Process Development of Halaven®: Synthesis of the C1–C13 Fragment from D-(–)-Gulono-1,4-lactone

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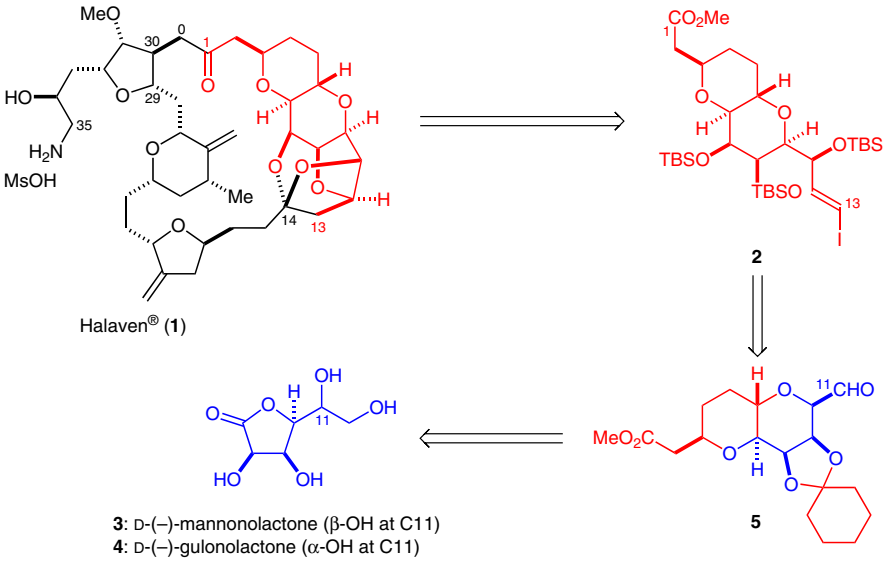
Abstract: A 12-step kilogram-scale synthesis of the C1–C13 fragment, common to halichondrin B and the totally synthetic analogue Halaven® (E7389, INN eribulin mesylate), is described. The synthesis features four crystalline intermediates which facilitates throughput, and enhances quality control of all stereogenic centers in the title compound.

Key words: carbohydrates, chiral pool, drugs, glycosylation, stereoselective synthesis

Halaven® (**1**; E7389, INN eribulin mesylate) is a fully synthetic analogue of the structurally complex marine natural product halichondrin B.[1] Eribulin has been recently approved by the FDA for the treatment of certain patients with metastatic breast cancer.[2] Although the structure of **1** is substantially simplified relative to the natural product (Halaven® contains 19 vs. 32 stereogenic centers and a 36 vs. 54 carbon backbone as compared to halichondrin B), the discovery and development of **1** by total synthesis still represents a significant challenge. The foundation for starting these research and development efforts was provided by the first total synthesis of halichondrin B by Kishi and co-workers at Harvard University.[3] The use of total synthesis allowed flexible modification of embedded structural elements of the original halichondrin macrolide. Specifically, the C29 and C30 sites of the macrolide were found to be productive areas for exploration to optimize biological activity. The macrocyclic ketone analogue **1**, bearing a suitably substituted tetrahydrofuran replacement for the halichondrin 'left half', emerged as the candidate compound for clinical evaluation.

Halaven® (**1**) is synthesized in a ten-step process from the C1–C13 fragment **2** and the C14–C35 fragment (not shown; see accompanying article). The C1–C13 fragment, common to both **1** and the halichondrins, has previously been synthesized by Kishi and co-workers from D-galactose,[4] D-(–)-mannonolactone,[5] and D-(–)-ribonolactone.[6] The initial synthesis of C1–C13 that was used to produce this fragment for clinical evaluation utilized D-mannonolactone (**3**)[5b] as the starting sugar. However, availability and cost of **3** became an obstacle to procuring larger quantities of **2** needed for full clinical evaluation. Although D-mannonolactone contains the correct stereochemistry for four of the stereogenic centers in **2** (C8, C9, C10, and C11), one of these centers, C11, is destroyed during the synthesis and subsequently re-established. Thus, D-gulonolactone (**4**), a sugar epimeric to D-mannonolactone at one stereogenic center (that corresponding to



Scheme 1 Synthetic strategy for Halaven® C1–C13 fragment **2**

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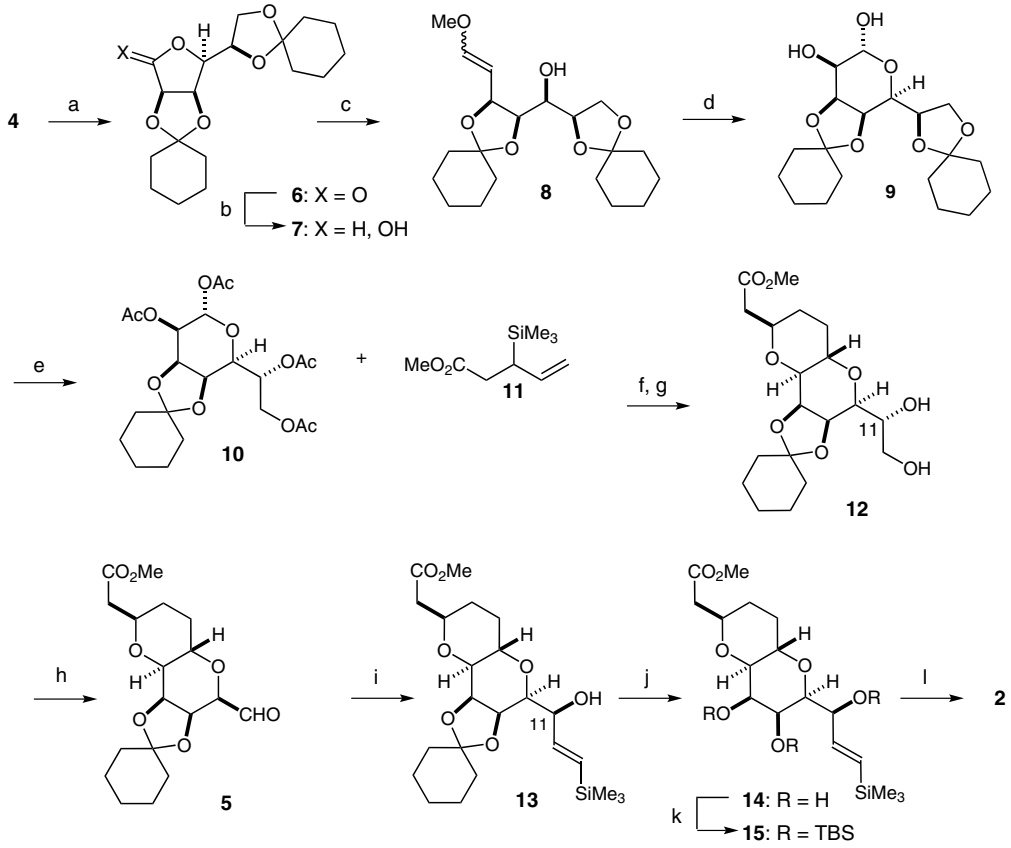
C11 in halichondrin.), could serve as a functionally equivalent starting carbohydrate. In other words, the stereochemistry at C11 is inconsequential in the raw material as both sugars degenerate to the common aldehyde intermediate **5** (Scheme 1). In order to establish the route from D-gulonolactone, the chemistry reported by the Kishi group on D-mannonolactone[5b] would need to be extended to the epimeric sugar, D-gulonolactone.[7]

This article describes the realization of the chemical sequence from D-gulonolactone to C1–C13 fragment **2**. During the course of this investigation, several reactivity differences in the behavior of the two carbohydrate epimers were noted and incorporated into the overall route design and purification strategy. The overall synthesis has been developed and executed on multikilogram scale in fixed equipment.

The synthetic scheme for transformation of D-gulonolactone (**4**) to **2** is depicted in Scheme 2. The known biscyclohexylidene lactone **6** was reduced with DIBAL-H to afford lactol **7**. The previously reported one-carbon homologation via Wittig methoxymethylenation in the mannono series was conducted in refluxing THF and did not specify removal of triphenylphosphine and triphenylphosphine oxide. Direct application of these conditions in the gulono series led to varying degrees of epimerization at C8. Furthermore the subsequent osmylation step was found to be sensitive to contamination by phosphines. These concerns were addressed by the following procedural modifications: (i) inverse addition of substrate to a preformed ylid at 0 °C, (ii) use of a maleic anhydride workup allowed for the removal of triphenylphosphine, and (iii) precipitation of triphenylphosphine oxide from MTBE–heptane afforded crude product with acceptable stereochemical and impurity profile for use in the next step without chromatographic purification. Stereoselective osmylation of **8**, proceeded as previously described in the mannonolactone series to provide ca. 3:1 mixture of crystalline α-hydroxylactols **9**.

Difficulties were encountered in the C-glycosidation of the diacetate corresponding to **9** due to the unexpected lability of the ancillary cyclohexylidene under the glycosidation conditions. Rather than trying to suppress this reactivity, we decided to combine cyclohexylidene monodeprotection with acetate formation.[8] A survey of catalysts for the combined process revealed that treatment with scandium(III) triflate or zinc(II) chloride in the pres-



Scheme 2 Synthesis of **2** (C1–C13) from D-(–)-gulonolactone (**4**). *Reagents and conditions*: a) cyclohexanone, PTSA, toluene, 110 °C, crystallization, 60%; b) DIBAL-H, toluene–THF, –5 °C, quant.; c) KO*t*-Bu, $MeOCH_2PPh_3^+Cl^-$, –5 °C to 30 °C, 81%; d) $K_2OsO_4·2H_2O$, NMO, acetone–H_2O, 30 °C, 55%; e) $ZnCl_2$, AcOH, Ac_2O, 30 °C, crystallization, 69%; f) **11**, $BF_3·OEt_2$, MeCN, 15 °C, 95%; g) NaOMe, MeOH, MTBE, 15 °C, crystallization, 62%; h) $NaIO_4$, EtOAc, 15 °C, quant.; i) $CrCl_2$, $NiCl_2$, 1-bromo-2-trimethylsilylethene, DMSO, MeCN, 30 °C, 45%; j) AcOH, H_2O, 95 °C, crystallization, 70%; k) TBSOTf, 2,6-lutidine, MTBE, 30 °C, crystallization, 75%; l) NIS, MeCN, toluene, TBSCl, 35 °C, 89%.

ence of acetic acid and acetic anhydride cleanly effected monocyclohexylidene removal and peracetylation to afford the crystalline tetraacetate **10**. C-Glycosidation of **10** with commercially available methyl 3-trimethylsilyl-4-pentenoate (**11**) proceeded as previously reported in the D-mannonolactone series, the product of which, upon direct treatment of with sodium methoxide, underwent global deacetylation, olefin conjugation, and oxy-Michael addition to form the crystalline diol-pyran **12**. The crystallinity of **12** stood in sharp contrast to the noncrystallinity of the C11 epimer corresponding to the D-mannonolactone series. Sodium periodate mediated cleavage of diol-pyran **12** generated aldehyde **5**, the intermediate common to both D-mannonolactone and D-gulonolactone synthetic sequences. The overall route from gulonolactone is one step shorter owing to the combined cyclohexylidene removal and tetraacetate formation.

Ni(II)/Cr(II)-mediated coupling, as previously reported, stereoselectively re-established the C11 alcohol of **13** with a 10:1 diastereomeric ratio at C11. The remaining cyclohexylidene ring was now cleaved under mild acidic conditions using AcOH–water to afford a crystalline triol **14**. Silylation with *tert*-butyldimethylsilyl triflate provided the crystalline trisilylether **15**. Interestingly, it was found that use of MTBE as solvent (in place of dichloromethane) for the reaction allowed complete suppression of silylation on the C11 epimer. Simple crystallization of the product provided the C1–C13 fragment with complete stereochemical homogeneity.

Completion of **2** is achieved by electrophilic substitution of the vinylsilane to form the vinyl iodide. The reaction was previously demonstrated using the known sensitizer chloroacetonitrile as reaction co-solvent. As these conditions pose an unnecessary risk to manufacturing personnel, an alternate process was required. In the Kishi group, conditions using stoichiometric TBSCl in acetonitrile were reported as a suitable reaction matrix for the vinyl silane–vinyl iodide transformation.[9] With this lead reference, we further investigated the reaction parameters and found that catalytic TBSCl in acetonitrile and toluene is sufficient for accomplishing *N*-iodosuccinimide (NIS) mediated conversion of **15** to target compound **2**.[10]

In summary, the synthesis of the halichondrin B and eribulin mesylate C1–C13 fragment **2** from readily available D-(–)-gulono-1,4-lactone **4** has been accomplished. The overall process is a direct extension of the D-(–)–mannonolactone route reported by the Kishi group. During the demonstration of this new route, several findings were noted which had practical consequences: (i) the lability of the ancillary cyclohexylidene group in the gulono series allowed combination of the deprotection and acetate formation steps, (ii) the C1–C12 diol **12** proved to be highly crystalline thus facilitating purification, and (iii) the penultimate intermediate **15** was found to be crystalline enabling a late-stage overall control of stereochemical quality.

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(10) (a) Experimental procedure for conversion of vinyl silane **15** into vinyl iodide **2**: Into the reactor were placed **15** (3.23 kg, 4.50 mol), NIS (4.04 kg, 30.2 mol), and TBSCl (0.032 kg, 0.21 mol) in a mixture of toluene (8.5 kg), acetonitrile (15.2 kg). The mixture was stirred at 25–30 °C for 22 hours. An aqueous mixture of $Na_2S_2O_3$/$KHCO_3$ ($Na_2S_2O_3$: 1.5 kg, $KHCO_3$: 2.9 kg, water: 29 kg) was added to the reaction mixture at 0–30 °C and stirring was continued for 30 min. After phase separation, the upper layer was washed with 9% aq NaCl (32 kg × 2). The organic layer was concentrated by distillation. The residue was dissolved with *n*-heptane (9 kg). The solution was purified by column chromatography on silica gel (39.2 kg; preconditioned with 91 kg *n*-heptane) with *n*-heptane–MTBE (100:0 → 93:7; 354 kg) as the eluent. The main fractions were combined in the reactor and concentrated by distillation (40–50 °C external temperature). The residue was dissolved with toluene and concentrated by distillation again (40–50 °C external temperature) to afford **2** (3.09 kg, 4.01 mol, 89% yield). Characterization of **2**: FT-IR (thin film): ν_{max} = 2953, 2930, 2857, 1745, 1607, 1472, 1361, 1255, 1080 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6): δ = 0.07–0.18 (m, 18 H), 0.90–0.99 (m, 27 H), 1.25–1.34 (m, 1 H), 1.31–1.41 (m, 1 H), 1.78–1.83 (m, 1 H), 1.85–1.90 (m, 1 H), 2.47–2.49 (m, 2 H), 3.03 (dd, *J* = 9.6, 2.4 Hz, 1 H), 3.49 (ddd, *J* = 10.1, 10.1, 4.5 Hz, 1 H), 3.63 (s, 3 H), 3.78–3.85 (m, 1 H), 3.83 (dd, *J* = 6.8, 3.6 Hz, 1 H), 4.03 (dd, *J* = 6.8, 2.8 Hz, 1 H), 4.15 (dd, *J* = 2.2, 2.2 Hz, 1H), 5.00 (ddd, *J* = 7.8, 3.8, 0.8 Hz, 1 H), 6.37 (dd, *J* = 14.8, 0.8 Hz, 1H), 6.88 (dd, *J* = 14.4, 8.0 Hz, 1H). ^{13}C NMR (100 MHz, acetone-d_6): δ = –4.45, –4.15, –4.18, –3.41, –3.35, –3.12, 18.79, 19.44, 19.70, 26.55, 26.91, 27.16, 29.65, 31.30, 41.14, 51.66, 65.11, 71.56, 73.83, 74.80, 75.10, 77.94, 79.45, 81.72, 147.85, 171.70. ESI-HRMS: m/z calcd for $C_{32}H_{63}IO_7Si_3$+Na^+: 793.2824 $[M+Na]^+$; found 793.2824. $[\alpha]_D^{20}$ –39.0 (*c* 1.25, toluene). (b) Characterization of **2**: FT-IR (thin film): ν_{max} = 2953, 2930, 2857, 1745, 1607, 1472, 1361, 1255, 1080 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6): δ = 0.07–0.18 (m, 18 H), 0.90–0.99 (m, 27 H), 1.25–1.34 (m, 1 H), 1.31–1.41 (m, 1 H), 1.78–1.83 (m, 1 H), 1.85–1.90 (m, 1 H), 2.47–2.49 (m, 2 H), 3.03 (dd, *J* = 9.6, 2.4 Hz, 1 H), 3.49 (ddd, *J* = 10.1, 10.1, 4.5 Hz, 1 H), 3.63 (s, 3 H), 3.78–3.85 (m, 1 H), 3.83 (dd, *J* = 6.8, 3.6 Hz, 1 H), 4.03 (dd, *J* = 6.8, 2.8 Hz, 1 H), 4.15 (dd, *J* = 2.2, 2.2 Hz, 1H), 5.00 (ddd, *J* = 7.8, 3.8, 0.8 Hz, 1 H), 6.37 (dd, *J* = 14.8, 0.8 Hz, 1H), 6.88 (dd, *J* = 14.4, 8.0 Hz, 1H). ^{13}C NMR (100 MHz, acetone-d_6): δ = –4.45, –4.15, –4.18, –3.41, –3.35, –3.12, 18.79, 19.44, 19.70, 26.55, 26.91, 27.16, 29.65, 31.30, 41.14, 51.66, 65.11, 71.56, 73.83, 74.80, 75.10, 77.94, 79.45, 81.72, 147.85, 171.70. ESI-HRMS: m/z calcd for $C_{32}H_{63}IO_7Si_3$+Na^+: 793.2824 $[M+Na]^+$; found 793.2824. $[\alpha]_D^{20}$ –39.0 (*c* 1.25, toluene).

