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TOTAL SYNTHESIS OF HALICHONDRIN B FROM COMMON SUGARS: AN F-RING INTERMEDIATE FROM D-GLUCOSE AND EFFICIENT CONSTRUCTION OF THE C1 TO C21 SEGMENT

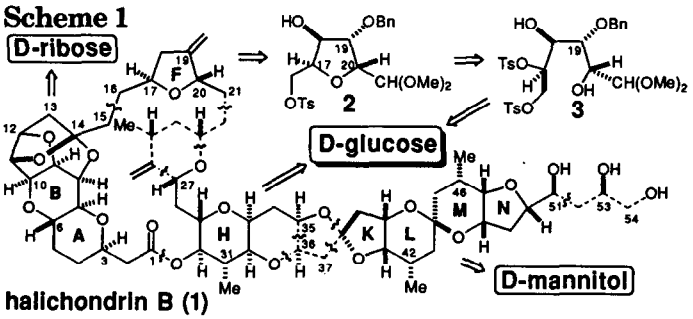
Arthur J. Cooper, Wenxi Pan, and Robert G. Salomon*

Department of Chemistry, Case Western Reserve University, Cleveland, OH 44106-2699

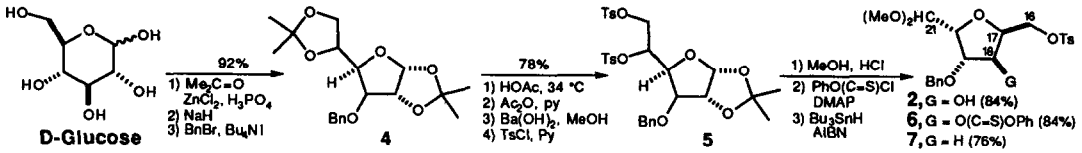
Summary: An F-ring intermediate **7**, with correct absolute configurations for the stereocenters at positions 17 and 20 of halichondrin B, is readily available from D-glucose. The practical utility of methoxybenzyl furanoside derivatives was demonstrated during incorporation of **7** into an acid-sensitive C1 to C21 segment.

Halichondrin B (**1**) is an architecturally unique polyether macrolide that exhibits cancer cell growth inhibition profiles most highly correlated to those produced by structurally unrelated, tubulin-binding standard agents such as vincristine and taxol.[1] However, medicinal applications are hampered because **1** is not readily available from its natural sources. Although its structural complexity makes synthesis a redoubtable challenge, its extremely high potency encourages consideration of total synthesis as a practical source of supply. Our synthetic strategy for **1** envisions the conjunction of stereochemically isolated segments with the requisite absolute configurations derived from inexpensive commercially available sugars (scheme 1). Previously, we reported syntheses of intermediates for the C1-15, C27-35, and C37-C51 subunits from D-ribose, D-glucose, and D-mannitol respectively.[2] The tetrahydrofuran **2**[3] seemed ideally suited as a precursor for the F-ring segment of **1** because: (1) it possesses the correct absolute configurations at positions 17 and 20 (halichondrin numbering), and (2) it is readily available from D-glucose by an S_N2 cyclization of ditosylate **3**. We now report a convenient synthesis of the F-ring C16-21 subunit **7**[4] and its efficient incorporation into a C1 to C21 fragment of the natural product.

Scheme 1



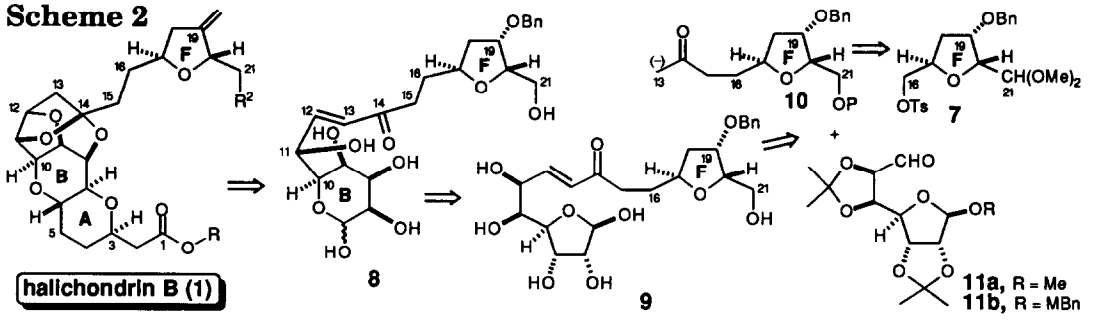
Furanoside benzyl ether **4**[5] is readily prepared in high yield from D-glucose[6] on a molar scale. Selective deprotection and tosylation followed by transketalization and intramolecular O-alkylation provided **2** in good yield. Hydrodehydroxylation of **2** in the presence of a tosylate was best accomplished by a Barton type tin hydride



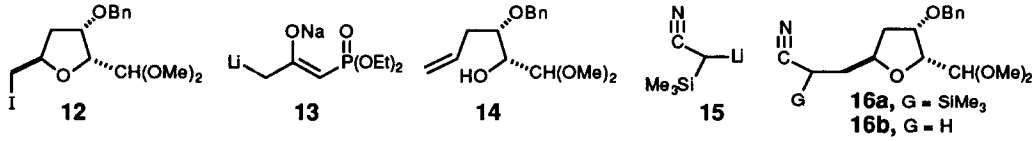
reduction[7] of the derived phenylthiocarbonate **6**.[8]

Our biomimetic approach to the intricate multicyclic polyether ABCDE-ring segment of **1** involves intramolecular Michael O-alkylation and ketalization of a pyranose **8** that is derived from a furanose precursor **9** (Scheme 2). Such an intermediate should be obtainable by condensation of a nucleophilic synthon **10** with the furanose aldehyde **11a** that is conveniently accessible from D-ribose.[2b] Furthermore, intermediates like **10** should be available by side chain extensions of **7**.

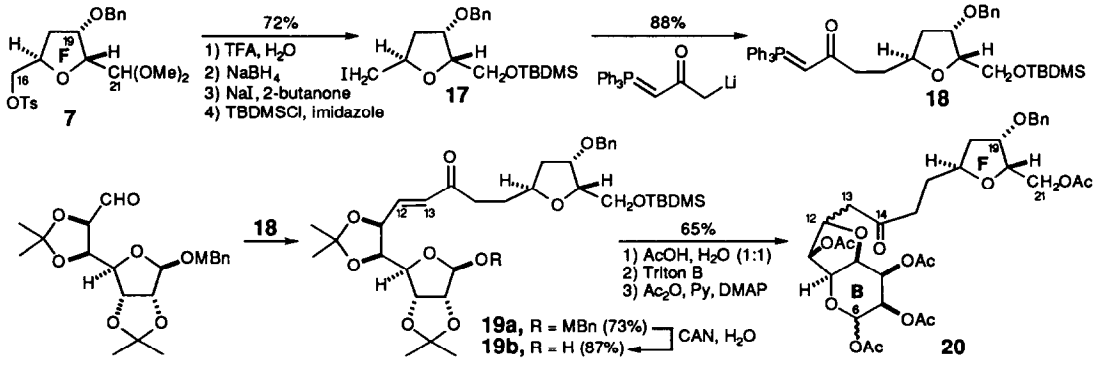
Scheme 2



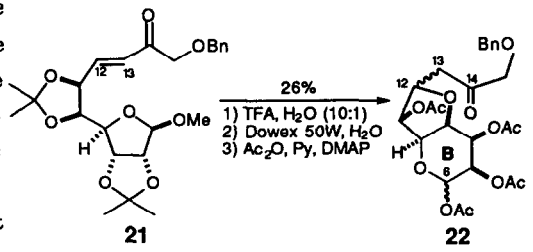
Alkylation of ketophosphonate dianion **13**[9] with iodide **12** (96% from **7** and NaI) was an attractive possibility for generating a synthetic equivalent of **10**. However, a proclivity toward nucleophilic attack at iodine led to **14** instead. A similar result was found with α-lithioacetonitrile. The desired C-C bond formation was finally achieved using the silicon-stabilized nucleophile **15**. Thus, reaction of **15** (generated in THF at -78 °C with n-BuLi) with **12** followed by aqueous workup afforded the desilylated nitrile **16b** in good (89%) yield. Apparently, desilylation of the intermediate α-silylnitrile **16a** occurs readily and conveniently during aqueous workup.



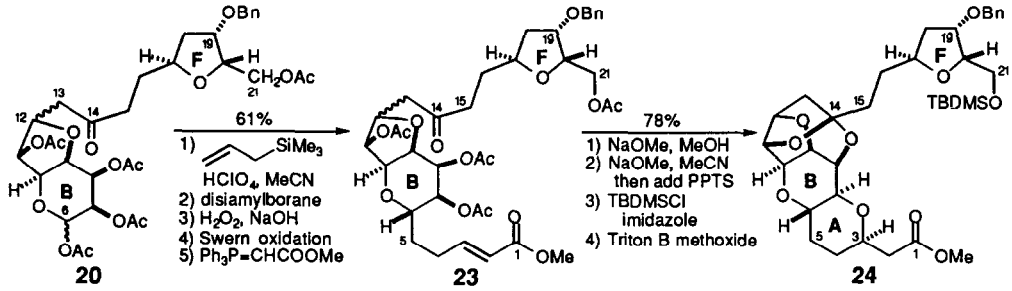
Concurrently, we developed another chain extension strategy that proved even more effective. Thus, alkylation of α'-lithioacetonylidenetriphenylphosphorane[10] with iodide **17** (from **7**) delivered **18** in good yield (24% overall in 16 steps from D-glucose).[11] This ylide provided *trans* enone **19a** (73% along with 15% of the *cis* isomer) upon condensation with the p-methoxybenzyl furanoside **11b**. Previously, we generated a benzyloxymethyl



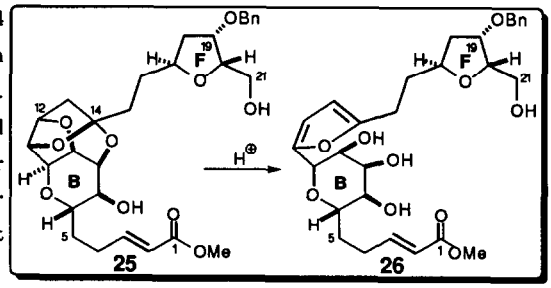
ketone analogue **21** of **19a** from the methyl furanoside **11a**.[2b] Acid catalyzed hydrolysis of the isopropylidene protecting groups in **21** could be readily achieved, but the methyl furanoside group was refractory. Unfortunately, undesired side reactions promoted by the acidic conditions needed to hydrolyze the methyl furanoside in **21** led to only a 26% yield of the rearrangement product **22**. It seemed likely that deprotection of the corresponding p-methoxybenzyl furanoside **19a** could be accomplished under milder conditions. In fact, the p-methoxybenzyl group could be selectively removed from **19a** with ceric ammonium nitrate in good (87%) yield. Subsequent mild acid hydrolysis sufficed to effect acetonide and silyl group removal. Evaporation of the solvents *in vacuo*, and brief treatment of the residue with Triton B in 95% ethanol, followed by acetylation of the crude product, gave **20** in 65% yield after HPLC purification. Apparently, after acetonide hydrolysis, furanose to pyranose equilibration is essentially complete, and the Michael addition occurs readily under basic conditions. Thus, the use of a p-methoxybenzyl furanoside ***more than doubled the yield*** for the rearrangement of **19b** into furopyranoside **20** compared with the similar conversion of methyl furanoside **21** into furopyranoside **22**.



While completing the synthesis of the multicyclic building block **24** for the C1 to C21 segment of halichondrin, we made several important discoveries. We found that the best results for allylation of **20** were accomplished with perchloric acid as catalyst. To our knowledge, there are no literature examples of Brønsted-acid catalyzed allylsilane additions on acetal substrates. Reaction of **23** with NaOMe in methanol produced the corresponding tetraol. Treatment of this tetraol with PPTS gave a low yield of the desired ketal **25** accompanied by furan **26** as the main product. Furthermore, storage of ketal **25** in $CDCl_3$ for 8h at room temperature (during a ^{13}C nmr acquisition) resulted in about 50% conversion to furans, presumably owing to traces of HCl in the solvent.



A more satisfactory alternative for the **23** to **24** conversion involved base catalyzed Michael addition followed by ketalization with mild acid catalysis. NaOMe in acetonitrile was effective for the Michael addition in contrast with NaOMe in methanol. After silylation of the remaining hydroxyl, a C3 epimer was converted into the natural isomer by treatment with methoxide to deliver **24** in 78% overall yield.



Although the acid-sensitivity of the halichondrins has been hinted at by others[1], a specific mode of decomposition has not previously been reported. Our discovery that the 2,6,9-trioxatricyclo[3.3.2.$0^{3,7}$]decane ABCDE-ring system in **25** is converted to furan byproducts under mild acid catalysis is important for the development of a practical total synthesis of halichondrin B. It is also conceivable that this reactivity has biological significance. Our growing awareness of the acid sensitivity problem inspired the use of α-methoxybenzyl furanosides. These masked sugars, that can be hydrolyzed under near neutral conditions, should prove especially useful in the synthesis of acid sensitive targets from readily available sugar precursors.

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REFERENCES AND NOTES

1. (a) Uemura, D.; Yamamoto, T.; Takahashi, K.; Katayama, C.; Tsukitani, Y.; Kikuchi, H.; Hirata, Y. *Tennen Tuki Kagobutsu Toronkai Koen Yoshishu* **1985**, *27*, 389. (b) Uemura, D.; Takahashi, K.; Yamamoto, T.; Katayama, C.; Tanaka, J.: Okumura, Y.; Hirata, Y. *J. Am. Chem. Soc.* **1985**, *107*, 4796. (c) Hirata, Y.; Uemura, D. *Pure Appl. Chem.* **1986**, *58*, 701. (d) Pettit, G. R.; Herald, C. L.; Boyd, M. R.; Leet, J. E.; Dufresne, C.; Doubek, D. L.; Schmidt, J. M.; Cerny, R. L.; Hooper, J. N. A.; Rützler, K. C. *J. Med. Chem.* **1991**, *34*, 3339.

2. (a) For our highly stereoselective synthesis from D-glucose of a homochiral H-ring pyran intermediate that incorporates carbons 27 to 35 of the halichondrin skeleton, see: Kim, S; Salomon, R. G. *Tetrahedron Lett.* **1989**, *30*, 6279. (b) For our stereoselective synthesis from D-ribose of a homochiral multicyclic C1-15 segment of halichondrin B, see Cooper, A. J.; Salomon, R. G. *Tetrahedron Lett.* **1990**, *30*, 3813. (c) For our highly stereoselective synthesis from D-mannitol of a homochiral tetracyclic C37-51 KLMN-ring segment of halichondrin B, see DiFranco, E.; Ravikumar, V. T.; Salomon, R. G. *Tetrahedron Lett.* **1993**, *34*, 3247.

3. Defaye, J.; Ratovelomanana, V. *Carbohydr. Res.* **1971**, *17*, 57.

4. All new compounds reported in this paper gave satisfactory spectroscopic data including high resolution MS exact mass or elemental analysis.

5. Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, 3535.

6. Glen, L. W.; Myers, G. S.; Grant G. A. *J. Chem. Soc.* **1951**, 2568.

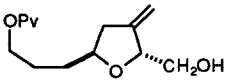
7. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin I*, **1975**, 1574.

8. Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059.

9. Grieco, P.A.; Pogonowski, C.S. *J. Am. Chem. Soc.* **1973**, *95*, 3071.

10. (a) Cooke, M. P., Jr. *J. Org. Chem.* **1973**, *38*, 4082. (b) Taylor, J. D.; Wolf, J. F. *Chem. Commun.* **1972**, 876.

11. The use of a sugar starting material for an F-ring building block for the total synthesis of halichondrins was reported recently: Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.*. **1992**, *114* 3162. However, in this case the sugar was L-arabinose from which the intermediate **27** was assembled in 16 steps and 23% overall yield.



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