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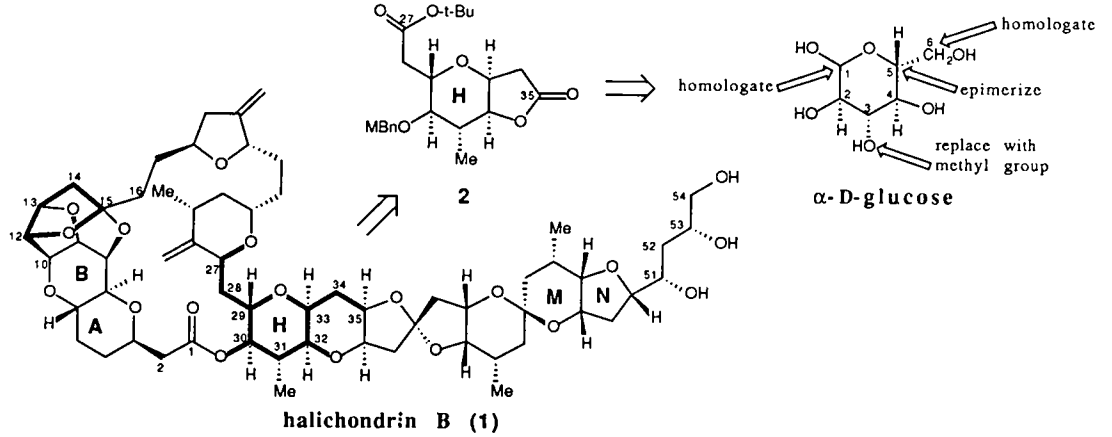
TOTAL SYNTHESIS OF HALICHONDRINS: HIGHLY STEREOSELECTIVE CONSTRUCTION OF A HOMOCHIRAL PENTASUBSTITUTED H-RING PYRAN INTERMEDIATE FROM α-D-GLUCOSE

Seokchan Kim and Robert G. Salomon*

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

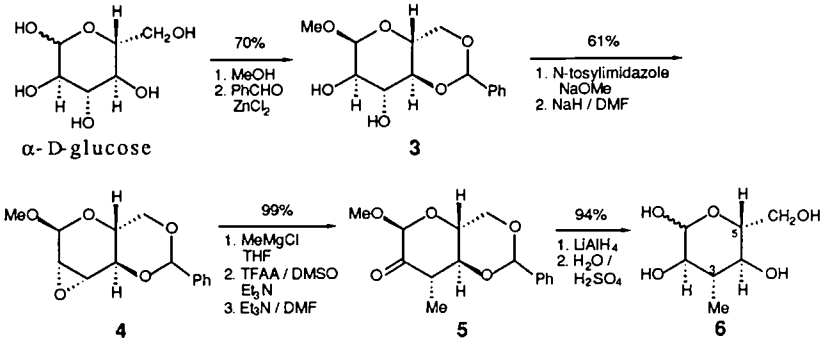
Summary: The functionality of α-D-Glucose is stereoselectively manipulated exploiting pyranose ⇋ furanose ⇋ pyranose interconversions and lactonization for selective masking to achieve a stereocontrolled synthesis of the densely substituted H-ring pyran of halichondrins.

Halichondrins, a family of macrolide polyethers, were isolated from a sponge, *Halichondria okadai* Kadota, in $4x10^{-7}$ to $5x10^{-6}$% yields.[1] Halichondrin B (**1**), the biologically most active member of this new family, is a remarkably effective antitumor agent *in vivo*. A few doses of 10 μg/Kg provide T/C >200 against B-16 melanoma and T/C >300 against P-388 leukemia in mice. The 32 asymmetric carbons in **1** allow more than four billion stereoisomers. Therefore, a practical total synthesis must be highly stereoselective. Furthermore, these asymmetric carbons are located in several regions of the molecule which are apparently insulated from one another. Therefore, it would be most difficult to generate a desired configuration within one region under a stereocontrolling influence of chirality already present in one of the other sectors. We envision a highly convergent synthesis of **1** constructing each stereochemically isolated segment in optically active form and of the properly specified absolute configuration from inexpensive commercially available sugars. We now report a synthesis from D-glucose of a homochiral H-ring pyran intermediate **2** which incorporates carbons 27 to 35 of the halichondrin skeleton.



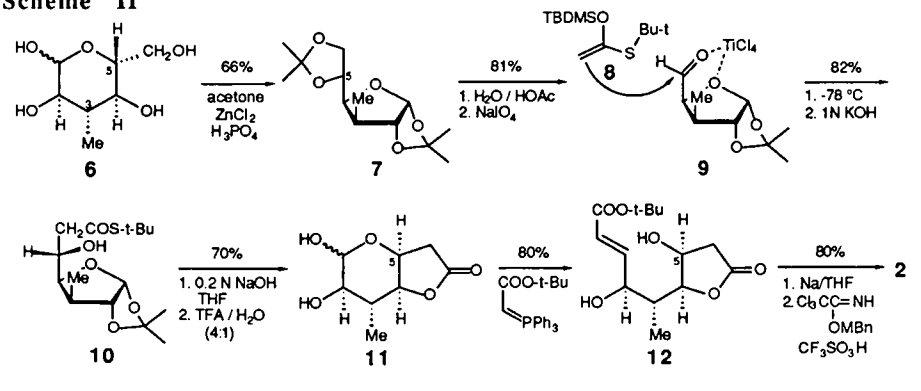
Replacement of the 3-hydroxyl in α-D-glucose by a methyl group (Scheme I) is initiated by selective masking of all but the trans hydroxyls at positions 2 and 3.[2] Selective activation of the 2-hydroxyl in **3** and cyclization provide epoxide **4**.[3] Regioselective opening of the epoxide by axial attack of MeMgCl followed by oxidation of the 2-hydroxyl and epimerization of the 3-methyl to the thermodynamically preferred (>99:1) equatorial configuration delivers ketone **5**. Stereoselective reduction followed by hydrolysis of the masking ketals provides 3-desoxy-3-methyl-D-glucose (**6**).[4]

Scheme I

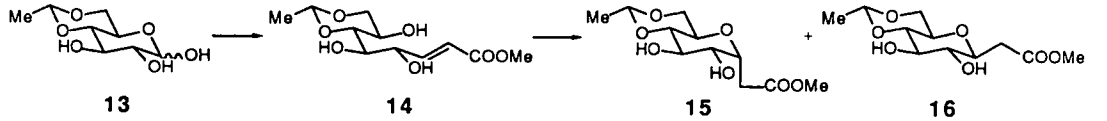


Inversion of the configuration at position 5 in **6** and elongation of the side chain (Scheme II) was achieved by a C-C bond cleavage-reformation sequence exploiting the pyranose to furanose interconversion which accompanies ketalization of glucose with acetone.[5] Diketals such as **7** are readily monodeketalyzed and oxidative cleavage of the intermediate vicinal diol with periodate destroys the center of incorrect chirality at position 5.[5] Entirely stereoselective (>99:1) generation of the requisite configuration at this center ensues upon chelation controlled condensation of the resulting aldehyde **9** with the t-butyl(dimethyl)silyl enol ether **8** of t-butyl thioacetate with catalysis by $TiCl_4$.[6] Hydrolysis of the thioester **10** with NaOH and deketalization with aqueous trifluoroacetic acid is accompanied by furanose to pyranose interconversion and lactonization to provide the cis lactone **11**. Wittig olefination of **11** and heterocyclization of the in-termediate α,β-unsaturated ester **12** followed by methoxybenzylation[7] delivers the target lactone **2**.

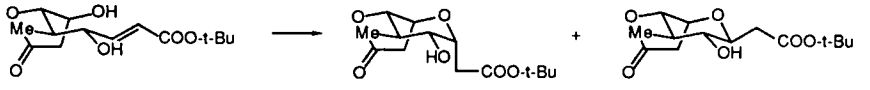
Scheme II[8]



Reversibility of the hetero-Michael cyclization of **12** was expected to lead to the thermodynamically favored carbo-t-butoxymethyl isomer. The chain extension of **13** by Wittig reaction with carbomethoxymethylene(triphenyl)phosphorane and cyclization of the resulting unsaturated ester **14** is a pertinent precedent.[9] Cyclization of **14** in the presence of dilute base initially produces a 1:1 mixture of products **15** and **16**. However equilibration generates pure **16** owing to a preference for the less sterically encumbered equatorial disposition of the carbomethoxyl substituent. If a chair conformation of the pyran ring were favored for the cyclization product **17** from **12**, the required trans isomer trans-**17**, with an equatorial carbo-t-butoxymethyl substituent should be favored over cis-**17** with that substituent axial.



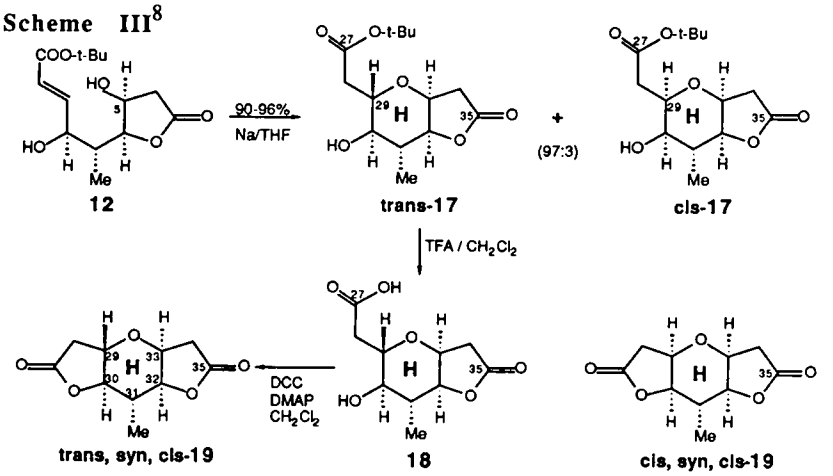
13 **14** **15** **16**



12 **cis-17** **trans-17**

Stereochemical characterization of the major (97:3) cyclization product from **12** was accomplished as outlined in scheme III. De-t-butylation upon treatment with trifluoroacetic acid de-

Scheme III[8]



12 **trans-17** **cis-17**

trans, syn, cis-19 **18** **cis, syn, cis-19**

livered a γ-hydroxy acid which did not lactonize under these conditions in contrast with the intermediate γ-hydroxy acid from **10** which produces the cis butyrolactone **11** even in aqueous TFA. This reluctance to lactonize is consistent with a trans disposition of the hydroxy and carboxymethyl substituents in **18**. Lactonization was accomplished upon treatment with N,N'-dicyclohexylcarbodiimide in the presence of p-(N,N-dimethylamino)pyridine. That the resulting dilactone (87% yield from **trans-17**) was the unsymmetrical isomer trans,syn,cis-**19** rather than the sym-

metrical isomer cis,syn,cis-**19** was readily apparent from the appearance of five distinct resonances corresponding to the nonequivalent hydrogens at positions 29 to 33 in its ^{1}H NMR spectrum.[8]

Although a shorter nonstereoselective synthesis producing **7** and its C3 epimer (1:2) from α-D-glucose was reported previously[10], the present *entirely stereoselective* synthesis gives an improved overall yield and, most importantly, avoids the odious task of a very difficult if not impossible separation of isomers. The *entirely stereoselective* generation of the stereocenters at C5 (in the **9** to **10** conversion) and C1 (in the **12** to **trans-17** conversion) now make the homochiral intermediates **18** and its masked derivative **2** readily available for the total synthesis of halichondrins.

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8. **2:** ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (d, 3 H), 1.47 (s, 9 H), 2.09 (m, 1 H), 2.50 (m, 4 H), 3.08 (m, 1 H), 3.81 (s, 3 H), 3.83 (m, 1 H), 4.27 (m, 1 H), 4.52 (m, 3 H), 6.92 (m, 2 H), 7.25 (m, 2 H); $[\alpha]_D$ = -38.1° (c 0.21 $CHCl_3$). **7 (l):** ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (d, 3 H), 1.22 (s, 3 H), 1.26 (s, 3 H), 1.32 (s, 3 H), 1.43 (s, 3 H), 2.35 (m, 1 H) δ 3.93 (m, 4 H), 4.27 (d, J = 3.5 Hz, 1 H), 5.69 (d, J = 3.5 Hz, 1 H); $[\alpha]_D$ = -8.20° (c 1.17 $CHCl_3$). **9 (l):** ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 (d, 3 H), 1.33 (s, 3 H), 1.52 (s, 3 H), 2.74 (m, 1 H), 4.43 (d, J = 3.5 Hz, 1 H), 4.63 (d, J = 4.8 Hz, 1 H), 5.99 (d, J = 3.5 Hz, 1 H), 9.76 (d, J = 1.6 Hz, 1 H). **10 (S):** ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, 3 H), 1.31 (s, 3 H), 1.47 (s, 9 H), 1.51 (s, 3 H), 2.27 (m, 1 H), 2.61 (m, 2 H), 4.10 (m, 2 H), 4.38 (d, 3.6 Hz, 1 H), 5.84 (d, 3.6 Hz, 1 H); $[\alpha]_D$ = -26.3° (c 1.15 $CHCl_3$). **11 (S):** ^{1}H NMR (200 MHz), CD_3CN) δ 1.16 (d, 3 H), 1.78 (m, 1 H), 2.61 (m, 2 H), 3.21 (dd, J = 11, 5.2 Hz, 1 H), 4.19 (dd, J = 7.2, 4.4 Hz, 1 H), 4.53 (dd, J = 6.4, 4.4 Hz, 1 H), 4.77 (d, J = 5 Hz, 1 H); m.p. 145°-146 °C; $[\alpha]_D$ = -91.0° (c 0.5 CH_3CN). **12 (S):** ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.19 (d, 3 H), 1.50 (s, 9 H), 2.65 (m, 3 H), 4.07 (dd, J = 10.4, 3 Hz, 1 H), 4.50 (m, 2 H), 6.05 (dd, J = 15.6, 1.8 Hz, 1 H), 6.90 (dd, J = 15.6, 5 Hz, 1 H); m.p. 119°-121°C; $[\alpha]_D$ = -37.9° (c 1.1 $CHCl_3$). **17 (S):** ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (d, 3 H), 1.46 (s, 9 H), 1.98 (m, 1 H), 2.62 (m, 4 H), 3.29 (m, 1 H) 3.87 (m, 1 H), 4.22 (m, 1 H), 4.52 (m, 1 H); m.p. 95-96 °C; $[\alpha]_D$ = -21.0 ° (c 0.1 $CHCl_3$). **Trans,syn,cis-19 (S):** ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (d, 3 H), 2.09 (m, 1 H), 2.81 (m, 4 H), 3.77 (m, 1 H), 4.04 (m, 1 H), 4.32 (9, 1 H), 4.89 (m, 1 H); m.p. 135°-137 °C; $[\alpha]_D$ = 45.0° (c 0.16 $CHCl_3$).

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