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Halichondrin B: Synthesis of the C1−C22 Subunit

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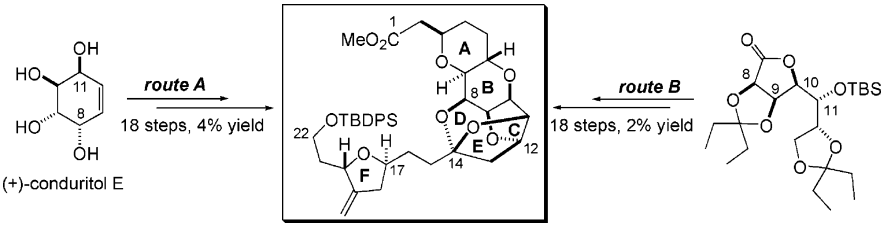

Two efficient routes to the C1−C22 subunit of halichondrin B are described. The cage ketal **7**, which contains 11 asymmetric centers embedded within the ABCDEF-ring framework, was assembled from (+)-conduritol E (**27**) in 18 steps and 4% overall yield. In a separate route, **7** was also synthesized in 18 steps and 2% overall yield from a derivative of α-D-glucoheptonic acid γ-lactone (**62**). While the former route installs the fully elaborated C-ring endowed with the correct C12 stereochemistry early in the synthesis, the latter features a late-stage introduction of the C12 stereocenter during the ultimate one-pot Michael addition/ketalization cascade to form the CDE-ring system of the cage. The importance of the C12 stereocenter to the crucial ketalization event is discussed through comparison of these two strategies.

Introduction

Halichondria okadai is a common marine sponge found off the coast of Japan. In 1986, Hirata and Uemura reported that extracts from this black-colored animal displayed compelling in vivo antitumor activity.[1a] Eight active compounds were separated from these extracts and purified and were subsequently named the halichondrins. The most potent of these was halichondrin B (Figure 1), isolated in low yield (1.8×10^{-6}%), which displayed an in vitro IC_{50} value for B-16 melanoma of 0.093 ng/mL. It was also found to have significant in vivo activity against B-16 melanoma, P-388 leukemia, and L-1210 leukemia.

Halichondrin B features 32 asymmetric centers that decorate a contiguous 54-carbon backbone. Structural features of note include a macrolactone spanning C1−C30, *exo*-methylene groups at C19 and C26, spiroketals at C38 and C44, and a 2,6,9-trioxatricyclo[3.2.2.0^{3,7}]-decane ketal (hereafter referred to as the "cage") embedded within the C8−C14 region of the molecule. The latter is an interesting structural motif unique to the halichondrins and is thought to be largely responsible for its remarkable biological activity. From their original data, Uemura and Hirata noted a strong correlation between the lipophilicity of the cage portion of the halichondrins and antitumor potency. Indeed, a C1−C38 diol (Figure 2) prepared by the Kishi group during the course of their synthetic studies[2] was found to display the same activity profile as that of halichondrin B over the 60 cell lines screened by the National Cancer Institute (NCI) and gave IC_{50} values within 1 order of magnitude of the natural product itself. However, the in vivo potency of this compound was substantially lower than that of halichon-

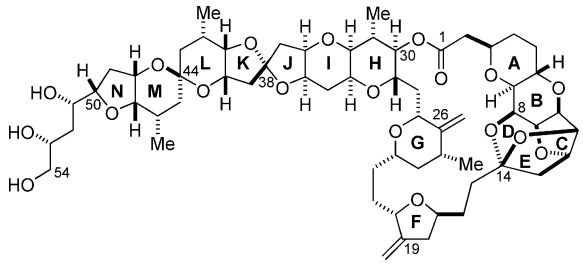

FIGURE 1. Halichondrin B.

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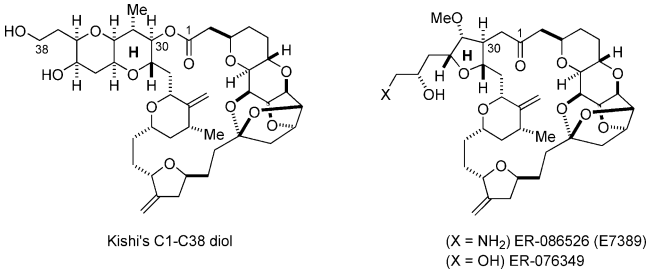

FIGURE 2. Biologically active halichondrin B analogues.

drin B. Recent drug discovery efforts at Eisai Research Institute have yielded many different halichondrin B analogues;[3] the two most highly active ones (ER-086526 and ER-076349, Figure 2) feature a truncated H-ring bearing a hydrophilic side chain. The replacement of the macrolactone functionality with a hydrolytically stable ketone unit at C1 was done in order to prolong the in vivo activity of these compounds. The primary amine ER-086526 (E7389), which displays greater aqueous solubility than ER-076349, is currently in phase I and phase II trials at the National Cancer Institute.[4]

The initial findings by Hirata and Uemura prompted further investigation of the biological activity displayed by halichondrin B. It was determined by the NCI that halichondrin B is a mitotic inhibitor which binds to the vinca domain of tubulin, resulting in inhibition of microtubule formation and tubulin-dependent GTP hydrolysis.[5] Halichondrin B was found to be extremely effective in vivo against human solid tumors which had been xenografted into immune-deficient mice.[5] It also exhibited an IC_{50} value of 0.3 nM against L-1210 murine leukemia cells, thereby surpassing in potency the best previously known agents dolastatin 10 (0.5 nM), rhizoxin (1 nM), and vinblastine (20 nM).[5]

Halichondrin B is currently in preclinical development by the NCI based on the data detailing its remarkable biological activity.[5,6] However, the extremely low yield of natural product obtained from the original sponge has thwarted progress toward this end. Although halichondrin B has since been isolated from three other sponge genera, the yields from these sources, which include *Axinella* (1.8×10^{-6}%),[1b,c] *Phakellia* (3.5×10^{-6}%),[1d] and *Lissodendoryx* (4.0×10^{-5}%),[1e] have also been disappointingly low. The isolation of the halichondrins from four different sources has led Munro et al. to suggest that the natural products are synthesized by a microbial sponge symbiont rather than by the sponges themselves.[7a] There are reports detailing attempts at aquacultural production of the most prolific sponge, *Lissodendoryx* n. sp. 1,[7a,b] but this work is in the very early stages of development, and the authors note that this would require a yearly output of nearly 5 million kg of sponge in order to satisfy the anticipated clinical demand of 5 kg per year of halichondrin B.

Chemical synthesis has proven to be a viable method by which scarce natural products of considerable structural complexity may be accessed in larger quantities.[8] The exceedingly small amounts of halichondrin B available from natural sources provides a strong impetus for its total synthesis. Efforts toward this end have been published by four groups, including Kishi,[9] Salomon,[10] Yonemitsu,[11] and our own.[12] Although a total synthesis of halichondrin B was published in 1992 by the Kishi group,[9a] its length (ca. 53 linear steps/ca. 115 total steps) limits its scalability. Among several reports describing halichondrin subunit syntheses,[12] we have previously published syntheses of a C1−C15 subunit,[12g] requiring 16 steps and proceeding in 0.6% overall yield from α-D-glucoheptonic acid γ-lactone, as well as a C1−C14 subunit model,[12j] which was obtained in 3% overall yield over 18 steps from (+)-conduritol E.

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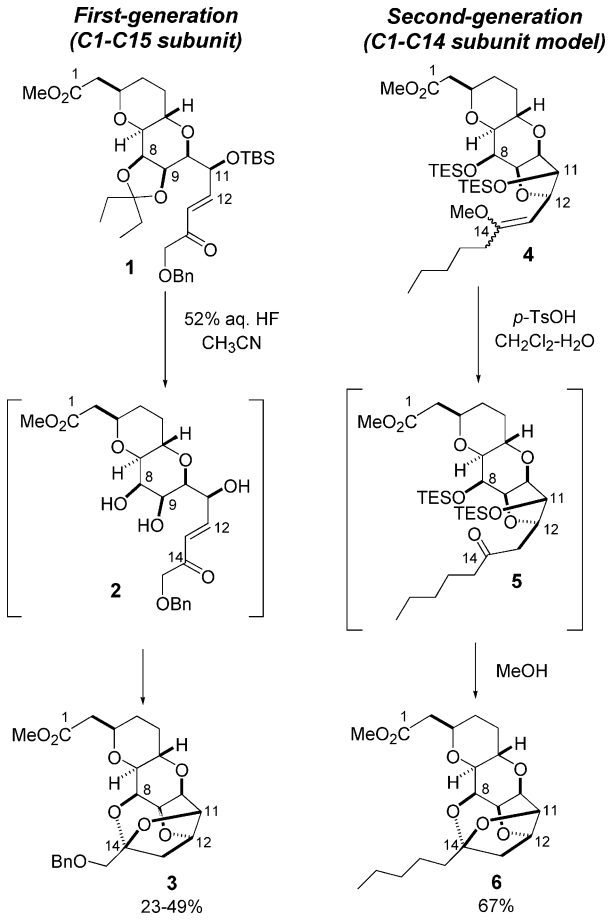
SCHEME 1



A key issue in both of our reported syntheses of the ABCDE-ring system was the late-stage construction of the acid-sensitive caged ketal. As shown in Scheme 1, C8, C9, and C11 hydroxyl unmasking in **1** gave the enone triol **2**, which then underwent Michael addition of the C9 hydroxyl to set the C12 stereocenter and ketalization of the C14 ketone with the C8 and C11 hydroxyl groups to provide the C1−C15 subunit model **3**. We hypothesized that poor control over the C12 stereochemistry during the Michael addition step led to low and variable yields of **3** in this first-generation synthesis.[12g] In our subsequent synthesis of the C1−C14 subunit model **6**,[12j] we introduced the C12 stereochemistry in a controlled manner early in the sequence by constructing the densely functionalized C-ring at the outset. Subjection of the enol ether substrate **4** to the acidic hydrolysis conditions shown led to clean formation of **6**, presumably proceeding through the intermediate ketone **5**. This favorable result appeared to validate our assertion that the C12 stereochemistry played a key role in facilitating cage formation by enforcing proximity between the reactive functionality. Furthermore, we were able to employ milder conditions in this case (*p*-TsOH, CH_2Cl_2, MeOH, H_2O) due to the absence of any robust protecting groups that resisted hydrolysis. The presence of the C8−C9 pentylidene ketal and the C11 TBS ether in our first synthesis necessitated the use of more forcing conditions (52% aq HF, CH_3CN) to induce the deprotection of the C8 and C9 alcohols, which preceded the Michael addition/ketalization cascade. We sought to modify the protecting group strategy of our first-generation synthesis in order to allow for the use of a milder acid promoter, thereby enabling a better comparison of the two ketalization protocols. We also desired to incorporate the adjacent F-ring into our synthesis in order to access the C1−C22 fragment of halichondrin B, incorporating our results in recently reported syntheses of the C14−C22 subunit.[12i,k] In this paper, we report the synthesis of the C1−C22 subunit **7** by two routes, which feature alternative protocols for setting the C12 stereocenter and for effecting the critical ketalization event. Our work leading to the synthesis of **6** is also discussed in full detail, including results not described in our earlier communication.[12j]

Results and Discussion

The retrosynthesis for our two routes to the C1−C22 subunit **7** are shown in Scheme 2.

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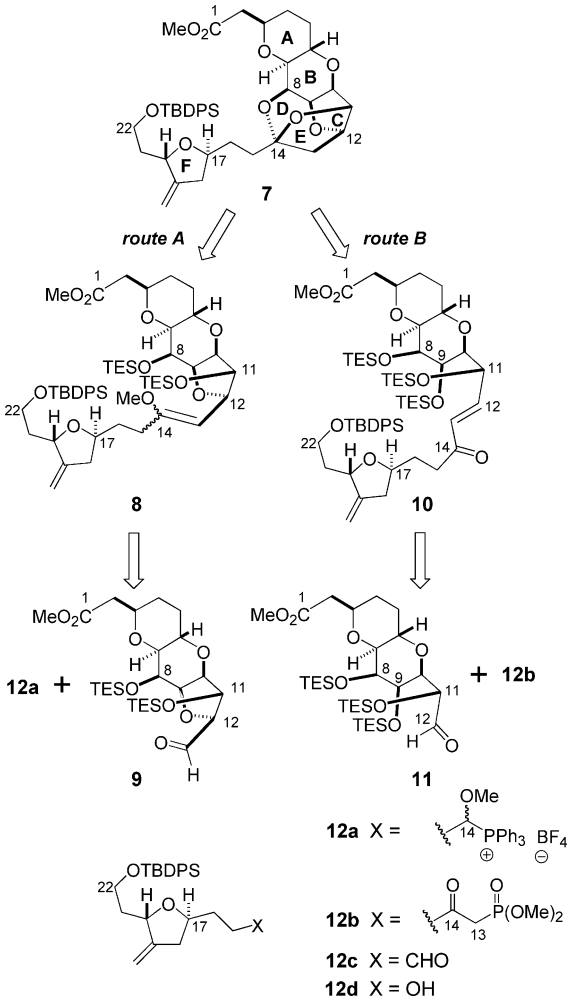
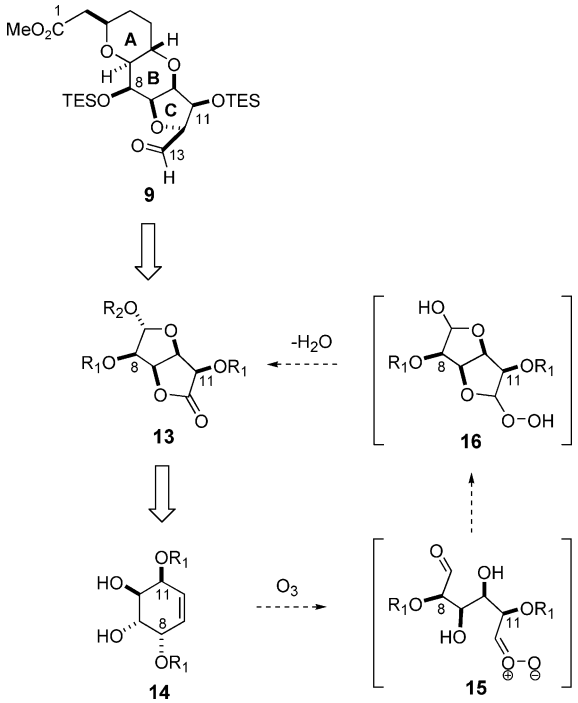
SCHEME 2



In route A, acidic hydrolysis of the enol ether mixture **8** is expected to lead to directly to the targeted subunit. Subunit convergence to form **8** will be realized via Wittig coupling of the C1−C13 aldehyde **9** with the ylide derived from the C14−C22 α-methoxyphosphonium salt **12a**. As mentioned previously, a potential advantage of this route is the preset configuration at C12, which is expected to facilitate the conversion of **8** to **7**. Our route B synthesis employs enone **10** as the penultimate intermediate, which is anticipated to arise via Horner−Wadsworth−Emmons coupling between C1−C12 aldehyde **11** and the C13−C22 β-ketophosphonate **12b**. As with our earlier C1−C15 subunit synthesis, this route relies upon the late-stage assembly of the C-ring via Michael addition of the C9-hydroxyl with C12 of the enone moiety, with the attendant issue of control at the C12 stereocenter prior to ketal formation.

Route A: Synthesis of the C1−C22 Subunit 7 from (+)-Conduritol E (27). Our retrosynthetic analysis of the pivotal route A intermediate **9** is depicted in Scheme 3. Recognizing an element of local C_2-symmetry about the C8−C11 region of the ABC-ring aldehyde **9**, we sought to preserve this substructure in our retrosynthetic simplification. We arrived at the L-mannose-configured γ-lactone **13**, which contains the C8−C11 stereocenters and features differentiated termini at C7 and C12 for further elaboration. The dissymmetric nature of **13** was

SCHEME 3

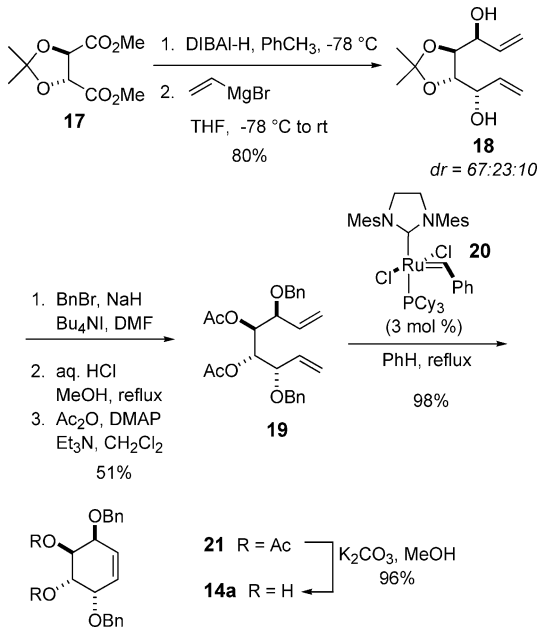


of some significance, as we had also considered the analogous C_2-symmetric bis(lactone) as a potentially attractive intermediate. At issue was the point at which desymmetrization could most effectively be accomplished. Our decision to pursue **13** was based on the proposal that it could be prepared via a symmetry-breaking ozonolytic cleavage of a C_2-symmetric cyclohexene diol endowed with the L-mannose configuration. Compound **14**, a protected derivative of (+)-conduritol E,[13] meets these criteria and was therefore seen as an attractive precursor to **13**. Ozonolytic cleavage of the carbon−carbon double bond in **14** was expected to give rise to the dissymmetric intermediate **15**, which should form upon retro-[3 + 2] cycloaddition of the initially formed primary ozonide. Intramolecular trapping of the carbonyl and carbonyl oxide moieties in **15** with the C9 and C10 hydroxyls should then lead to formation of the dioxabicyclo[3.3.0]-octane **16**. Although the carbonyl oxide and carbonyl groups normally undergo intramolecular [3 + 2] cycloaddition to afford a secondary ozonide, the carbonyl oxide residues can be trapped intermolecularly by methanol to form peroxyacetals. Schreiber et al. has used this strategy for the desymmetrization of simple cycloalkenes.[14] Moreover, Criegee et al. has demonstrated the intramolecular trapping of carbonyl oxides with tethered oxygen nucleophiles.[15] Our prediction that **16** would be formed upon ozonolysis of **14** was predicated on this body of work. We

(13) For syntheses of (+)-conduritol E via RCM, see: (a) Jørgensen, M.; Iversen, E. H.; Paulsen, A. L.; Madsen, R. *J. Org. Chem.* **2001**, *66*, 4630−4634. (b) Ackermann, A.; Tom, D. E.; Fürstner, A. *Tetrahedron* **2000**, *56*, 2195−2202. (c) Lee, W.-W.; Chang, S. *Tetrahedron: Asymmetry* **1999**, *10*, 4473−4475. For other syntheses of (+)-conduritol E, see: (d) Hudlicky, T.; Luna, H.; Olivo, H. F.; Andersen, C.; Nugent, T.; Price, J. D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2907−2917. (e) Takano, S.; Yoshimitsu, T.; Ogasawara, K. *J. Org. Chem.* **1994**, *59*, 54−57. (f) Sanfilippo, C.; Patti, A.; Piattelli, M.; Nicolosi, G. *Tetrahedron: Asymmetry* **1997**, *8*, 1569−1573. (g) Cerè, V.; Mantovani, G.; Peri, F.; Pollicino, S.; Ricci, A. *Tetrahedron* **2000**, *56*, 1225−1231.

(14) Schrieber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867−3870.

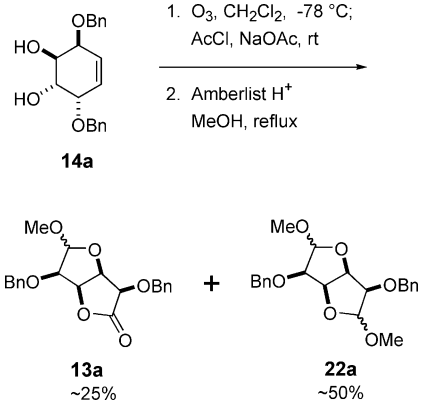
SCHEME 4



have found only one isolated example in which these cyclization and desymmetrization tactics have been applied in tandem.[16] Dehydration of the cyclic peroxyacetal in **16** with Ac_2O/Et_3N in line with Schreiber's method would then give rise to lactone **13**. In this way, the C8−C11 stereochemical array of halichondrin B would be assembled from a readily available C_2-symmetric precursor. By virtue of its symmetry, the C8 and C11 stereocenters in **14** are homotopic, as are the C9 and C10 stereocenters. This reduces the problem of its synthesis to one involving the formation of *two* asymmetric centers instead of *four*. Desymmetrization of **14** effectively produces two new stereocenters by breaking this degeneracy, resulting in a substantial increase in molecular complexity.[17]

The synthesis of an appropriate (+)-conduritol E derivative for this purpose is shown in Scheme 4. Subjection of dimethyl L-tartrate acetonide **17**[18] to a one-pot DIBAl-H reduction/Grignard addition sequence provided diol **18** as a 67:23:10 mixture of diastereomers in 80% yield.[13a−c] Benzylation and acetonide hydrolysis was then followed by acetylation to provide a chromatographically separable mixture of diacetates, and the L-mannitol-configured diene **19** was isolated as the major product in 51% overall yield over the three steps. Slow addition of the Grubbs second-generation ruthenium benzylidene catalyst **20**[19] (3 mol %) to a refluxing solution of **19** in benzene induced ring-closing metathesis (RCM) to afford the (+)-conduritol E derivative **21** in 98% yield. Subsequent treatment of **21** with K_2CO_3 in MeOH provided the expected diol **14a** in 96% yield.

SCHEME 5

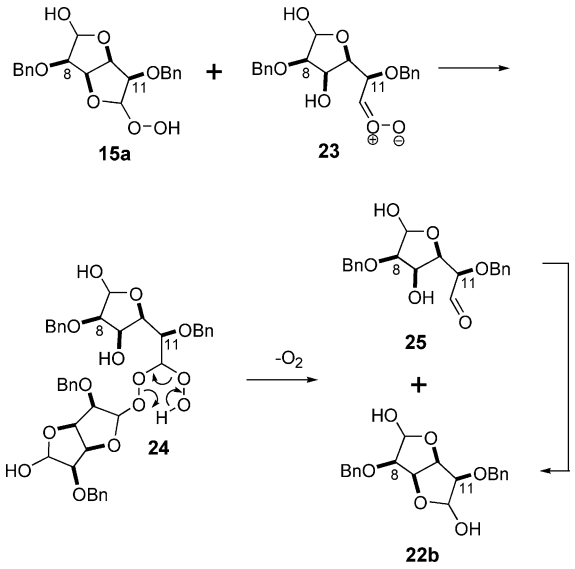


With **14a** in hand, the stage was now set for ozonolytic desymmetrization. However, treatment of a solution of **14a** in CH_2Cl_2 (−78 °C) with O_3 followed by quenching with Ac_2O and Et_3N provided none of the expected lactone. We reasoned that the desired γ-lactone product may suffer decomposition in the presence of Et_3N via a β-elimination pathway. Fortunately, the use of AcCl (TsCl and MsCl were also effective) in conjunction with a heterogeneous base (NaOAc) effected the desired dehydration reaction without inducing subsequent product decomposition, and lactone **13a** was obtained in ca. 25% yield following treatment of the crude product mixture with Amberlist H^+ resin in refluxing MeOH (Scheme 5). The methanolysis step was necessary since the methoxy acetals so obtained proved more stable to purification by silica gel chromatography than the intermediate hemiacetals. However, the bis(methoxy acetal) **22a** was isolated as the major product of this reaction in ca. 50% yield (ca. 21% yield of the C_2-symmetric isomer), which pointed to a deleterious reduction pathway. This side reaction temporarily foiled our goal of desymmetrization, since the termini at C7 and C12 were rendered equivalent with respect to oxidation state.

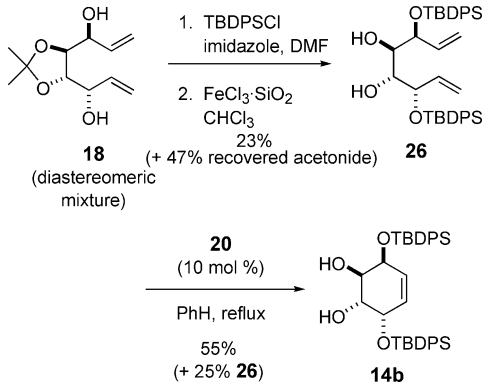
A plausible mechanistic rationale for the formation of **22a** is depicted in Scheme 6. Since it is known that carbonyl oxides can undergo dimerization followed by extrusion of a molecule of O_2,[20] we reasoned that a related process might be occurring in our system. The peroxyacetal **15a**, which contains a highly nucleophilic hydroperoxide residue, could compete with intramolecular carbonyl oxide capture via an intermolecular process with the hemiacetal-carbonyl oxide species **23**. Since the desired intramolecular closure results in the formation of a strained bicyclic system, the intermolecular process (which involves an inherently more potent nucleophile) may have a comparable rate, thus allowing it to compete effectively. This would result in the formation of the geminal bis(alkylperoxide) dimer **24**, which can lose O_2 as shown to afford the hydroxy aldehyde **25** and the bis(hemiacetal) **22b**. Rapid closure of **25** to the hemiacetal form would then give another molecule of **22b**. Since O_2

(15) Criegee, R.; Banciu, A.; Keul, H. *Chem. Ber.* **1975**, *108*, 1642−1654.
(16) Wu, H.-J.; Chao, C.-S.; Lin, C.-C. *J. Org. Chem.* **1998**, *63*, 7687−7693.
(17) (a) Bertz, S. H. *New J. Chem.* **2003**, *27*, 860−869. (b) Bertz, S. H. *New J. Chem.* **2003**, *27*, 870−879.
(18) Mash, E. A.; Nelson, K. A.; Van Deusen, S.; Hemperly, S. B. *Org. Synth.* **1990**, *68*, 92−103.
(19) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956. (b) Morgan, J. P.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 3153−3155. (c) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546−2558.
(20) (a) Fliszár, S.; Gravel, D.; Cavalieri, E. *Can. J. Chem.* **1966**, *44*, 1013−1019. (b) Fliszár, S.; Chyliñska, J. B. *Can. J. Chem.* **1967**, *45*, 29−31. (c) Fliszár, S.; Chyliñska, J. B. *Can. J. Chem.* **1968**, *46*, 783−788. For a review on carbonyl oxides, see: (d) Bunnelle, W. H. *Chem. Rev.* **1991**, *91*, 335−362.

SCHEME 6



SCHEME 7

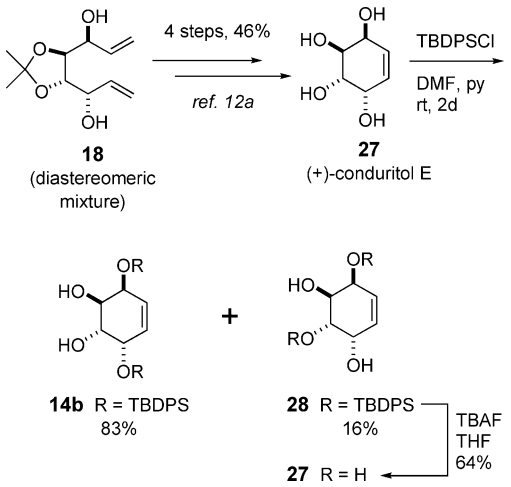


is lost, this fragmentation process does indeed represent a net reduction and would account for the formation of the bis(acetal) product **22a**. Conducting the ozonolysis under high dilution conditions in an attempt to thwart this dimerization/reductive fragmentation pathway did not noticeably improve the ratio of lactone (**13**) to bis(acetal) (**22**) products.

Although disappointed by the interference of this unanticipated side reaction, we were nonetheless encouraged by the isolation of lactone **13a**, which validated our proposal that the desymmetrization of C_2-symmetric cyclohexene diols typified by **14a** could be achieved by ozonolysis. We reasoned that an increase in steric bulk adjacent to the reactive functionality might retard intermolecular processes such as the dimerization/reductive fragmentation pathway that plagued our earlier studies. The easiest way to achieve this would be to modify the protecting groups at the C8 and C11 alcohols. Accordingly, protection of diol **18** (Scheme 7) as its bis(TBDPS ether) followed by acetonide cleavage with $FeCl_3$ adsorbed on silica gel[21] provided the diastereomerically pure diene diol **26** in 23% yield after chromatography, with 47% of recovered acetonide isolated as well. Since the TBDPS ethers suffered cleavage with other acidic conditions

(21) Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404−407.

SCHEME 8

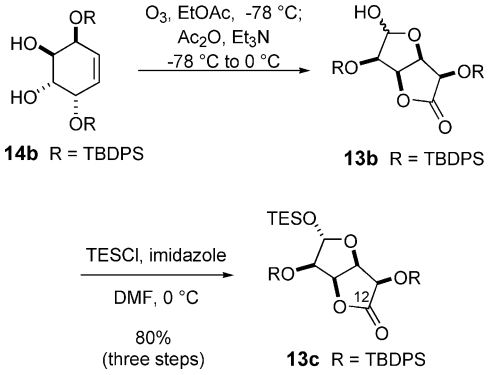


employed for the hydrolysis of the acetonide group, the use of the more chemoselective $FeCl_3$ reagent was required; however, the reaction could not be driven to completion in this case. Moreover, these yields were obtained only after recovering and resubjecting the acetonide-protected bis(TBDPS) ether mixture to $FeCl_3$·SiO_2 for a total of three cycles. Subjection of **26** to RCM with 10 mol % of the Grubbs catalyst **20**[19] in refluxing benzene provided diol **14b** in 55% yield along with 25% of recovered **26**. The increased steric bulk adjacent to the vinyl groups apparently hinders the RCM reaction, as a substantial portion of the starting material failed to react even at high catalyst loadings. This setback, coupled with the inefficiency of the acetonide cleavage step, ultimately led us to develop a more satisfactory synthesis of **14b**.

We were hopeful that the TBDPS groups could be introduced after RCM had been achieved, which suggested that (+)-conduritol E itself might be employed as an intermediate. Although several syntheses of this biologically active natural product have been reported,[14] there has been much recent activity in the preparation of conduritol derivatives (including the E-subtype) via RCM.[13a−c] Accordingly, (+)-conduritol E (**27**) was prepared in four steps and 46% overall yield from diol **18** with only minor modification of the published procedures (Scheme 8). Treatment of **27** with 2.5 equiv of TBDPSCl in DMF in the presence of pyridine for 2 days at room temperature provided the desired diol **14b** in 83% yield, accompanied by 16% of the undesired regioisomer **28**, which could be recycled to **27** with TBAF. Interestingly, substitution of imidazole for pyridine greatly increased the reaction rate; however, **14b** and **28** were formed in a ratio of ca. 1:1 in this case.

With ample quantities of **14b** in hand, we turned our attention once again to the ozonolytic desymmetrization step. We were delighted to find that passing ozone through a −78 °C solution of **14b** in EtOAc followed by addition of Ac_2O/Et_3N and warming to 0 °C resulted in the formation of the desired lactone **13b** as a ca. 2:1 mixture of anomers as evidenced by ^1H NMR analysis of the crude product mixture (Scheme 9). Subsequent treatment with TESCl/imidazole provided lactone **13c** as a single diastereomer in 80% yield. A small amount of the bis(TES acetal) was also formed, indicating that the dimerization/reductive fragmentation pathway had not

SCHEME 9

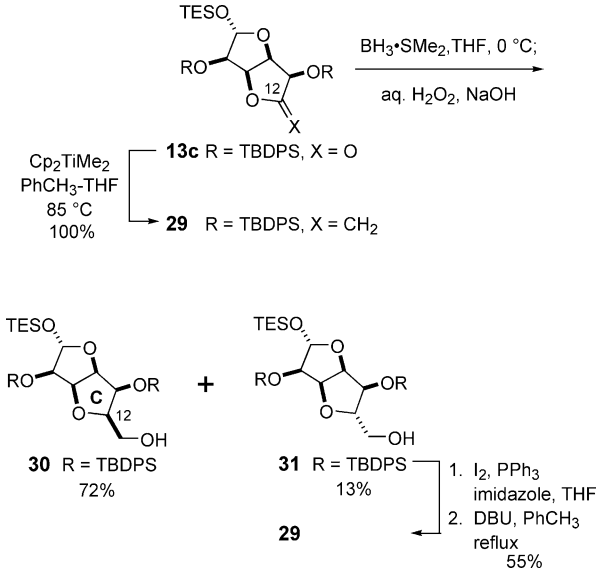


been suppressed entirely (cf. **22b**, Scheme 6). Another noteworthy feature of this reaction is the stability of **13b** and **13c** to Et_3N, demonstrating that the bulky TBDPS groups effectively shield the base-sensitive γ-lactone from decomposition.

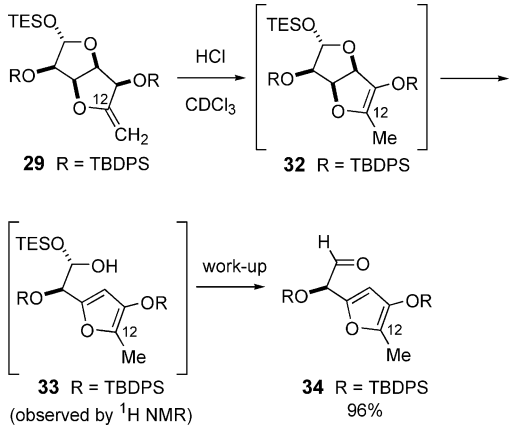
Having differentiated the two termini of the L-mannitol-configured backbone, we sought to construct the highly oxygenated C-ring of the natural product, thereby setting the stereochemical configuration at C12 at an early stage. We envisioned hydroboration−oxidation of an exocyclic enol ether[12e,h,22] derived from the C12 carbonyl in **13c** as the most expedient method for achieving this goal. Engagement of the enol ether double bond by a borane reagent would be expected to occur on the convex face of the bicyclic system, thereby providing the desired 12*R* stereochemistry. The highly polarized nature of such olefins leads to exceptionally high levels of regioselectivity as well, leading to exclusive production of the anti-Markovnikov net hydration product.

Treatment of lactone **13c** with a slight excess of dimethyltitanocene (Petasis' reagent)[23] in $PhCH_3$ at 85 °C cleanly afforded enol ether **29** in quantitative yield (Scheme 10). This compound could be purified on silica gel without decomposition or isomerization of the double bond to the endocyclic position, a process that plagued the isolation of a similar exocyclic enol ether in our work.[12e,h] Although the steric bulk afforded by the adjacent TBDPS ethers may explain the exceptional stability of **29**, another possible reason is that the adjacent oxygen substituent at C11 destabilizes any developing positive charge at C12, thereby attenuating the reactivity of the double bond. Although we had success with the Tebbe reagent[24] in this transformation as well, we found the preparation and handling of the Petasis reagent[23b] more convenient for large-scale applications. Treatment of **29** with $BH_3{\cdot}SMe_2$ followed by the addition of H_2O_2 and NaOH gave the desired C-ring alcohol **30** in 72% yield accompanied by 13% of its C12 epimer **31**. We found the use of bulkier borane reagents unsuccessful, with catecholborane giving lower yields and 9-BBN failing to react with **29** altogether. The imposing

SCHEME 10



SCHEME 11



bulk of the TBDPS groups seems a likely cause of this sluggish reactivity, as the reaction is complete within 1 h at room temperature with the comparatively small BH_3 reagent. The undesired C12 epimer **31** was recycled to enol ether **29** by base-induced elimination of the derived iodide.

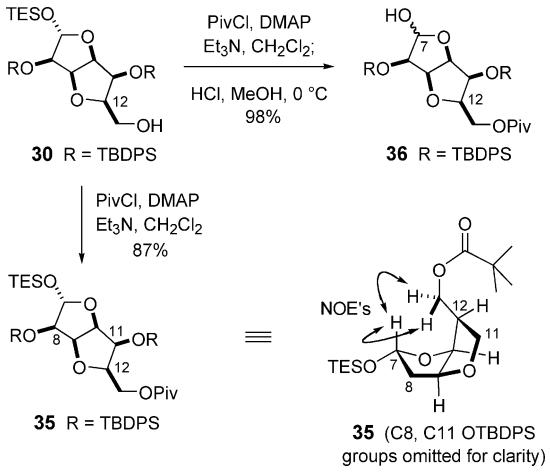
While **29** proved reasonably stable to acidic media such as silica gel, we encountered an acid decomposition pathway for this compound during the course of this work. Upon dissolution in $CDCl_3$ (of somewhat poor quality) that contained HCl, we observed the clean formation of the acyclic hemiacetal **33** as a single diastereomer by ^1H NMR analysis, with presumed intermediacy of the endocyclic enol ether **32** (Scheme 11). After concentration and chromatography on silica gel, the hemiacetal collapsed with loss of TESOH to afford aldehyde **34** in 96% yield. While acyclic hemiacetals are not normally sufficiently stable to be observed, **33** may be stabilized by an intramolecular hydrogen bond with the furan oxygen. The acidic medium in which **33** was formed may also prevent the dissociation of the hemiacetal. The fact that only one diastereomer of **33** was observed spectroscopically suggests that the hemiacetal stereochemistry was retained under these conditions. Exposure of **29** to an excess of PPTS in CH_2Cl_2, on the

(22) Untersteller, E.; Xin, Y. C.; Sinaÿ, P. *Tetrahedron Lett.* **1994**, *35*, 2537−2540.

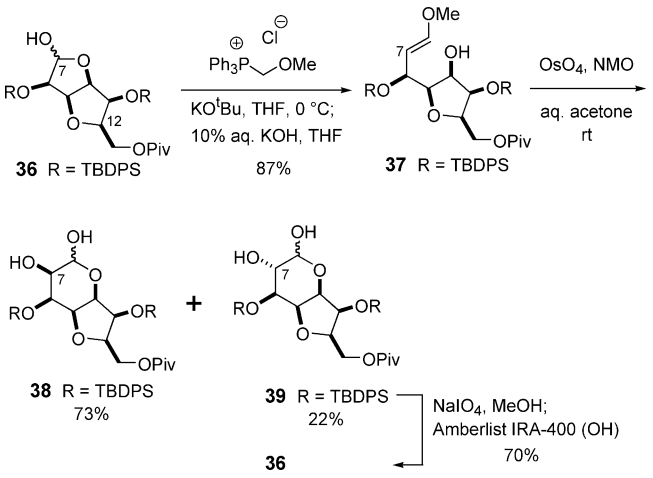
(23) (a) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392−6394. For the preparation of dimethyltitanocene, see: (b) Payack, J. F.; Hughes, D. L.; Cai, D.; Cottrell, I. F.; Verhoeven, T. R. *Org. Synth.* **2002**, *79*, 19−26.

(24) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611−3613. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270−3272.

SCHEME 12



SCHEME 13



other hand, gave only a mixture of enol ether products, of which **32** was a major component. This indicates that fragmentation of the bicyclic system to give furan byproducts requires more strongly acidic conditions.

The tentative C7 and C12 stereochemical assignments were verified by NOE studies of pivalate **35**, obtained in 87% yield upon treatment of **30** with PivCl/DMAP (Scheme 12). Irradiation of the anomeric proton at C7 led to enhancement of the C12 methylene proton signals, an observation that is only possible if these protons reside within the concave face of the bicyclic framework. Since we sought to carry the C12 pivaloate ester throughout the synthesis, and the C7 hemiacetal had to be unmasked prior to further elaboration, we did not normally isolate **35** except for the purpose of the NOE study. A one-pot procedure was developed from **30** in which the pivalation reaction mixture was simply quenched with HCl in MeOH, thereby inducing chemoselective cleavage of the TES group to provide hemiacetal **36** in 98% yield.

Having confirmed the correct stereochemistry at C12, we turned our attention to the C7 hemiacetal moiety at the other end of the molecule, which would serve as the starting point for the assembly of the A- and B-rings. Kishi and co-workers have developed an efficient protocol for constructing the C1−C7 portion of halichondrin B from a C7 hemiacetal,[9f,g] and we sought to employ a modification of this method for our purpose. Treatment of **36** with an excess of (methoxymethylene)triphenylphosphorane at 0 °C followed by stirring the crude product mixture in a biphasic mixture of THF/10% aq KOH provided **37** in 87% yield (Scheme 13), with only trace amounts of the corresponding *Z* isomer detected by ^{1}H NMR analysis. The aqueous base treatment was necessary due to the observation that silyl ether migration had occurred during the Wittig step. We found that KOH induced equilibration of the crude product mixture to give **37**, with only a trace of its silyl ether migration regioisomer remaining. Treatment of **37** with a catalytic amount of OsO_4 in aqueous acetone in the presence of *N*-methylmorpholine-*N*-oxide (NMO)[25] yielded hemiacetal **38** in 73% yield, which features the desired 7*R* stereochemistry, along with 22% of its C7 epimer **39**. The stereoselectivity observed for this reaction is consistent with Kishi's empirical rule,[26] a rationale formulated to explain the high levels of diastereofacial selectivity exhibited by chiral allylic ethers in addition reactions. It was possible to recycle **39** by oxidative cleavage followed by hydrolysis of the intermediate formate ester with Amberlist-IRA-400 (OH) resin, affording **36** in 70% yield. The overall sequence from **36** to **38** represents a net ring expansion in which the C7 carbinol unit has been formally inserted in a stereoselective manner.

Attachment of a suitably functionalized C1−C5 chain at C6 would simultaneously complete construction of the B-ring and set the stage for A-ring closure. The Lewis-acid-promoted *C*-glycosidation with an allylic silane nucleophile constitutes an appropriate tool for this task and has been employed by Kishi during his synthesis of this fragment of the halichondrins.[9g,j] Accordingly, we sought to activate **38** as a glycosyl donor via acetylation of the two hydroxyl groups. Treatment of **38** with Ac_2O/DMAP/py[27] at room temperature provided diacetate **40** in 68% yield as a single diastereomer (Scheme 14). Approximately 30% of a monoacetate product mixture was also isolated, which could not be converted to **40** upon resubjection to the reaction conditions. Fortunately, use of the more powerful combination of Ac_2O/TMSOTf[28] gave **40** in 65% yield[29] along with its C6 anomer, **41**, in 35% yield after ca. 10 min at 0 °C. Apparently, the C7 hydroxyl of the β-hemiacetal **38** is quite difficult to acetylate, as **41** was not isolated from the milder reaction conditions.

With anomeric epimers **40** and **41** in hand, the stage was now set for the stereoselective installation of an A-ring handle at C6 via *C*-glycosidation followed by assembly of the complete AB-ring system. In the event, exposure of **40** to $BF_3{\cdot}OEt_2$ in the presence of Kishi's

(25) (a) VanRheenen, V.; Cha, D. Y.; Hartley, W. M. *Org. Synth., Coll. Vol.* **1988**, *6*, 342. (b) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett*. **1976**, *17*, 1973−1976.

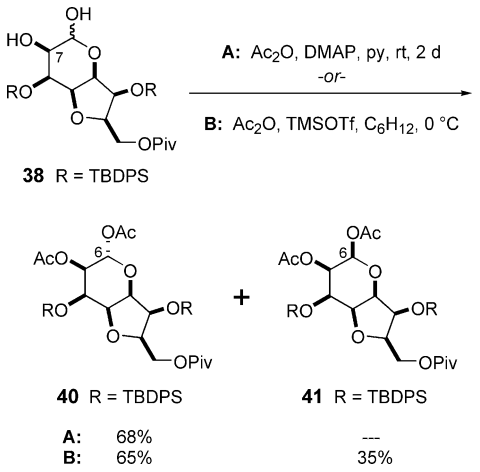
(26) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247−2255. (b) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943−3946. (c) Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947−3950.

(27) (a) Steglich, W.; Höfle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981. For a review, see: (b) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569−583.

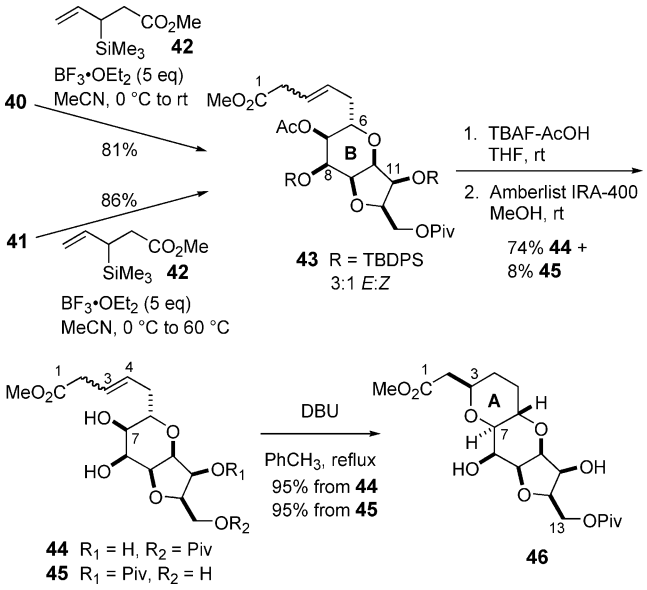
(28) Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *J. Org. Chem.* **1998**, *63*, 2342−2347.

(29) Recrystallization of **40** from heptane/CH_2Cl_2 provided crystals suitable for X-ray crystallographic analysis. See the Supporting Information.

SCHEME 14

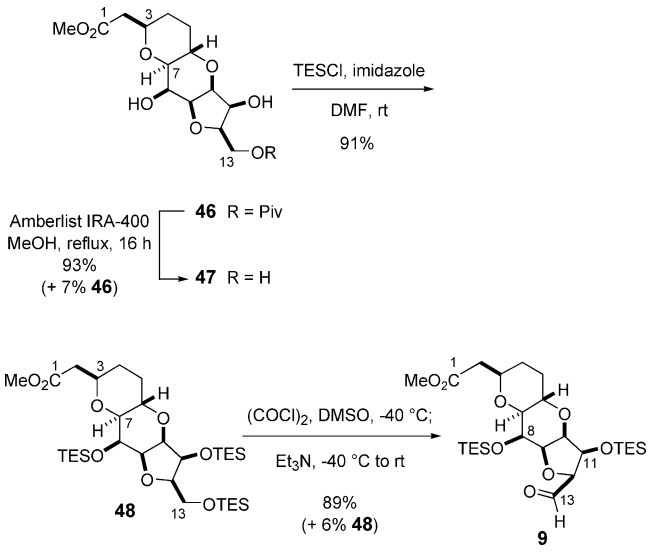


SCHEME 15



allylic silane **42**[9g] provided the β,γ-unsaturated ester **43** in 81% yield as a ca. 3:1 (*E*)- to (*Z*)-mixture of isomers (Scheme 15). Although the analogous conversion of **41** to **43** proceeded sluggishly at room temperature, heating the reaction mixture to 60 °C resulted in complete conversion within 5 h, and **43** was isolated in 86% yield. The lower reactivity of **41** relative to **40** is probably stereoelectronic in nature, since the β-C6 acetate in **41** is equatorially disposed and hence more difficult to ionize due to the absence of an anomeric effect and the lack of anchimeric assistance by the C7 acetate. The construction of the B-ring had now been completed, and all of the carbons necessary for subsequent assembly of the fully elaborated A-ring were in place. Cleavage of the TBDPS ethers with TBAF buffered with AcOH followed by acetate cleavage with a basic resin provided triol **44** in 74% yield for two steps, with 8% yield of the pivalate migration product **45** also being isolated. Treatment of **44** with excess DBU in refluxing toluene resulted in isomerization of the C3−C4 double bond to the α,β-unsaturated isomer, which then underwent Michael addition by the C7 hydroxyl. A mixture of **46** (desired) and its C3 epimer was observed by TLC analysis upon consumption of starting material (ca. 1 h). Equilibration

SCHEME 16

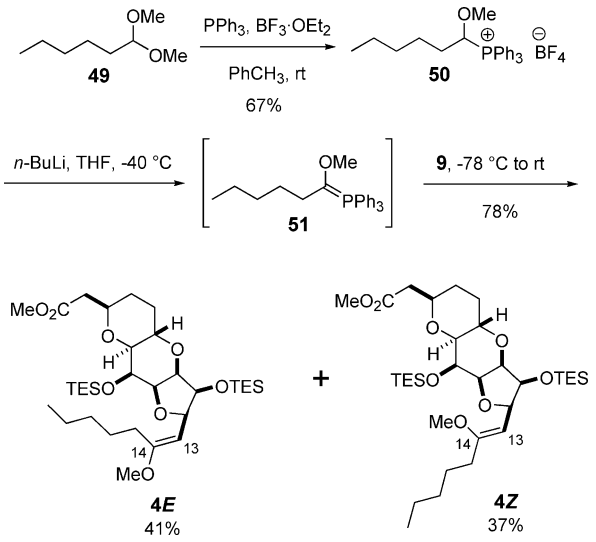


for another 16 h resulted in exclusive formation of **46** in 95% yield. A mixture (ca. 3:1) of **46** and the corresponding 3*S* isomer could be isolated in 94% yield when the reaction was conducted in refluxing benzene for 16 h, although no equilibration of the two was observed in this case. Apparently, the retro-Michael addition step that initiates the C3 epimerization requires the higher temperature afforded by the use of refluxing toluene. In like fashion, triol **45** was also converted to **46** in 95% yield, with migration of the pivalate group to the C13 hydroxyl occurring in this case. Although we had initially explored A-ring assembly directly from **43** using Triton-B methoxide, the C7 acetate proved resistant to cleavage in this case, prompting us to remove the bulky TBDPS ethers at C8 and C11 prior to cyclization.

To access the targeted C13 aldehyde **9**, we had planned to first mask the C8 and C11 alcohols in **46** followed by pivalate cleavage and oxidation of the resultant C13 alcohol. We encountered a procedure,[30a,b] however, whereby a primary TMS or TES ether may be chemoselectively oxidized to the corresponding aldehyde in the presence of secondary TMS or TES ethers under Swern conditions.[30c] This prompted us to modify our plans for oxidation at C13 accordingly. Cleavage of the pivalate ester in **46** was accomplished with a basic resin in refluxing methanol to provide triol **47** in 93% yield, along with 7% of recovered **46** (Scheme 16). It should be noted that 1.64 g (5.15 mmol) of **47** has been prepared by the present route. Subsequent treatment of **47** with an excess of TESCl afforded the tris(TES ether) **48** in 91% yield. Oxidation of **48** under standard Swern conditions[30a,c] at −40 °C proceeded cleanly, providing aldehyde **9** in 89% yield, with recovery of unreacted **48** in 6% yield. No products from oxidation at either C8 or C11 were detected. Since **9** is an α-alkoxy aldehyde, and hence prone to epimerization at C12 to a presumably more stable product, it was purified by chromatography on Florisil and used in subsequent reactions without delay.

(30) (a) Rodríguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J. *Tetrahedron Lett.* **1999**, *40*, 5161−5164. For a review on the oxidative deprotection of silyl ethers, see: (b) Muzart, J. *Synthesis* **1993**, 11−27. (c) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651−1660.

SCHEME 17

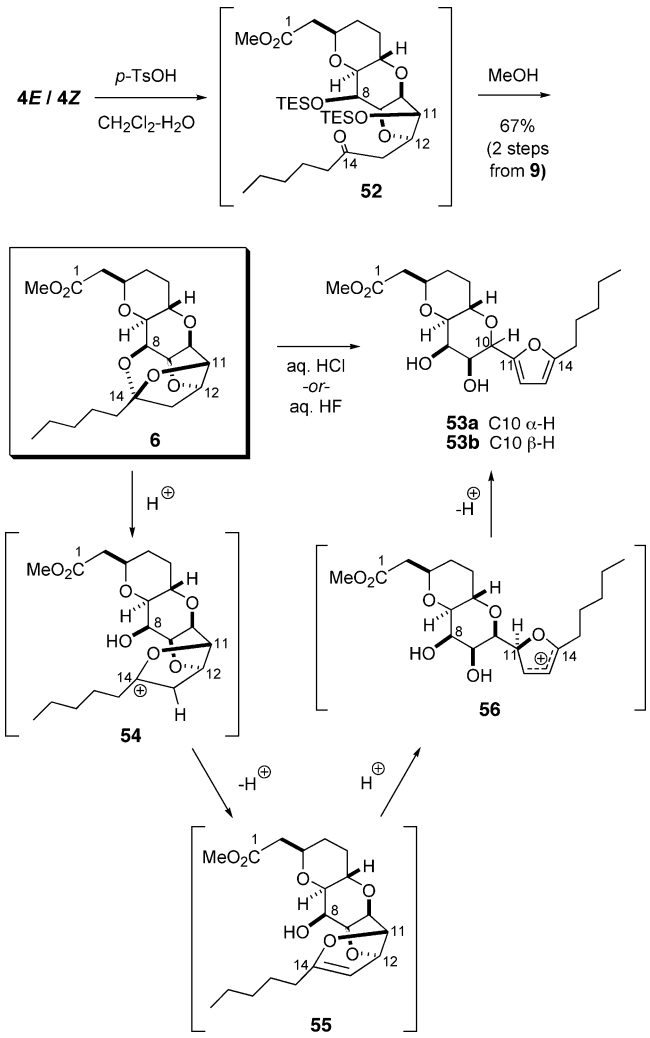


We had now arrived at the point of investigating the Wittig reaction of **9** with a suitable (α-methoxyalkyl)-triphenylphosphorane.[31] This reaction would serve a dual purpose, as subunit convergence would occur simultaneously with the installation of a C14-ketone surrogate (in the form of a C13−C14 enol ether) as a prelude to the ultimate cage-forming event. The use of (α-methoxyalkyl)triphenylphosphoranes as Wittig partners for fragment coupling in complex natural products synthesis is, to the best of our knowledge, unprecedented. Therefore, we sought to explore its viability through the synthesis of a model system that would incorporate a simple alkyl chain at C14 in the cage product.

The preparation and use of a Wittig reagent appropriate for this task is shown in Scheme 17. Treatment of commercially available 1,1-dimethoxyhexane (**49**) with PPh_3 and $BF_3{\cdot}OEt_2$[31a] provided the (α-methoxyalkyl)-triphenylphosphonium tetrafluoroborate salt **50** in 67% yield after recrystallization from THF. Since (α-methoxyalkyl)triphenylphosphoranes are known to be unstable at temperatures above −40 °C,[31b] their generation from the corresponding phosphonium salts must be conducted at or below this temperature. Accordingly, deprotonation of **50** with *n*-BuLi at −40 °C resulted in the formation of the blood-red (α-methoxyalkyl)triphenylphosphorane **51**. Cooling this solution to −78 °C followed by addition of aldehyde **9** and warming to room temperature resulted in the isolation of enol ethers **4*E*** and **4*Z*** in 41% and 37% yields, respectively. Since these sensitive compounds suffered decomposition on silica gel, Florisil was again employed for their chromatographic separation and purification.

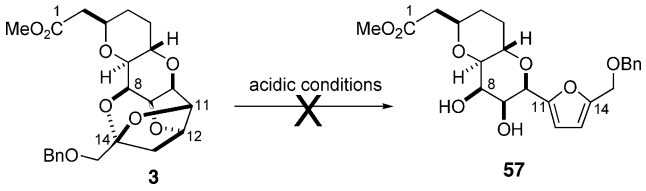
All of the functionality required for formation of the caged ketal is present in **4*E*** and **4*Z***. Since hydrolysis of the enol ether moiety will provide a C14 ketone, both **4*E*** and **4*Z*** are potentially viable precursors to the desired cage product. For this reason, the subsequent step in the synthetic sequence was most conveniently conducted on the mixture of geometrical isomers without chromatographic purification. We were pleased to observe that treatment of the crude Wittig product mixture with *p*-TsOH in $CH_2Cl_2-H_2O$ for 1 h followed by the addition of MeOH provided the cage ketal **6** in 67% yield over two steps from aldehyde **9** via the intermediate ketone **52** (Scheme 18). The ^1H NMR data we obtained for **6** (vide infra) were in excellent agreement with the literature data for its enantiomer, ***ent*-6**, which was synthesized by Aicher and Kishi in 1987.[9b] It was determined (TLC analysis) that enol ether hydrolysis in the biphasic $CH_2Cl_2-H_2O$ solvent system was complete within 1 h, although silyl ether cleavage and subsequent ketalization were not realized until the mixture was homogenized with MeOH. The choice of conditions for this reaction was critical, as the C11−C14 furans **53a** and **53b**, epimeric at C10, were observed as side products with other acid promoters. For example, **53a** was isolated in ca. 30% yield upon treatment of a **4*Z*/4*E*** mixture with 52% aq HF in CH_3CN (5:95 v/v), while the use of a biphasic aq HCl−THF system with the same substrate resulted in formation of **53b** and **6** in 21% and 41% yields, respectively. In these cases, the desired ketal **6** was observed to form alongside **53a/53b**, and TLC analysis of the reaction mixture revealed that the latter were slowly formed at the expense of the former. A likely mechanism for furan formation involves protonation of the C8 oxygen in **6** and

SCHEME 18



(31) (a) Tückmantel, W.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1986**, *27*, 5617−5618. (b) Coulsen, D. R. *Tetrahedron Lett.* **1964**, *5*, 3323−3326. (c) Ley, S. V.; Lygo, B.; Organ, H. M.; Wonnacott, A. *Tetrahedron* **1985**, *41*, 3825−3836.

SCHEME 19

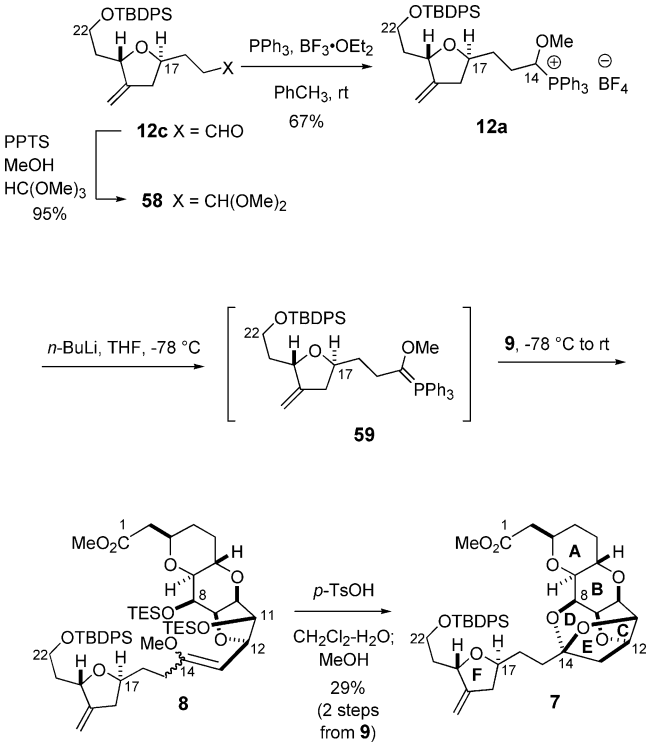


ionization to form the oxocarbenium ion **54**. Loss of a proton at C13 would give the endocyclic enol ether **55** which, upon protonation of the allylic C9 oxygen, would suffer C-ring rupture via elimination to give the delocalized oxocarbenium species **56**. Loss of the C11 proton would then give furan **53a**. Epimerization at C10 to give **53b**, in which the furanyl side chain is deployed equatorially on the tetrahydropyranyl ring, most likely proceeds via the intermediacy of a furanylic C10 carbocation. This cage-to-furan pathway is suppressed under the conditions given above (*p*-TsOH, $CH_2Cl_2-H_2O$; MeOH), an observation initially noted by Hart et al. on their work detailing the acid lability of the halichondrins.[32] They reported an analogous furan-forming process upon exposure of homohalichondrin B (which contains the same cage unit as halichondrin B) to various acids (TFA, CD_3OD; PPTS, $CDCl_3$). Their observation that no furan was formed in the presence of a large excess of *p*-TsOH in either CH_2Cl_2 or $CH_2Cl_2-H_2O$ prompted us to employ these conditions.

The cage-to-furan transformation deserves further comment. The C1−C15 cage model **3** (Scheme 1) does not give rise to any of the corresponding furan **57** (Scheme 19) upon exposure to a variety of acids, an observation made by both us[12g] and Cooper and Salomon[10b] in our respective syntheses of **3**. It is well-known that α-alkoxy substituents destabilize carbenium ion species through the inductive withdrawal of electron density, thereby rendering the oxocarbenium ion derived from **3** less stable than **54**. The acid lability of **6** relative to that of **3** strongly suggests a correlation between the facility of furan formation and C14-oxocarbenium ion stability.

Having established a reliable set of reaction conditions for the introduction of the sensitive cage functionality, we sought to apply this Wittig coupling/ketalization strategy toward the synthesis of a complete C1−C22 subunit. This would entail the preparation of a C14−C22 fragment endowed with (α-methoxyalkyl)triphenylphosphonium salt functionality at the C14 terminus. We have previously described the synthesis of the C14−C22 subunit **12c** (Scheme 20), which bears an aldehyde at C14, via two different symmetry-based routes.[12i,k] To install the requisite phosphonium salt at C14, **12c** was first treated with PPTS in MeOH/$HC(OMe)_3$ to provide the dimethyl acetal **58** in 95% yield. Without further purification, **58** was treated with $PPh_3/BF_3{\cdot}OEt_2$[31a] as done previously with **49**, affording the (α-methoxyalkyl)-triphenylphosphonium tetrafluoroborate salt **12a** in 80% yield as a mixture of C14 epimers. This compound proved somewhat moisture-sensitive, giving aldehyde **12c** and triphenylphosphine as decomposition products. Additionally, **12a** could not be rigorously purified either by silica

SCHEME 20



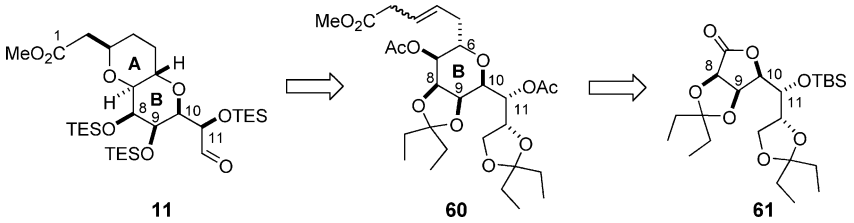
gel chromatography or recrystallization. Without delay, a THF solution of **12a** in a base-washed round-bottom flask was treated with a slight deficiency of *n*-BuLi at −78 °C. We observed immediate formation of a blood-red solution of the (α-methoxyalkyl)triphenylphosphorane **59** under these conditions. Subsequent addition of aldehyde **9** in THF at −78 °C was followed by slow warming to room temperature. Since we were unsuccessful in isolating the intermediate enol ether **8** in pure form by chromatography on Florisil, the crude mixture was simply exposed to the hydrolysis/ketalization conditions we had developed earlier for **4***E*/*Z*. We were delighted to find that the expected C1−C22 subunit of halichondrin B **7**, which contains the complete ABCDEF-ring system of the natural product, was formed to the exclusion of any furan products in a two-step yield of 29%. It should be noted that the transformation of **8** into cage ketal **7** requires four distinct reactions, including hydrolysis of the enol ether and two silyl ethers, and a dehydrative ketalization of the resulting keto diol. Thus, despite the poorer efficiency relative to our model system (possibly a consequence of the purity of **12a** relative to that of **50**), overall efficiency of subunit convergence and cage assembly was still acceptable. The overall yield of **7** from (+)-conduritol E (**27**) was 4% over 18 linear steps.

Route B: Synthesis of the C1−C22 Subunit 7 from α-D-Glucoheptonic γ-Lactone (62). The fully elaborated C1−C22 subunit (**7**) was also constructed as depicted through Route B in Scheme 2. The retrosynthesis for the formation of **11** is shown in Scheme 21.

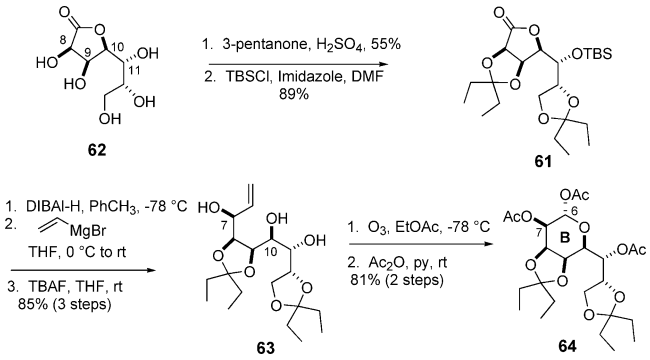
Tris(TES)-protected aldehyde **11** is available from β,γ-unsaturated ester **60**, through construction of the A-ring, followed by inversion at C11 and protecting group manipulations. β,γ-Unsaturated ester **60** comes from **61**, available in two steps from commercially available and relatively inexpensive α-D-glucoheptonic γ-lactone (**62**)

(32) Hart, J. B.; Blunt, J. W.; Munro, M. H. G. *J. Org. Chem.* **1996**, *61*, 2888−2890.

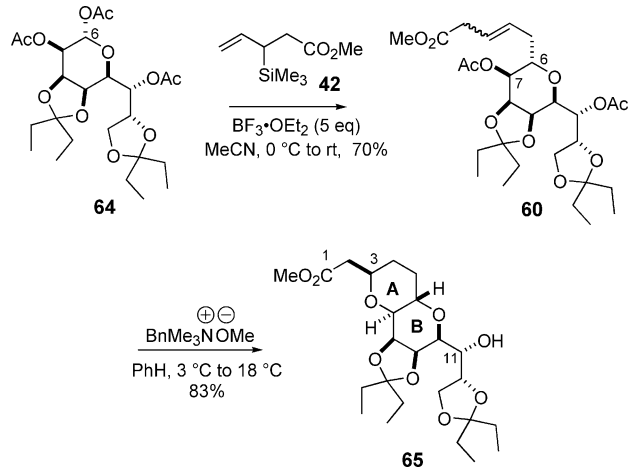
SCHEME 21



SCHEME 22



SCHEME 23



($0.07/g, Aldrich) through a ring expansion from the γ-lactone to form the B-ring. This starting material is extremely attractive for this synthesis, as it contains the correct stereochemistry for the C8, C9, and C10 stereocenters and the opposite stereochemistry for C11. This is also the same starting material that was used in our initial synthesis of the C1−C15 subunit.[12g] Several problems arose in the previous synthesis using this starting material, and modifications to address these issues will be elaborated below.

Lactone **62** was regioselectively protected as the bis(pentylidene) ketal,[12b,33] which left the C11 hydroxyl open for orthogonal protection as TBS ether **61** (Scheme 22). This fully protected lactone was then treated with DIBAl-H at −78 °C to yield the crude hemiacetal, which was treated with an excess of vinylmagnesium bromide[34] to give triol **63** after cleavage of the TBS group with TBAF (85% yield over the three steps). The selective formation of the C7 stereocenter is consistent with observations on related reactions of carbohydrate derivatives.[35]

Ring expansion to form the B-ring was achieved through ozonolysis of **63** to yield the corresponding aldehyde, which was intramolecularly trapped with the C10 hydroxyl to form the B-ring pyran.[36] This was followed by protection of the remaining hydroxyls as acetates by treatment with acetic anhydride in pyridine to yield glycoside triacetate **64** as the major diastereomer by ^{1}H NMR in 81% yield over the two steps.

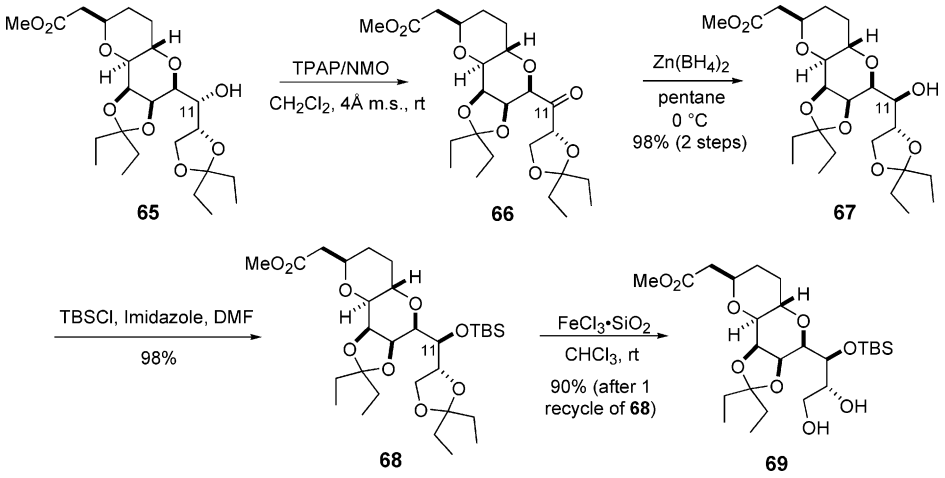
In the early stages of our previously published synthesis of the C1−C15 subunit from **61**,[12g] an α-alkoxyorganolithium reagent was added to the γ-lactone, followed by pinacol ring expansion of the corresponding diol to form the B-ring. This method suffered from lack of stereoselectivity and regioselectivity in the formation and rearrangement of the diol, which thus resulted in low yield of the target product. Additionally, the instability of the α-alkoxyorganostannane and its α-hydroxystannane precursor made that route unsuitable for supplying enough material for further chemical studies. This current sequence avoids those problems and forms the B-ring in high yield and high stereocontrol.

With the B-ring now installed, attention turned to the construction of the A-ring of halichondrin B. As predicted, glycoside triacetate **64** undergoes axial *C*-allylation[37] at the C6 anomeric center with Kishi's allylic silane **42**[9g] and an excess of BF_3·OEt_2 in acetonitrile to yield β,γ-unsaturated ester **60**, as a mixture of *E* and *Z* isomers in 70% yield (Scheme 23). The ratio of the *E* and *Z* isomers could not be determined, but proved to be inconsequential, as treatment of with benzyltrimethylammonium (Triton B) methoxide[9b] leads to concomitant acetate cleavage, double bond migration, and intramolecular Michael addition from the unprotected C7 hydroxyl group to the enoate moiety. This initially produces a mixture of C3 epimers, which then equilibrates to the more stable equatorial isomer **65**, thus completing the A-ring in excellent yield.

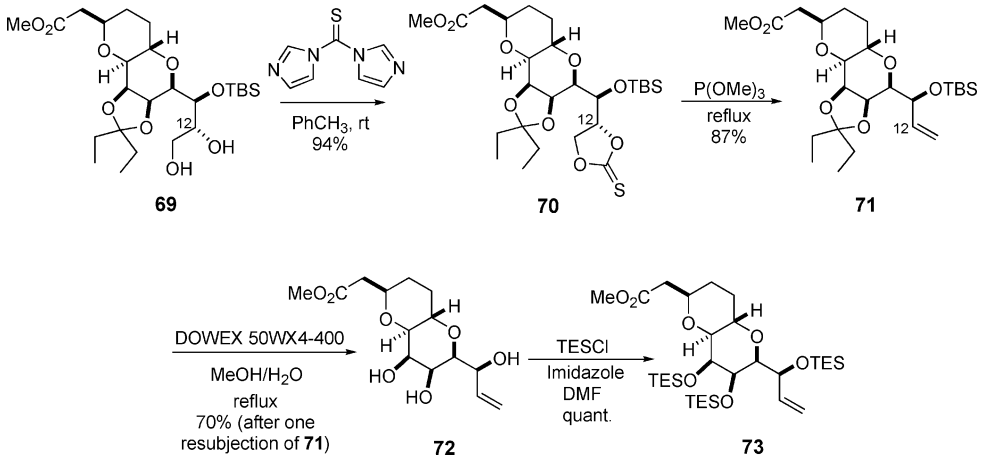
Once the A-ring had been assembled, the next step was to invert the C11 hydroxyl to the desired halichondrin stereochemistry (Scheme 24). The oxidation/reduction protocol utilized by us developed previously was revisited.[12g] Oxidation of the C11 hydroxyl with TPAP/NMO[38]

(33) Masamune, S.; Ma, P.; Okumoto, H.; Ellingboe, J. W.; Ito, Y. *J. Org. Chem.* **1984**, *49*, 2834−2837.
(34) Mekki, B.; Singh, G.; Wightman, R. H. *Tetrahedron Lett.* **1991**, *32*, 5143−5146.
(35) (a) Lygo, B.; Swiatyj, M.; Trabsa, H.; Voyle, M. *Tetrahedron Lett.* **1994**, *35*, 4197−4200. (b) Shing, T. K. M.; Elsley, D. A.; Gillhouley, J. G. *J. Chem. Soc., Chem. Commun.* **1989**, 1280−1282.
(36) Lay, H.; Lehmann, J.; Ziser, L.; Reutter, W. *Carbohydr. Res.* **1989**, *195*, 145−149.
(37) (a) Giannis, A.; Sandhoff, K. *Tetrahedron Lett.* **1985**, *26*, 1479−1482. (b) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976−4978. (c) Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1982**, *23,* 2281−2284.

SCHEME 24



SCHEME 25



delivers ketone **66**, which was followed by a chelation-controlled reduction with $Zn(BH_4)_2$ in pentane at 0 °C. Our previous work[12g] called for reaction at room temperature, which yielded the inverted C11 alcohol with 14:1 stereoselectivity. Performing the reaction at 0 °C lead to exclusive formation of the desired C11 epimer **67** in 98% yield (two steps), with no inhibition of the reaction rate (the reaction was done in 10 min), and no trace of **65** by ^{1}H NMR spectroscopy. The inverted alcohol was then protected as the TBS ether (**68**) in excellent yield.

The next step required selective cleavage of the terminal pentylidene ketal, which was achieved utilizing $FeCl_3$ on SiO_2 in $CHCl_3$[21] and optimized to yield exclusively 1,2 diol **69** in 90% yield after one recycle of **68**.[39]

Because of what we had learned about the acid-induced decomposition of the CDE-ring cage ketal to a furan (Scheme 18), it was clear that the protecting groups for the C8, C9, and C11 hydroxyls in **69** were too robust. To address this issue and to establish a C12 aldehyde for subunit coupling, the conversion of **69** to **73** (Scheme 25) was executed.

Installation of a terminal alkene as a C12 aldehyde precursor preceded the C8, C9, C11 protecting group switch and was synthesized from diol **69** using the Corey–Winter protocol[40] to yield alkene **71** via thionocarbonate **70** (Scheme 25).[41]

Protecting group removal was facilitated with acidic DOWEX 50WX4-400 resin in refluxing MeOH yielding 70% of triol **72** after one resubjection of starting material. This triol was then protected as the tris-TES ether (**73**) in quantitative yield.

Ozonolysis of **73** at −78 °C in CH_2Cl_2 and quenching with PPh_3 yielded aldehyde **11**, which was concentrated, redissolved in DME, and combined with the anion formed from commercially available dimethyl-2-oxoheptyl phosphonate to form α,β-unsaturated ketone **74** in 64% yield over the two steps (Scheme 26). Several other Horner–Wadsworth–Emmons conditions were also attempted[42] but were either low yielding or led to decomposition.

(38) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625–1627.

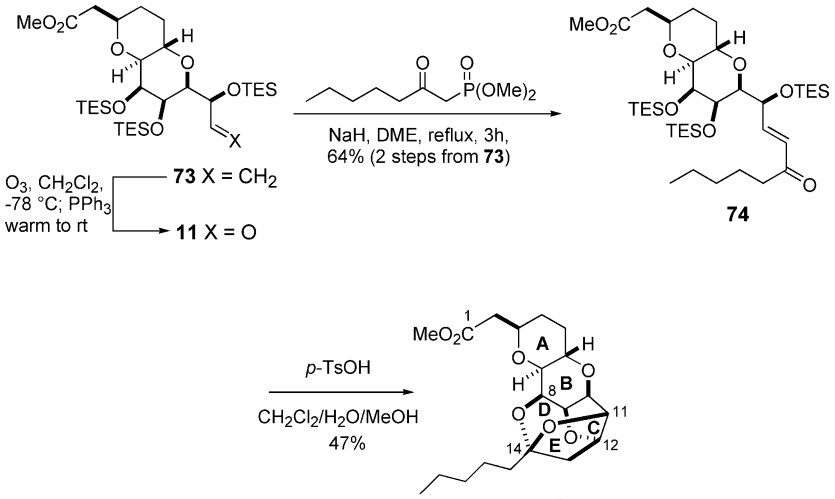
(39) Use of 80% aqueous AcOH[12g] led to extended reaction times (20–24 h), some TBS cleavage, and lower yields (maximum yields were 75%, also after one recycle of recovered SM).

(40) Winter, R. A. E.; Corey, E. J. *J. Am. Chem. Soc.* **1963**, *85*, 2677–2678.

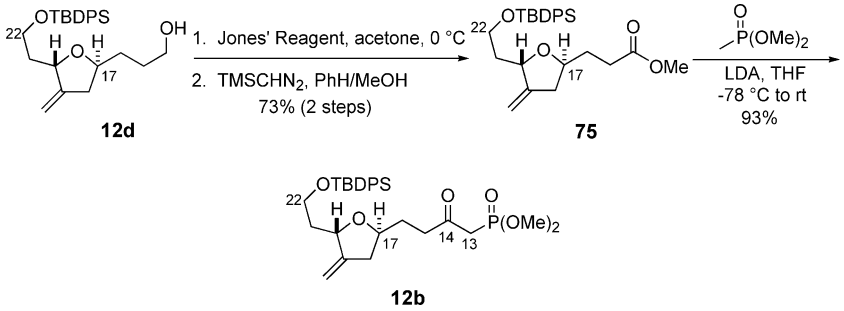
(41) Gratifyingly, thionocarbonate **70** produced crystals suitable for X-ray crystallography, which allowed us to unambiguously determine the C11 stereochemistry. See the Supporting Information.

(42) (a) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186. (b) Paterson, I.; Keown, L. E. *Tetrahedron Lett.* **1997**, *38*, 5727–5730. (c) Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624–2626. (d) Watanabe, R.; Kita, M.; Uemura, D. *Tetrahedron Lett.* **2002**, *43*, 6501–6504.

SCHEME 26



SCHEME 27



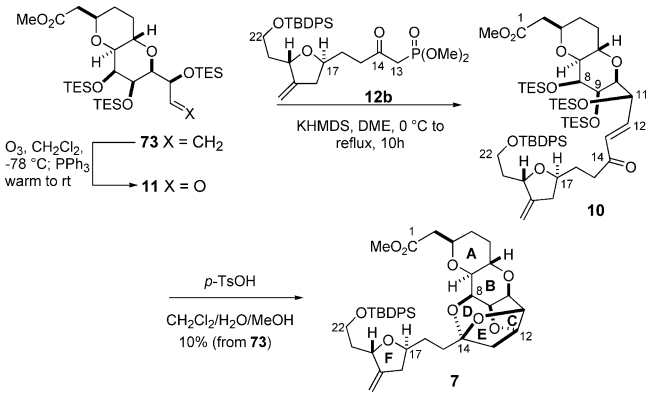
The final step for the production of the ABCDE-ring model involved treatment of **74** under mildly acidic conditions (*p*-TsOH in CH_2Cl_2/MeOH/H_2O) to afford cage product **6** in 47% yield. All spectral data matched that of **6** synthesized as shown in Scheme 18, and Kishi's subunit model ***ent-6***.[9b]

Once the model study was complete, coupling of the ABC-ring and F-ring subunits followed by caged ketal formation to complete the C1−C22 subunit was explored (Scheme 27). Oxidation of F-ring alcohol **12d**[12k] with freshly prepared Jones' reagent[43] followed by esterification with $TMSCHN_2$ yielded methyl ester **75** in 73% over the two steps. *β*-Ketophosphonate **12b** was synthesized in 93% yield by addition of the lithium anion of dimethyl methylphosphonate to **75** in THF at −78 °C.

Aldehyde **11** was formed in the same manner as before and was subjected to a quick purification on silica gel to remove triphenylphosphine oxide, which we discovered was interfering with recovery of excess **12b** after the Horner−Wadsworth−Emmons coupling step. This aldehyde was then coupled to F-ring *β*-ketophosphonate **12b** through a Horner−Wadsworth−Emmons reaction in refluxing DME to yield enone **10** (Scheme 28). Unfortunately, coupling of the C13−C22 subunit to the C1−C12 subunit proved to be problematic using the conditions employed for the synthesis of enone **74**.

The use of sodium hydride proved not to be feasible due to the uncertainties in weighing out such a small amount; therefore, a more easily handled base, KHMDS, was employed. Enone **10** was also found to be extremely difficult to isolate, as an unknown byproduct constantly coeluted with **10** during chromatography. Thus, enone **10** and this byproduct were carried on crude through the Michael addition/ketalization cascade to form ketal **7** in 10% yield over the three steps. Again, the complexity of this transformation deserves comment, in that three silyl ether cleavages, a Michael addition, and a ketalization constitute the conversion of **10** into **7**. This sample of **7** was identical in all respects to the one synthesized via the less problematic Route A as shown in Scheme 20.[44]

SCHEME 28



Efforts are underway to complete the total synthesis of halichondrin B.

(43) Guanti, G.; Banfi, L.; Riva, R. *Tetrahedron* **1995**, *51*, 10343−10360.

Experimental Section

Hemiacetal 13b. A solution of diol **14b** (11.6 g, 18.7 mmol) in EtOAc (746 mL, 0.025 M) was cooled to −78 °C in a three-necked round-bottom flask fitted with a gas inlet tube. The solution was purged with ozone until a blue color was seen (40 min) that persisted for 2−3 min. At this point the solution was purged with N_2 until the blue color dissipated. To the resulting colorless solution was added Ac_2O (2.64 mL, 28.0 mmol, 1.5 equiv) and Et_3N (5.16 mL, 37.3 mmol, 2 equiv), and the solution was warmed to 0 °C and stirred for 2 h. The solution was quenched with water (300 mL) and warmed to room temperature, where it stirred for 1 h. After extraction with EtOAc (3×), the combined organic layers were washed sequentially with 5% aq HCl and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude hemiacetal **13b** (ca. 2:1 mixture of anomers) was isolated as a white foam and was used directly in the next reaction without further purification. Data for **13b**: R_f 0.27 (20% EtOAc in hexanes); $[\alpha]^{23}_D$ −85 (*c* 1.8, $CHCl_3$); IR (thin film) 3631−3134 (br), 1803 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) see S48; ^{13}C NMR (75 MHz, $CHCl_3$) see S49; HRMS calculated for $C_{38}H_{44}O_6Si_2$ $(M + Na)^+$ 675.2574, found 675.2588 (2.1 ppm).

Aldehyde 9. To a solution of oxalyl chloride (0.263 mL of a 2 M solution in CH_2Cl_2, 0.526 mmol, 2.2 equiv) in CH_2Cl_2 (1.2 mL) was added DMSO (0.075 mL, 1.1 mmol, 4.4 equiv) at −50 °C. After stirring for 10 min at this temperature, **48** (158 mg, 0.239 mmol) in CH_2Cl_2 (1.2 mL) was added via cannula. The mixture was warmed to −40 °C and stirred for 1 h, at which point Et_3N (0.291 mL, 2.10 mmol, 8.8 equiv) was added. After stirring at −40 °C for 5 min, the reaction mixture was warmed to room temperature. The mixture was diluted with water (8 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the crude product on Florisil (10% to 20% EtOAc in hexanes) provided aldehyde **9** (116 mg, 0.213 mmol, 89%) as a colorless oil along with recovered **48** (10 mg, 0.015 mmol, 6%). Data for **9**: R_f 0.18 (20% EtOAc in hexanes); $[\alpha]^{23}_D$ −124 (*c* 1.38, $CHCl_3$); IR (thin film) 2732, 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.56−0.69 (m, 12 H), 0.92−1.00 (m, 18 H), 1.26−1.51 (m, 2 H), 1.70−1.80 (m, 1 H), 2.05−2.14 (m, 1 H), 2.41 (*A*BX, J_{ab} = 15.4 Hz, J_{ax} = 5.0 Hz, 1 H), 2.58 (A*B*X, J_{ab} = 15.4 Hz, J_{bx} = 8.25 Hz, 1 H), 3.01 (dd, J = 9.6, 2.1 Hz, 1 H), 3.69 (s, 3 H), 3.81−3.92 (m, 1 H), 4.06−4.15 (m, 2 H), 4.20−4.30 (m, 3 H), 4.45−4.50 (m, 1 H), 9.75 (d, J = 2.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 4.6 (CH_2), 5.0 (CH_2), 6.8 (CH_3), 7.0 (CH_3), 29.5 (CH_2), 30.1 (CH_2), 40.5 (CH_2), 51.6 (CH_3), 65.2 (CH), 67.3 (CH), 74.3 (CH), 74.4 (CH), 75.2 (CH), 76.1 (CH), 77.1 (CH), 85.4 (CH), 171.7 (C), 203.7 (CH); HRMS calculated for $C_{26}H_{48}O_8Si_2$ $(M + Na)^+$ 567.2785, found 567.2773 (2.1 ppm).

Enol ethers 4*Z* and 4*E*. A slurry of phosphonium salt **50** (112 mg, 0.242 mmol, 2.4 equiv) in THF (1 mL) was cooled to −40 °C for the dropwise addition of *n*-BuLi (0.125 mL of a 1.8 M solution in hexanes, 0.222 mmol, 2.2 equiv). The resulting blood-red solution was stirred at this temperature for 10 min before being cooled to −78 °C, and aldehyde **9** (55 mg, 0.10 mmol) in THF (1 mL) was added via cannula. After stirring at −78 °C for another 5 min, the mixture was warmed to room temperature and quenched with brine (4 mL). The layers were separated, and the aqueous later was extracted with Et_2O. The combined ether layers were then dried over Na_2SO_4 and concentrated in vacuo. The residue was triturated with hexanes to separate the product from excess phosphonium salt and triphenylphosphine oxide, and the combined hexane washings were concentrated in vacuo. Although the crude product could be used directly in the next step, analytically pure samples of enol ethers **4*Z*** (24 mg, 0.037 mmol, 37%) and **4*E*** (27 mg, 0.042 mmol, 42%) were obtained as oils by FCC on Florisil (5% to 10% to 20% EtOAc in hexanes). Data for **4*Z***: R_f 0.33 (20% EtOAc in hexanes); $[\alpha]^{23}_D$ −62 (*c* 1.1, $CHCl_3$); IR (thin film) 1743, 1653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.58−0.69 (m, 12 H), 0.87 (t, J = 6.8 Hz, 3 H), 0.94−1.02 (m, 18 H), 1.15−1.55 (m, 8 H), 1.69−1.78 (m, 1 H), 2.03−2.28 (m, 3 H), 2.38 (*A*BX, J_{ab} = 15.2 Hz, J_{ax} = 4.9 Hz, 1 H), 2.55 (A*B*X, J_{ab} = 15.2 Hz, J_{ax} = 8.2 Hz, 1 H), 2.96 (dd, J = 9.4, 2.2 Hz, 1 H), 3.56 (s, 3 H), 3.68 (s, 3 H), 3.78−3.79 (m, 1 H), 3.93 (dd, J = 5.2, 3.6, 1 H), 4.00 (dd, J = 9.8, 5.3 Hz, 1 H), 4.06−4.17 (m, 2 H), 4.30 (dd, J = 9.9, 5.2 Hz, 1 H), 4.45 (dd, J = 9.3, 3.5 Hz, 1 H), 4.74 (d, J = 9.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 5.1 (CH_2), 5.2 (CH_2), 7.1 (CH_3), 7.2 (CH_3), 14.0 (CH_3), 22.5 (CH_2), 27.8 (CH_2), 29.8 (CH_2), 30.2 (CH_2), 31.0 (CH_2), 31.6 (CH_2), 40.7 (CH_2), 51.6 (CH_3), 54.2 (CH_3), 64.8 (CH), 67.1 (CH), 73.6 (CH), 74.0 (CH), 74.9 (CH), 76.1 (CH), 77.4 (CH), 78.2 (CH), 93.8 (CH), 160.5 (C), 171.9 (C); HRMS calculated for $C_{33}H_{62}O_8Si_2$ $(M + Na)^+$ 665.3881, found 665.3911 (5.0 ppm). Data for **4*E***: R_f 0.18 (20% EtOAc in hexanes); $[\alpha]^{23}_D$ −63 (*c* 1.1, $CHCl_3$); IR (thin film) 1743, 1675 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.57−0.68 (m, 12 H); 0.75−1.06 (m, 21 H), 1.24−1.53 (m, 8 H), 1.68−1.80 (m, 1 H), 2.03−2.20 (m, 3 H), 2.38 (*A*BX, J_{ab} = 15.4 Hz, J_{ax} = 5.0 Hz, 1 H), 2.55 (A*B*X, J_{ab} = 15.2 Hz, J_{ax} = 8.2 Hz, 1 H), 2.94 (dd, J = 9.3, 1.9 Hz, 1 H), 3.54 (s, 3 H), 3.68 (s, 3 H), 3.75−3.89 (m, 1 H), 3.97 (dd, J = 5.3, 1.2 Hz, 1 H), 3.99 (dd, J = 7.6, 5.4 Hz, 1 H), 4.04−4.17 (m, 2 H), 4.27 (dd, J = 9.5, 5.5 Hz, 1 H), 4.78 (dd, J = 9.3, 3.4 Hz, 1 H), 4.88 (d, J = 8.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 5.0 (CH_2), 5.2 (CH_2), 7.0 (CH_3), 7.2 (CH_3), 13.9 (CH_3), 22.6 (CH_2), 26.7 (CH_2), 29.7 (CH_2), 30.2 (CH_2), 31.2 (CH_2), 31.7 (CH_2), 40.7 (CH_2), 51.6 (CH_3), 56.0 (CH_3), 64.8 (CH), 67.1 (CH), 74.0 (CH), 74.4 (CH), 75.2 (CH), 76.1 (CH), 77.5 (CH), 104.8 (CH), 158.2 (C), 171.9 (C); HRMS calculated for $C_{33}H_{62}O_8Si_2$ $(M + Na)^+$ 665.3881, found 665.3911 (5.0 ppm).

ABCDE Cage Ketal 6, Route A. A crude mixture of **4*Z*** and **4*E*** (ca. 1:1) was prepared as described above from aldehyde **9** (35 mg, 0.064 mmol) and dissolved in CH_2Cl_2 (2.1 mL). Water (0.5 mL) was added, followed by *p*-TsOH·H_2O (12 mg, 0.063 mmol, 1 equiv). The biphasic mixture was stirred vigorously at room temperature for 1 h before MeOH (1.5 mL) was added. The mixture became homogeneous, and stirring was continued at room temperature for another 2 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$, and the reaction mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. FCC (20% to 30% EtOAc in hexanes) provided the desired ketal **6** (17 mg, 0.043 mmol, 67%) as a yellow oil. Data for **6**: R_f 0.25 (50% EtOAc in hexanes); $[\alpha]^{23}_D$ −46 (*c* 1.0, $CHCl_3$); IR (thin film) 1740, 1437, 1189, 1140, 1082 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 0.92 (t, J = 7.3 Hz, 3 H), 1.25−1.45 (m, 7 H), 1.46−1.55 (m, 1 H), 1.55−1.65 (m, 1 H), 1.69 (ddd, J = 13.5, 11.2, 5.1 Hz, 1 H), 1.75−1.85 (m, 2 H), 1.98 (dd, J = 13.2, 5.0 Hz, 1 H), 2.04 (d, J = 13.2 Hz, 1 H), 2.45 (*A*BX, J_{ab} = 15.7 Hz, J_{ax} = 5.0 Hz, 1 H), 2.52 (A*B*X, J_{ab} = 15.7 Hz, J_{bx} = 7.8 Hz, 1 H), 2.96 (dd, J = 9.5, 1.9 Hz, 1 H), 3.66 (s, 3 H), 3.79−3.86 (m, 1 H), 4.11 (dd, J = 6.6, 4.3 Hz, 1 H), 4.17 (dd, J = 6.6, 4.6 Hz, 1 H), 4.29 (app td, J = 10.0, 4.8 Hz, 1 H), 4.33 (dd, J = 4.0, 2.0 Hz, 1 H), 4.58 (app t, J = 4.5 Hz, 1 H), 4.68 (app t, J = 4.6 Hz, 1 H); ^{13}C NMR (75 MHz, CD_3OD) δ 14.5 (CH_3), 24.0 (CH_2), 25.1 (CH_2), 31.3 (CH_2), 31.8 (CH_2), 33.3 (CH_2), 40.0 (CH_2), 41.4 (CH_2), 48.2 (CH_2), 52.3 (CH_3), 69.7 (CH), 75.4 (CH), 76.1 (CH), 76.2 (CH), 78.1 (CH), 79.6 (CH), 82.4 (CH), 83.8 (CH), 112.1 (C), 173.5 (C); HRMS calculated for $C_{20}H_{30}O_7$ $(M + Na)^+$ 405.1889, found 405.1896 (1.728 ppm).

ABCDEF Cage Ketal 7, Route A. A solution of phosphonium salt **12a** (29 mg, 0.037 mmol, 2 equiv) in THF (0.4 mL) was cooled to −78 °C for the dropwise addition of *n*-BuLi (15 μL of a 2.3 M solution in hexanes, 0.035 mmol, 1.9 equiv). The resulting blood-red solution was stirred at this temperature for 10 min before aldehyde **9** (10 mg, 0.018 mmol, 1 equiv) in THF (0.3 mL) was added via cannula. After stirring at −78

(44) The ^1H and ^{13}C NMR data for **6** and **7** prepared via both routes A and B described here (Schemes 18, 20, 26, and 28) were in excellent agreement with that for halichondrin B itself.[1a] See the Supporting Information.

°C for another 5 min, the mixture was warmed to room temperature and quenched with brine (4 mL). The layers were separated and the aqueous later was extracted with Et_2O. The combined ether layers were then dried over Na_2SO_4 and concentrated in vacuo. The resultant residue was passed through a plug of Florisil to give a crude enol ether mixture (ca. 11 mg, ca. 0.011 mmol, ca. 62%). As further purification was not feasible, this material was carried directly into the subsequent acid hydrolysis procedure. To this mixture was added water (0.1 mL) and CH_2Cl_2 (0.4 mL) followed by *p*-TsOH·H_2O (ca. 2 mg, ca. 0.010 mmol). The biphasic mixture was stirred vigorously at room temperature for 1 h before MeOH (0.3 mL) was added. The mixture became homogeneous, and stirring was continued at room temperature for another 3 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$, and the reaction mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. FCC (40% to 50% EtOAc in hexanes) provided the desired C1−C22 ketal **7** (3.7 mg, 0.0053 mmol, 29% from **9**) as a yellow oil. Data for **7**: R_f 0.25 (50% EtOAc in hexanes); $[\alpha]^{23}_D$ −36 (*c* 0.50, $CHCl_3$); IR (thin film) 3070, 2928, 2855, 1739, 1428, 1360, 1177, 1111, 1078, 996, 918 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.04 (s, 9 H), 1.32−1.42 (m, 2 H), 1.58−1.77 (m, 4 H), 1.80−1.92 (m, 4 H), 1.96−2.03 (m, 2 H), 1.97 (dd, J = 13.3, 4.8 Hz, 1 H), 2.05 (d, J = 13.0 Hz, 1 H), 2.24−2.31 (m, 1 H), 2.40 (dd, J = 15.8, 5.1 Hz, 1 H), 2.51 (dd, J = 15.8, 7.7 Hz, 1 H), 2.64−2.70 (m, 1 H), 2.95 (dd, J = 9.6, 1.9 Hz, 1 H), 3.62 (s, 3 H), 3.75−3.83 (m, 2 H), 3.83−3.91 (m, 2 H), 4.01−4.07 (m, 1 H), 4.11 (J = 6.3, 3.8 Hz, 1 H), 4.17 (dd, J = 6.7, 4.3 Hz, 1 H), 4.28 (ddd, J = 9.7, 9.7, 4.4, 1 H), 4.33 (dd, J = 3.7, 2.0 Hz, 1 H), 4.53−4.62 (m, 2 H), 4.59 (app t, J = 4.6 Hz, 1 H), 4.67 (app t, J = 4.6 Hz, 1 H), 4.89 (aq, J = 1.8 Hz, 1 H), 4.99 (aq, J = 2.1 Hz, 1 H), 7.38−7.46 (m, 6 H), 7.66−7.71 (m, 4 H); ^{13}C NMR (125 MHz, CD_3OD) δ 20.5 (C), 27.9 (CH_3 × 3), 31.3 (CH_2), 31.6 (CH_2), 32.1 (CH_2), 36.6 (CH_2), 39.9 (CH_2), 40.0 (CH_2), 41.8 (CH_2), 48.8 (CH_2), 52.6 (CH_3), 62.4 (CH_2), 70.1 (CH), 75.7 (CH), 76.3 (CH), 76.5 (CH), 78.0 (CH), 78.5 (CH), 79.0 (CH), 79.8 (CH), 82.8 (CH), 84.2 (CH), 105.8 (CH_2), 112.1 (C), 129.3 (CH × 4), 131.31 (CH), 131.33 (CH), 135.5 (C), 135.6 (C), 137.18 (CH × 2), 137.20 (CH × 2), 153.8 (C), 173.4 (C); HRMS calculated for $C_{40}H_{52}O_9Si$ $(M + Na)^+$ 727.3278, found 727.3281 (0.41 ppm).

Aldehyde 11. Alkene **73** (60 mg, 0.093 mmol for synthesis of enone **74**; 28.5 mg, 0.0462 mmol for synthesis of enone **10**) was dissolved in CH_2Cl_2 (3 mL) and cooled to −78 °C. Ozone was bubbled through the reaction mixture for 5 min, and then the mixture was purged with N_2 for 3 min. Triphenylphosphine (24 mg, 1.5 equiv for synthesis of enone **74**; 12 mg, 1.5 equiv for synthesis of enone **10**) was added to the reaction mixture at −78 °C, and then, the bath was removed and reaction mixture was stirred at room temperature for 30 min. The contents of the flask were concentrated under a stream of N_2 and then were put under high vacuum for 1 h. The resulting aldehyde was used without further purification.

α, β-Unsaturated Enone 74. To a suspension of dry NaH (8.7 mg, 0.3627 mmol, 3.9 equiv), in DME (1 mL) was added dimethyl-2-oxoheptyl phosphonate (0.077 mL, 0.372 mmol, 4 equiv). The reaction mixture bubbled slightly, and then went clear. This was stirred at room temperature for 5 min with gentle heating by a heating mantle. Crude aldehyde **11** (based on 60 mg, or 0.093 mmol of alkene **73**) from the previous reaction was dissolved in DME (1 mL) and transferred via cannula with an additional 1 mL of DME to assist in the transfer. The reaction mixture was then heated at reflux for 3 h. After this time, the reaction was cooled and quenched by addition of water, and the reaction mixture was extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. FCC (9% Et_2O in hexanes) yielded enone **74** as an oil (44.2 mg, 64%). Data for **74**: R_f 0.62 (50% hexanes in Et_2O); $[\alpha]^{23}_D$ −34.9 (*c* 0.00235, $CHCl_3$); IR (thin film) 2954, 2876, 1743, 1676, 1630, 1081 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.57 (q, J = 7.7 Hz, 6 H), 0.65 (q, J = 8.1 Hz, 6 H), 0.66 (q, J = 8.2 Hz, 6 H), 0.92 (t, J = 8.0 Hz, 9 H), 0.98 (t, J = 8.1 Hz, 9 H), 0.99 (t, J = 7.9 Hz, 9 H), 1.21−1.34 (m, 9 H), 1.61−1.68 (m, 3 H), 1.80−1.85 (m, 1 H), 2.35 (*A*BX, J_{ab} = 15.3 Hz, J_{ax} = 8.4 Hz, 1 H), 2.50 (A*B*X, J_{ab} =15.3 Hz, J_{bx} = 4.9 Hz, 1 H), 2.56 (dt, J = 7.4, 5.8 Hz, 2 H), 2.91 (dd, J = 9.6, 2.2 Hz, 1 H), 3.38 (app dt, J = 9.9, 4.1 Hz, 1 H), 3.68 (s, 3 H), 3.81 (dd, J = 7.1, 2.5 Hz, 2 H), 3.94 (dd, J = 6.9, 3.5 Hz, 1 H), 4.00 (m, 1 H), 5.07 (dd, J = 7.3, 3.0 Hz, 1 H), 6.28 (dd, J = 16.1, 0.8 Hz, 1 H), 7.09 (dd, J = 16.2, 7.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.7 (CH_2 × 3), 5.1 (CH_2 × 3), 5.3 (CH_2 × 3), 6.9 (CH_3 × 3), 6.99 (CH_3 × 3), 7.04 (CH_3 × 3), 13.9 (CH_3), 22.5 (CH_2), 24.1 (CH_2), 28.7 (CH_2), 30.5 (CH_2), 31.5 (CH_2), 39.8 (CH_2), 40.5 (CH_2), 51.6 (CH_3), 64.6 (CH), 69.9 (CH), 71.5 (CH_2), 72.2 (CH), 74.0 (CH), 78.7 (CH), 82.3 (CH), 130.3 (CH), 146.1 (CH), 171.7 (C), 200.8 (C); HRMS calculated for $C_{38}H_{74}O_8Si_3(M + Na)^+$ 765.4589, found 765.4626 (5 ppm).

ABCDE Cage Ketal 6, Route B. To a solution of enone **74** (35 mg, 0.047 mmol) in a mixture of CH_2Cl_2/water (0.5 mL/0.25 mL) was added *p*-TsOH (8.96 mg, 0.047 mmol, 1 equiv), and this was stirred at room temperature for 30 min, followed by the addition of MeOH (0.25 mL). The reaction mixture was stirred for 5 min and was then quenched by addition of saturated aqueous $NaHCO_3$ (ca. 2 mL), followed by extraction with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. FCC (10% to 20% to 50% hexanes in EtOAc to 100% EtOAc) yielded desired ABCDE ketal **6** (8.5 mg, 47%) as an oil. Data for **6** are given above.

α, β-Unsaturated Enone 10. To a cooled (0 °C) orange-colored solution of dry KHMDS (32 mg, 0.160 mmol, 3.6 equiv) in DME (1 mL) was added β-ketophosphonate **12b** (99.7 mg, 0.183 mmol, 4.1 equiv, dissolved in 1 mL of DME) via cannula. An additional 1 mL of DME was used to assist in the transfer. This mixture stirred at 0 °C for 30 min. In another flask, aldehyde **11** (based on 28.5 mg, or 0.0462 mmol of alkene **73**) was dissolved in DME (0.5 mL) and transferred via cannula to the reaction flask. An additional 0.5 mL of DME was used to assist in the transfer. This was stirred at 0 °C for 10 min, warmed to room temperature, and then heated at reflux for 10 h. The reaction was then cooled and quenched with addition of water and extracted with EtOAc (4×) and CH_2Cl_2 (2×). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The desired enone could not be separated from an impurity that coelutes, so FCC (10% to 20% Et_2O in hexanes followed by 50% EtOAc in hexanes) gave a mixture of enone **10** plus the unknown impurity (∼35% pure), which was carried on without further purification.

ABCDEF Cage Ketal 7, Route B. To a solution of crude enone **10** from above in CH_2Cl_2 (2 mL) and 5 drops of water was added *p*-TsOH (4.8 mg, 0.025 mmol, 1 equiv), and the reaction mixture was stirred for 5 min. MeOH (2 mL) was added, and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, followed by extraction with CH_2Cl_2 (4×). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. FCC (50% EtOAc in hexanes) yielded desired ketal **7** (3.4 mg, 10% from **73**). Data for **7** are given above.

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Supporting Information Available: Description of general procedures, additional experimental data, ^{1}H and ^{13}C NMR spectra for all new compounds, and crystallographic information for **40** and **70**. This material is available free of charge via the Internet at http://pubs.acs.org.

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