, THF, 0 °C; (b) 2,4,6-trichlorobenzoyl chloride, EtN^iPr_2, then DMAP, toluene, 90 °C; (c) aqueous HF, MeCN, −15 °C.

was used as the base to generate the ylide. In a similar fashion, and despite poor and irreproducible results during initial attempts with alternative bases (LiHMDS, KHMDS, *n*-BuLi), the adoption of Crimmins' method with our system led to a repeatable 55−60% overall yield of the (*Z*)-alkene Wittig product **25** from iodide **24** (Scheme 5).

With the complete carbon skeleton of altohyrtin C now assembled, the tasks of selective deprotection, macrolactonization, and final, global deprotection could be addressed. As alluded to previously, our synthesis had now arrived at a late-stage intermediate very similar to those featured in published syntheses of altohyrtin C, and, consequently, it was hoped that similar reaction conditions would provide success. For the selective deprotection of a C1-TIPS ester and a TES ether at C41, Evans had reported the use of HF·pyridine buffered with pyridine.[16] Protected *seco*-acid **25** also required cleavage of the same two silicon groups and an additional TES ether at C42. The expectation that compound **25** would be more robust than the Evans intermediate due to the increased steric encumbrance around C41/C42 proved correct, and the use of HF·pyridine in pyridine led to unsatisfactory results; even after long reaction times, starting material remained, and the selectivity was compromised. After experimenting with various reagents for silyl ether cleavage (triethylamine trihydrofluoride, ammonium fluoride), we determined that the optimum method for conducting this transformation involved the slow addition of 3 equiv of TBAF to a solution of the protected *seco*-acid **25** at 0 °C (Scheme 6). This procedure cleanly afforded partially deprotected *seco*-acid **26** in 80% yield and allowed progress to the macrolactonization. Concerns regarding regioselectivity in the macrolactonization of a substrate such as **26** containing two possible reactive alcohols were allayed by previous observations with the spongistatins by other groups, following the initial synthesis by Evans and co-workers.[16] Thus, following a modified Yamaguchi procedure, the intermediate active mixed anhydride was cyclized in toluene at 90 °C to the 42-membered ring **27** in 80% yield.

All that remained was the global desilylation and hydrolysis of the methyl ketal to the hemiketal. Once again, there was ample literature precedent, all of which suggested the employment of relatively dilute aqueous HF in acetonitrile. However, subjection of protected macrolactone **27** to the same conditions produced a mixture of starting material and products from which altohyrtin C was isolated in relatively low yield. Given our long-term goal of synthesizing multigram quantities of the material, such inefficiency in this crucial ultimate reaction was unacceptable. Consequently, it was pleasing to discover alternative conditions that bring about clean deprotection of macrolactone **27**. The initial result with the dilute HF prompted testing of more concentrated acid solutions and shorter reaction times, with a view to increasing the yield of the natural product. These conditions provided total conversion of the starting material, but, despite a relatively clean TLC, the crude isolated yield was only around 50%. Moreover, it was clear that this more promising yield would be further diminished upon recognition that what appeared to be a single compound by TLC analysis was actually a mixture of products by ^{1}H NMR. Further chromatographic analysis revealed a minor component (ca. 5%) that could be separated on a flash column and was subsequently identified from its ^{1}H NMR and mass spectra as an E-ring dehydrated analogue **28**. Paterson recently reported a similar observation in his work on spongistatin 1 and, furthermore,

found that the dehydrated version of spongistatin 1 was even more biologically active than the parent natural product in in vitro tests.[18] Preliminary results in the altohyrtin C series suggest that this dehydration product of altohyrtin C is exceedingly potent, possibly even more potent than altohyrtin C itself in a number of tumor cell lines.[19]

While these findings were certainly of interest, the yield of the desired natural product was still less than satisfactory. Further work on this final deprotection led to the optimum conditions in which the use of fairly concentrated HF in combination with lower temperature, a shorter reaction time, and a low-temperature quench furnished clean altohyrtin C (**1**, spongistatin 2) in 92% isolated yield. Relative to our initial efforts, this represented a 3-fold increase in the yield of this valuable macrolide and should be of significant benefit in future attempts to prepare even greater quantities of altohyrtin C. The synthetic (+)-altohyrtin C obtained from this work was identical in all respects (500 MHz ^{1}H NMR, LR-MS, HR-MS, optical rotation, TLC, and HPLC) to an authentic sample kindly provided by Professor Evans. Additionally, ^{13}C NMR data for synthetic (+)-altohyrtin C (spongistatin 2) were in agreement with data originally obtained from the natural product by Professor Pettit.

(18) Paterson, I.; Aceña, J. L.; Bach, J.; Chen, D. Y.-K.; Coster, M. J. *Chem. Commun.* **2003**, 462.

(19) **Note Added in Proof.** Compound **28** exhibits picomolar GI50 against several tumor cell lines (e.g., 2×10^{-11} in HL-60 leukemia; 5×10^{-11} in HCT-116 colon cancer; 3×10^{-11} in UACC-62 melanoma; 3×10^{-11} in MDA-MB-435 breast cancer). In addition, this analogue has nanomolar GI50 against a number of other cancer lines, including eight nonsmall cell lung cancers, five other colon cancers, four CNS cancers, six other melanomas, six ovarian cancers, seven renal cancers, and two other breast cancers. Edward Sausville, National Cancer Institute, private communication, August 14, 2003.

In summary, the synthesis of the C29−C51 subunit of altohyrtin C requires a total of 44 steps and delivers the subunit in 6.8% yield over the longest linear sequence starting from the commercially available tri-*O*-acetyl-D-glucal. The full total synthesis of altohyrtin C that is reported here requires 113 total steps with a longest linear sequence of 37 steps from either (*S*)-malic acid or tri-*O*-acetyl-D-glucal. A total of 0.25 g of the marine natural product has been prepared by this route, and, although still far from our long-term goal, this quantity is more altohyrtin C (spongistatin 2) than has ever existed from the original isolation and all previous syntheses combined. Continuing efforts in our laboratory have the goal of further refining our synthetic route such that we may ultimately achieve the synthesis of multigram quantities of altohyrtin C (spongistatin 2), thereby facilitating meaningful in vivo studies with this fascinating family of natural cytotoxins.

Acknowledgment. This work was supported by a research grant from the United States Public Health Service (AI15027). The Center for New Directions in Organic Synthesis is supported by Bristol-Myers Squibb as a Sponsoring Member and Novartis as a Supporting Member.

Supporting Information Available: Experimental procedures and characterization for all new compounds, ^{1}H and ^{13}C NMR spectra of synthetic altohyrtin C, ^{1}H NMR spectrum of dehydration product **28**, charts showing the convergency of the synthesis (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA030317+