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A Method for Constructing the C44–C51 Side Chain of Altohyrtin C

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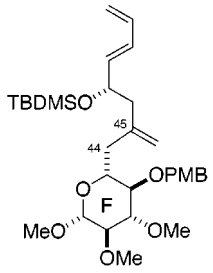
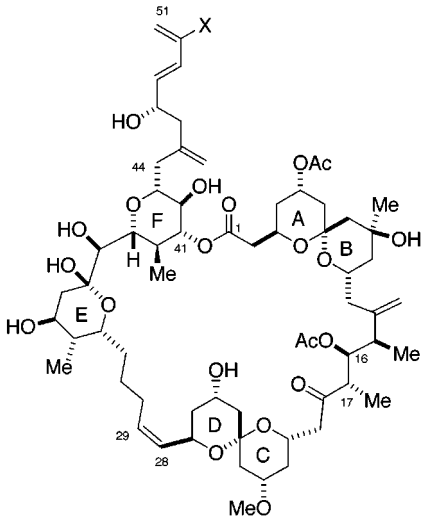
ABSTRACT



A method to construct the C44–C51 side chain of altohyrtin C has been developed and applied to a model aldehyde derived from D-glucose. The approach relies on a Wittig reaction to couple the side chain to an aldehyde and utilizes an allylic diazene rearrangement to place the C45 double bond in the correct position.

The altohyrtins (**1**−**3**),[1] spongistatins,[2] and cinachrylide A[3] represent a growing class of sponge-derived macrolides that display unique, highly complex architecture and very potent cytotoxicity. The above criteria have made these molecules attractive targets for total synthesis.[4] As part of our research directed toward the total synthesis of the altohyrtins,[5] we have developed a method for introducing the side chain moieties to an appropriate F-ring model compound. This method uses a Wittig olefination of an appropriate aldehyde and an allylic diazene rearrangement to introduce the side chain geminal olefin.



altohyrtin A, X = Cl, **1**
altohyrtin B, X = Br, **2**
altohyrtin C, X = H, **3**

The advanced F-ring in our synthesis is ultimately be derived from tri-*O*-acetyl-D-glucal, with the C6 position of

(1) (a) Kobayashi, M.; Aoki, S.; Sakai, H.; Kawazoe, K.; Kihara, N.; Sasaki, T.; Kitigawaw, I. *Tetrahedron Lett.* **1993**, *34*, 2795. (b) Kobayashi, M.; Aoki, S.; Kitigawa, I. *Tetrahedron Lett.* **1994**, *35*, 1243.

(2) Bai, R.; Taylor, G. F.; Cichacz, Z. A.; Herald, C. L.; Kepler, J. A.; Pettit, G. R.; Hamel, E. *Biochemistry* **1995**, *34*, 9741.

(3) Fusetani, N.; Shinoda, K.; Matsunaga, S. *J. Am. Chem. Soc.* **1993**, *115*, 3977.

(4) (a) Evans, D. A.; Coleman, P. J.; Dias, L. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2738. (b) Evans, D. A.; Trotter. B. W.; Cote, B.; Coleman, P. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2741. (c) Evans, D. A.; Trotter, B. W.; Cote, B.; Coleman, P. J.; Dias, L. C.; Tyler, A. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2744. (d) Guo, J. S.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, *37*, 187. (e) Hayward, M. M.; Roth, R. M.; Duffy, K. J.; Dalko, P. I.; Stevens, K. L.; Guo, J. S.; Kishi, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 192.

(5) (a) Claffey, M. M.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 7646. (b) Hayes, C. J.; Heathcock, C. H. *J. Org. Chem.* **1997**, *62*, 2678. (c) Claffey, M. M.; Hayes, C. J.; Heathcock, C. H. *J. Org. Chem.*, in press.

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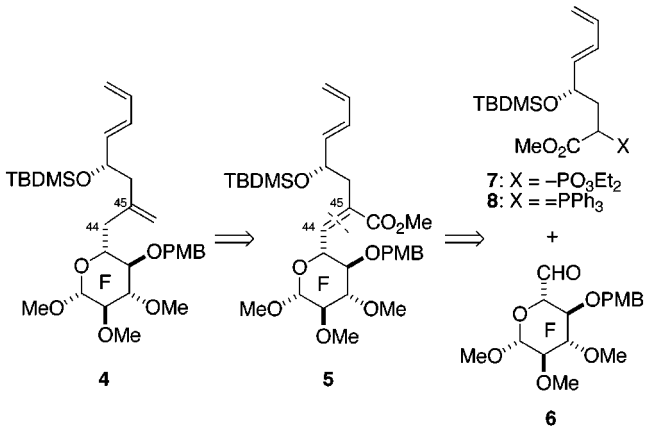
the of the glucal eventually becoming C44 (altohyrtin numbering). This would require formation of the carbon−carbon bond of the side chain at the C44−C45 linkage. Compound **4** (Scheme 1) was chosen as an appropriate target

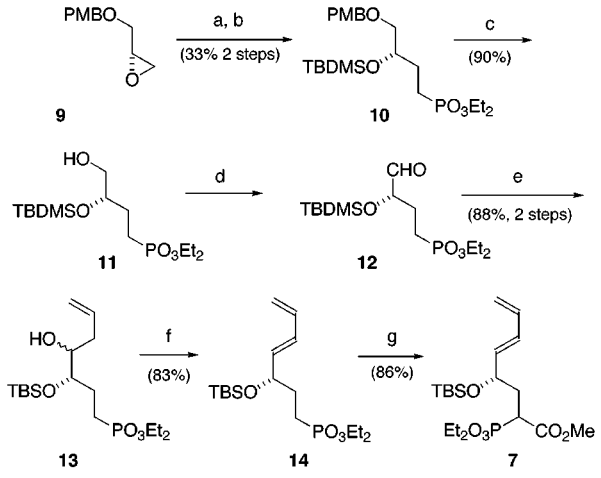
Scheme 1



to model the introduction of our side chain. We envisioned disconnecting the C44−C45 (altohyrtin numbering) linkage as a double bond; thus our approach relies on an allylic transposition of the C45 geminal olefin to give the ester **5**. The α,*β*-unsaturated ester **5** can arise through a Horner−Emmons or Wittig reaction with either **7** or **8** and the model F-ring aldehyde **6**.

The Horner−Emmons reagent **7** (Scheme 2) was available from PMB-protected glycidol **9**[6] by epoxide opening with the lithium anion of diethyl methylphosphonate.[7] The secondary alcohol was subsequently protected as the *tert*-butyldimethylsilyl (TBDMS) ether. Unmasking of the primary alcohol (DDQ) followed by Swern oxidation and

Scheme 2

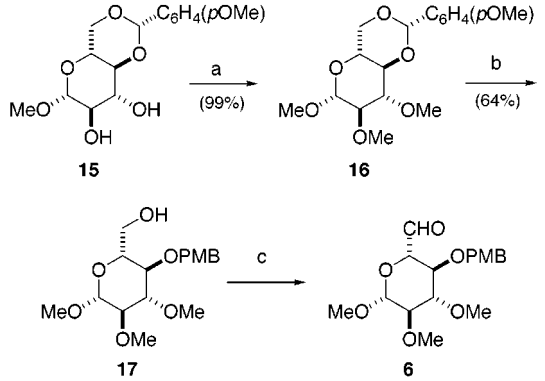


a. BuLi, $CH_3PO_3Et_2$. b. TBSCl, imid. c. DDQ. d. Moffatt-Swern. e. allyl bromide, Zn. f. Martin's sulfurane. g. LDA; $(MeO)_2CO$

allylation using the Luche protocol[8] gave the homoallylic alcohol **13** as mixture of diastereomers (ca. 2−3:1). The mixture of isomers was treated with Martin's sulfurane dehydrating reagent[9] to yield the trans diene **14**. Completion of the Horner−Emmons reagent **7** entailed installation of the carbomethoxy group (LDA, dimethyl carbonate) to give the substituted phosphonoacetate as a 1:1 mixture of diastereomers.

The F-ring model is available in three steps from methyl 4,6-*O*-(4-methoxybenzylidene)-*β*-D-glucopyranoside (Scheme 3).[10] Methylation of the free hydroxyls gave **16** which was

Scheme 3



a. NaH, MeI. b. $LiAlH_4$, $AlCl_3$. c. Swern oxidation

subjected to lithium aluminum hydride reduction in the presence of $AlCl_3$ yielding primary alcohol **17** (64%).[11] Swern oxidation afforded the unstable aldehyde **6** which was prepared fresh and used directly in the olefin-forming reactions.

Coupling of **6** and **7** proved to be more difficult than expected. For example, when treated with bases such as NaH, LiCl/DBU,[12] or KHMDS/18-C-6,[12] olefin formation required several hours to several days at room temperature for completion and was complicated by elimination of the OPMB group. Use of LDA as the base helped to suppress elimination of the OPMB group (Scheme 4), but the reaction still required 16 h at room temperature for completion and suffered from poor mass recovery (40%). It was apparent that the Horner−Emmons approach was not going to be viable.

At this stage, we decided to focus on the stabilized Wittig reagent **8** (Scheme 5). Hydroxy ester **19**,[13] available from

(6) Smith, A. B.; Zhuang, L. H.; Brook, C. S.; Boldi, A. M.; McBriar, M. D.; Moser, W. H.; Murase, N.; Nakayama, K.; P. R., V.; Lin, Q. *Tetrahedron Lett.* **1997**, *38*, 8667.
(7) Li, Z. G.; Racha, S.; Dan, L.; Elsubbagh, H.; Abushanab, E. *J. Org. Chem.* **1993**, *58*, 5779.
(8) Petrier, C.; Luche, J.-L. *J. Org. Chem.* **1985**, *50*, 910.
(9) Martin, J. C.; Arhart, R. J.; Franz, J. A.; Perozzi, E. F.; Kaplan, L. J. *Org. Synth.* **1977**, *57*, 22.
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(11) Stick, R. V.; Tilbrook, D.; Matthew, G. *Aust J. Chem.* **1990**, *43*, 1643.
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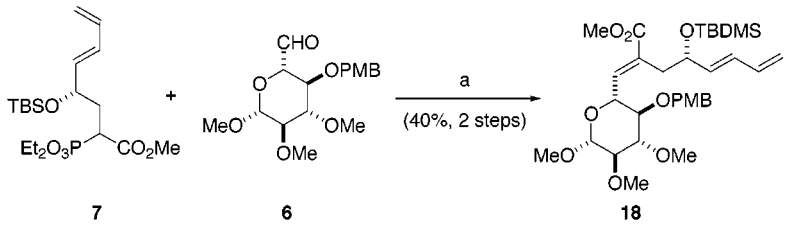
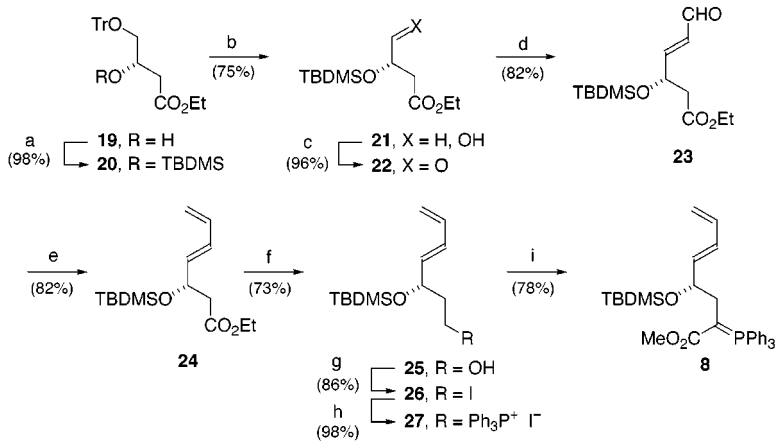
Scheme 4



7 **6** **18**

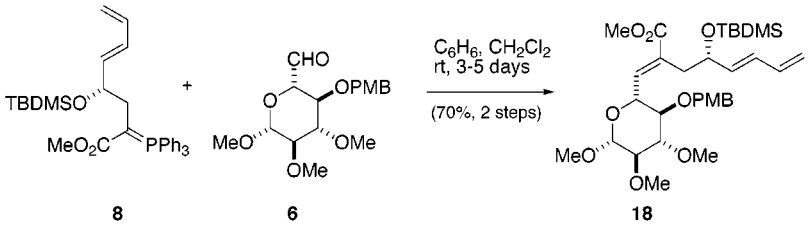
a. LDA, THF, rt ,16h

Scheme 5



a. TBSCl, imid. b. H_2, Pd/C, EtOH. c. Swern [O]. d. $Ph_3PCHCHO$, tol. e. Ph_3PCH_3I, NaHMDS.
f. DIBAL. g. MsCl; NaI. h. Ph_3P, C_6H_6. i. NaHMDS, $ClCO_2Me$

Scheme 6



8 **6** **18**

L-malic acid in three steps, was protected as its TBDMS ether and subjected to hydrogenolysis to afford primary alcohol **21**. Swern oxidation followed by a two-step Wittig protocol ($Ph_3PCHCHO$; $Ph_3P{=}CH_2$) installed the requisite trans diene. Ester **24** was reduced (DIBAL), and the derived alcohol was converted to the iodide and then to the phosphonium salt. Deprotonation of phosphonium salt **27** with excess NaHMDS and trapping with methyl chloroformate provided the phosphorylidene species **8**.[14]

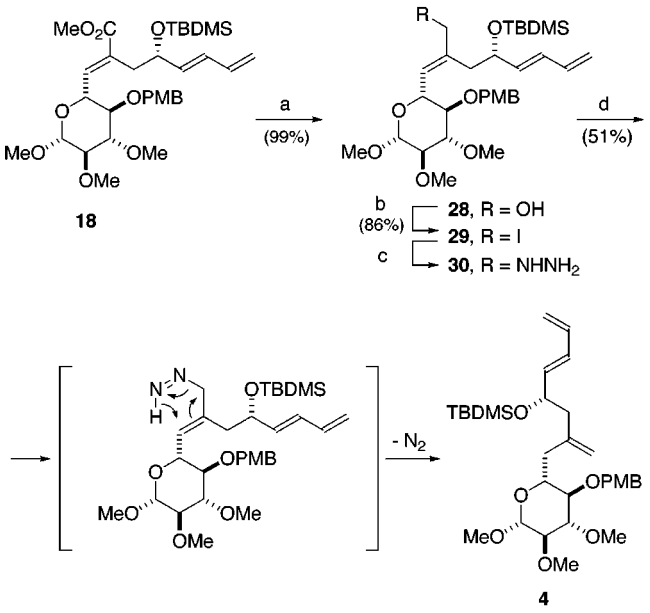
With the stabilized Wittig reagent in hand, we proceeded onto the coupling with our model F-ring aldehyde. The instability of aldehyde **6** precluded the use of elevated temperatures generally used for these reactions (ca. 80−100 °C). At ambient temperature, however, olefin formation was quite clean, albeit a bit slow (ca. 3−5 days) yielding **18** as a single isomer in 70% yield (Scheme 6). Now that we had secured a reliable protocol for formation of the α,β-unsaturated ester, we next required a method for allylic transposition of the α,β-unsaturated ester to the geminal olefin.

To address this issue, we had hoped to take advantage of recent advances in the area of allylic diazene rearrangements. Specifically, we wished to utilize those introduced by Myers and co-workers[15] which entail Mitsunobu displacement of an allylic alcohol with *o*-nitrobenzenesulfonyl hydrazine

(13) Thiam, M.; Slassi, A.; Chastrette, F.; Amouroux, R. *Synth. Commun.* **1992**, *22*, 83.
(14) Bestmann, H. J. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 645.
(15) Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841.

(NBSH).[16] Toward this end, the ester was reduced (DIBAL) to provide the allylic alcohol **28** (Scheme 7). Unfortunately,

Scheme 7



a. DIBAL. b. MsCl; NaI. c. $NH_2NH_2 \cdot H_2O$, 1-hexene/EtOH. d. Air, 1-hexene

28 was completely unreactive toward Mitsunobu displacement with NBSH, yielding only recovered alcohol. This led us to consider a more traditional approach, namely displacement of an allylic iodide with hydrazine followed by air oxidation to the diazene intermediate.[17] This was achieved by conversion of the alcohol to the iodide (MsCl; NaI) followed by treatment with $NH_2NH_2 \cdot H_2O$ in deoxygenated 1-hexene/ethanol (1:1) at 40 °C for 1 h. Following consumption of the starting iodide, and aqueous workup, the crude allylic hydrazine was stirred in dichloromethane/1-hexene under an air atmosphere to oxidize **30** to the diazene intermediate which undergoes 1,5-hydride transfer with loss of dinitrogen to produce **4** in 51% yield for the two-step procedure. The 1-hexene was added to suppress concomitant reduction of the remaining olefins caused by adventitious diimide.

In summary, a stereoselective synthesis of the desired model **4** has been achieved. We have developed an efficient coupling process to attach the altohyrtin side chains to a model F-ring aldehyde. We have also demonstrated that we can introduce the geminal olefin using an allylic diazene rearrangement. The strategies developed in this model study are directly applicable for the introduction of the altohyrtin side chains to an advanced EF, C29−C44 aldehyde. Studies directed toward this goal are currently underway.

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

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(17) (a) Corey, E. J.; Wess, G.; Xiang, Y. B.; Singh, A. K. *J. Am. Chem. Soc.* **1987**, *109*, 4717. (b) Corey, E. J.; Xiang, Y. B. *Tetrahedron Lett.* **1987**, *28*, 5403.