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TOTAL SYNTHESIS OF HALICHONDRINS: ENANTIOSELECTIVE CONSTRUCTION OF A HOMOCHIRAL TETRACYCLIC KLMN-RING INTERMEDIATE FROM D-MANNITOL

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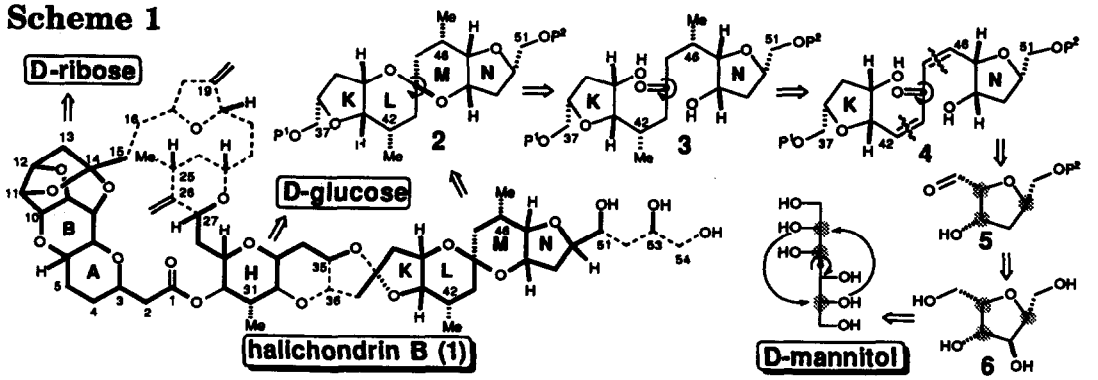
Summary: An efficient strategy exploiting C2 symmetry and featuring diastereoselective conjugate addition of Li_2Me_2CuCN to a γ-alkoxy-α,β-unsaturated acylsilane and diastereoselective spiroketalization provides a key tetracyclic KLMN-ring intermediate for halichondrin B from D-mannitol.

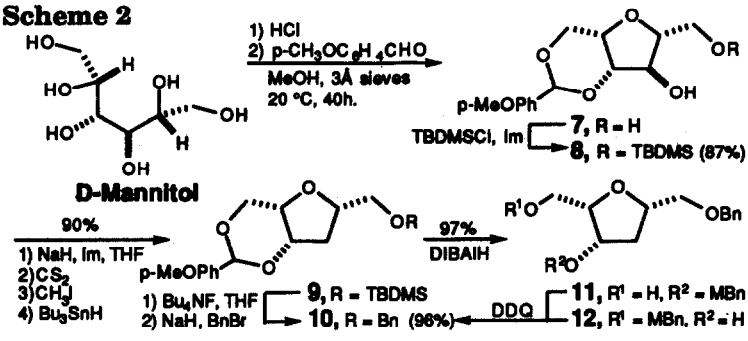
Halichondrin B (1) is a structurally unique polyether macrolide cancer cell growth inhibitor that is not readily available from its natural sources.[1] Considering its intricate structure comprising 32 centers of chirality, the feasibility of total synthesis as a practical source of supply would not merit serious consideration if it were not for the fact that halichondrin B is outstandingly potent *in vivo*. A few doses at 10μg/Kg provide T/C >200 against B-16 melanoma and T/C >300 against P-388 leukemia in mice. Our strategy for synthesis of 1 envisions the conjunction of stereochemically isolated segments that are derived in optically active form and of the requisite absolute configuration from inexpensive commercially available sugars (Scheme 1). Our syntheses of intermediates for the C1-15 and C27-35 subunits from D-ribose and D-glucose were reported previously.[2] We now report an efficient synthesis of the KLMN-ring C37-51 subunit 2. Owing to a double anomeric effect[3] and the preference for a diequatorial disposition of the methyl substituents on the L and M-rings, we reasoned that thermodynamic control would favor diastereoselective spiroketalization of a ketodiol precursor 3. Acyclic stereoselection in the conjugate addition[4] of two methyl nucleophiles to 4 would provide 3 diastereoselectively. With the protecting groups P^1 and P^2 the same, the intermediates 2-4 are C2 symmetrical. Aldol condensation of two equivalents of an aldehyde 5 with acetone might deliver 4. The three stereocenters of 5 can be derived from D-mannitol, an inexpensive C2 symmetrical starting material that is known to cyclize to a single 2,4-disubstituted tetrahydrofuran 6.[5]

Scheme 1



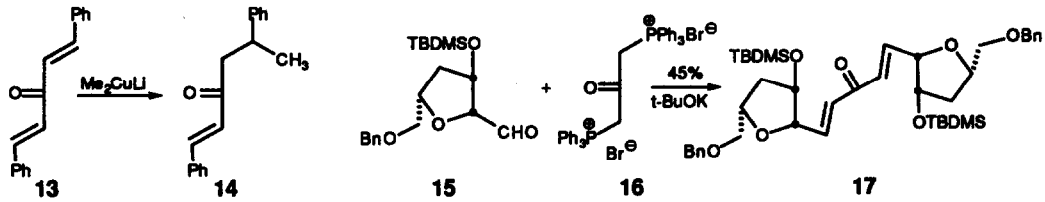
Acid catalyzed cyclization of D-mannitol generates tetraol **6** that readily affords a mono acetal **7**[6] (scheme 2). Hydrodehydroxylation of the derived monosilyl ether **8** by the Barton protocol[7] and replacement of TBDMS with benzyl affords **10**. The p-methoxybenzylidene acetal array in **10** is

Scheme 2



especially useful for preparing either of the p-methoxybenzyl ether derivatives **11** or **12**. Thus, reductive cleavage of **10** with DIBAlH[8] generates a 6:4 mixture of **11** and **12** in excellent yield, and either **11** or **12** can be quantitatively recycled to the starting acetal **10** by oxidation with DDQ under anhydrous conditions.[9]

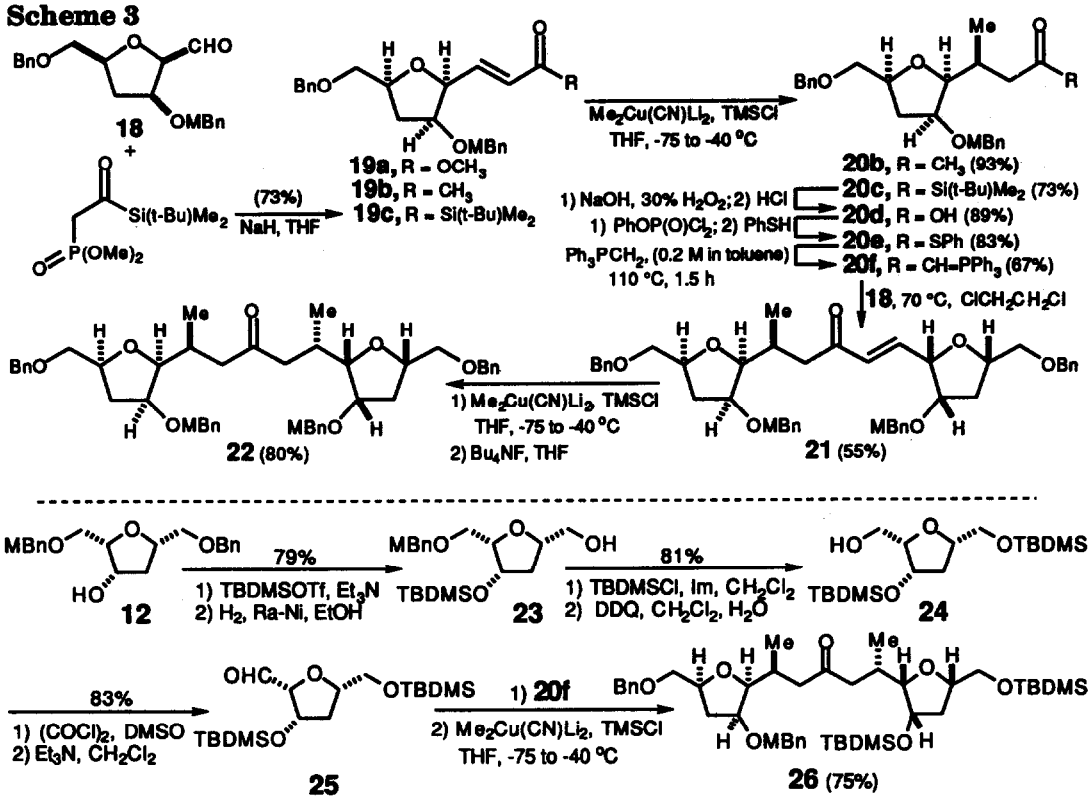
A model study with dibenzylideneacetone (**13**) showed that a dienone could undergo normal conjugate addition of a methyl nucleophile to give **14**. A dienone **17** was prepared by a one pot condensation of **15** (2 equivalents) with **16**.[10] However, the highly oxygenated dienone **17** was relatively unreactive toward Me_2CuLi and the use of Me_3SiCl to promote the conjugate addition[11] led to undesired alternative reactions of **17**.[12] This is apparently characteristic of dienones since **13** gave no trace of **14** with the Me_2CuLi-Me_3SiCl reagent. Therefore, a



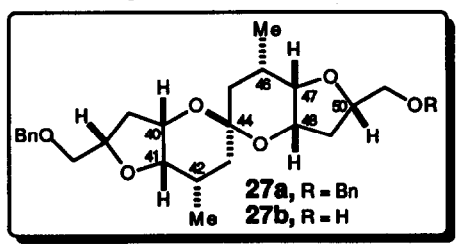
stepwise approach was adopted for assembling the KLMN-ring carbon skeleton starting with aldehyde **18** obtained from primary alcohol **11** in 93% yield by Swern oxidation (Scheme 3). The derived α,β-unsaturated ester **19a** was recovered quantitatively from attempted addition of methyl cuprates even in the presence of TMSCl. In contrast, the more electrophilic α,β-unsaturated ketone **19b** underwent cleanly diastereoselective 1,4-addition upon treatment with $Me_2Cu(CN)Li_2$[13] in the presence of TMSCl. The failure of all efforts to generate enone **21** by aldol condensation between aldehyde **18** and methyl ketone **20b** led us to devise a less direct route to **21** exploiting acylsilane chemistry. Thus, acylsilane **19c** underwent cleanly diastereoselective 1,4-addition affording **20c**. Oxidative desilylation, conversion of the resulting acid **20d** into thioester **20e** followed by acylation of methylenetriphenylphosphorane and condensation of the resulting ylide **20f** with aldehyde **18** delivered enone **21**. A second diastereoselective 1,4-addition of $Me_2Cu(CN)Li_2$ in the presence of TMSCl then afforded the C2-symmetrical ketone **22**.

Since the symmetry of our KLMN-ring fragment must be broken during incorporation into halichondrin B, a nonsymmetric analogue of **22** was needed. This was conveniently assembled from one equivalent of each of the differently protected mannitol-derived intermediates **11** and **12**. Thus, **12** was converted into a silylated analogue **24** of **11** by manipulation of protecting groups exploiting the selective hydrogenolysis with Raney nickel of a benzyl in the presence of 4-methoxybenzyl ether.[14] Condensation of the silyl protected aldehyde **25** with the benzyl protected ylide **20f** provided an enone that gave the unsymmetrical analogue **26** of **22** upon conjugate methylation.

Scheme 3



The viability of our strategy for generating the multicyclic polyether C37 to C51 segment of halichondrin B was established upon treatment of **22** with ceric ammonium nitrate in 10% aqueous acetonitrile. A single diastereomericlly pure C2-symmetrical spiroketal **27a** was produced.[15] Deprotection of **26** with DDQ and then Bu_4NF delivered a triol that afforded a single diastereomerically pure spiroketal **27b**[15] upon treatment with 1% HCl in THF. Since the stereocenters of the D-mannitol-derived starting material **6** have the absolute configurations corresponding to positions 40, 41, 47, 48, and 50 in halichondrin B, the final product **27** must have the correct absolute configuration for an enantioselective construction of the natural product.[16]



ACKNOWLEDGMENT. This research was assisted financially by a grant CA31595 from the National Cancer Institute of the National Institutes of Health. We thank Jason Sperry for assistance in optimizing some yields.

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Atom(s)	Halichondrin B (360 MHz)	Compound **27a** (300 MHz)
H-40	4.05(dd, 1H, J = 2.4, 3.0 Hz)	3.97 (dd, J = 2.0, 4.7 Hz)
H-48	4.10 (m, 1H)	"
Hs-43	1.31 (1H), 1.51 (1H)	1.02 (dd, 2H, J = 4.5, 13.1 Hz)
Hs-45	1.43 (1H), 1.50 (1H)	1.23 (dd, 2H, J = 4.6, 12.8 Hz)
Me-42	0.94 (d, 3H, J= 6.9 Hz)	0.96 (d, 3H, J = 7.1 Hz)
Me-46	1.01 (d, 3H, J= 6.9 Hz)	"
H-42	2.28	2.18
H-46	2.34	"
Hs-39	2.34	1.68 (dd, 2H, J = 3.2, 13.7 Hz)
Hs-49	1.83, 2.27	2.18 (2H)
H-38		4.12-4.22 (m, 1H)
H-50	4.00 (ddd, 1H, J = 9.0, 4.2, 4.2 Hz)	

Atom(s)	Halichondrin B (90.6 MHz)	Compound **27b** (75.5 MHz)
C-44	98.4	98.0
Me-42, Me-46	18.1, 18.3	18.3, 18.3
C-42, C-46	27.2, 27.1	27.0, 27.0
C-41, C47	80.8, 81.3	81.3, 81.5

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