Synthesis of a C(22)−C(34) Halichondrin B Precursor via Ring Opening−Double Ring Closing Metathesis

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Halichondrin B (Figure 1) is the most cytotoxic member of a class of polyether macrolides isolated in low yield (1.8×10^{-8} to 4.0×10^{-5}%) from *Halichondria okadai* Kadota and several other marine sponges.[1] It is a tubulin-interactive antimitotic agent that displays an in vitro IC_{50} value of 0.3 nM against L1210 leukemia and potent in vivo activities against various chemoresistant human solid tumor xenografts.[2] On the basis of these data, halichondrin B has been recommended by the National Cancer Institute for stage A preclinical development.[2c,d] The structural complexity, biological activity, and scarcity of this natural product have stimulated several synthetic efforts,[3] including a total synthesis by Kishi et al.[3d]

A previously reported effort[3g,i] toward the synthesis of the C(20)−C(36) subunit of halichondrin B utilized a two-directional chain synthesis/terminus differentiation strategy[4] that involved a key double dioxanone-to-dihydropyran Ireland−Claisen rearrangement[5] to form the bis(dihydropyran) intermediate **1**, which was further elaborated. In this paper,

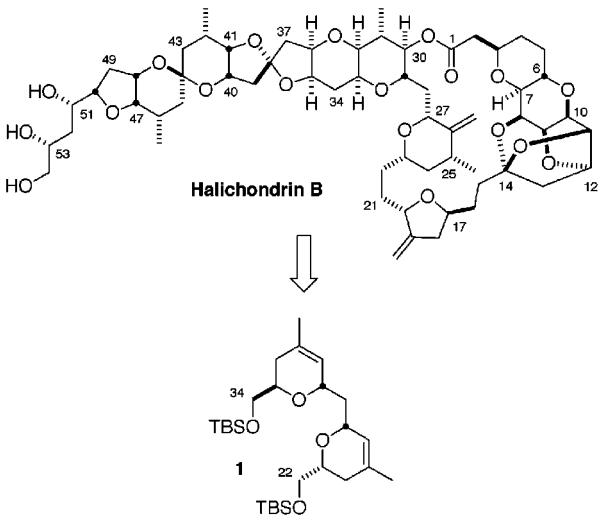
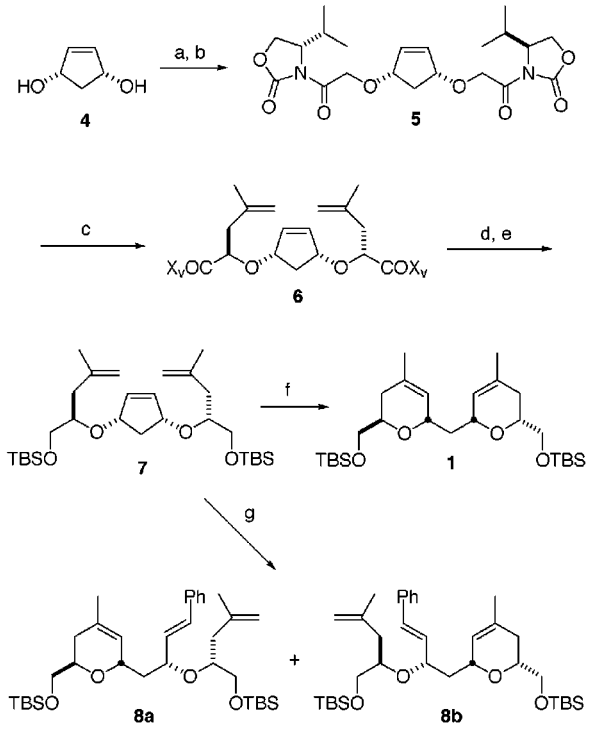


Figure 1.

Scheme 1[a]



[a] Reagents and conditions: (a) NaH, Bu_4NI, $BrCH_2CO_2H$, THF, 60 °C (86%); (b) PivCl, Et_3N, THF, −78 °C; X_yH, *n*-BuLi, THF, 0 °C (80%); (c) NaHMDS, 3-bromo-2-methylpropene, THF, −78 to −30 °C (72%); (d) $LiBH_4$, MeOH, THF, 23 °C (93%); (e) TBSCl, imidazole, CH_2Cl_2, 23 °C (95%); (f) 25 mol % **2**, PhH, 60 °C (79%); (g) 25 mol % **3**, PhH, 80 °C (21%).

we report a considerably more efficient synthesis of **1** via a one-pot ring opening-double ring closing metathesis[6] of triene **7** (Scheme 1) employing the Schrock molybdenum carbene complex **2** (Figure 2).[7]

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(1) (a) Hirata, Y.; Uemura, D. *Pure Appl. Chem.* **1986**, *58*, 701. (b) Pettit, G. R.; Herald, C. L.; Boyd, M. R.; Leet, J. E.; Dufresne, C.; Doubek, D. L.; Schmidt, J. M.; Cerny, R. L.; Hooper, J. N. A.; Rutzler, K. C. *J. Med. Chem.* **1991**, *34*, 3339. (c) Pettit, G. R.; Tan, R.; Gao, F.; Williams, M. D.; Doubek, D. L.; Boyd, M. R.; Schmidt, J. M.; Chapuis, J.-C.; Hamel, E.; Bai, R.; Hooper, J. N. A.; Tackett, L. P. *J. Org. Chem.* **1993**, *58*, 2538. (d) Litaudon, M.; Hart, J. B.; Blunt, J. W.; Lake, R. J.; Munro, H. H. G. *Tetrahedron Lett.* **1994**, *35*, 9435.

(2) (a) Bai, R.; Paull, K. D.; Herald, C. L.; Malspeis, L.; Pettit, G. R.; Hamel, E. *J. Biol. Chem.* **1991**, *266*, 15882. (b) Paull, K. D.; Lin, C. M.; Malspeis, L.; Hamel, E. *Cancer Res.* **1992**, *52*, 3892. (c) Pettit, G. R. *Pure Appl. Chem.* **1994**, *66*, 2271. (d) Personal correspondence with Dr. Michael R. Boyd, National Institutes of Health, National Cancer Institute.

(3) (a) Stamos, D. P.; Chen, S. S.; Kishi, Y. *J. Org. Chem.* **1997**, *62*, 7552. (b) Stamos, D. P.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8643. (c) Duan, J. J.-W.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 7541. (d) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.* **1992**, *114*, 3162 and references therein. (e) Cooper, A. J.; Pan, W.; Salomon, R. G. *Tetrahedron Lett.* **1993**, *34*, 8193 and references cited therein. (f) Horita, K.; Hachiya, S.; Ogihara, K.; Yoshida, Y.; Nagasawa, M.; Yonemitsu, O. *Heterocycles* **1996**, *42*, 99 and references therein. (g) Burke, S. D.; Buchanan, J. L.; Rovin, J. R. *Tetrahedron Lett.* **1991**, *32*, 3961. (h) Burke, S. D.; Jung, K. W.; Phillips, J. R.; Perri, R. E. *Tetrahedron Lett.* **1994**, *35*, 703. (i) Burke, S. D.; Zhang, G.; Buchanan, J. L. *Tetrahedron Lett.* **1995**, *36*, 7023. (j) Burke, S. D.; Phillips, J. R.; Quinn, K. J.; Zhang, G.; Jung, K. W.; Buchanan, J. L.; Perri, R. E. In *Anti-infectives: Recent Advances in Chemistry and Structure−Activity Relationships*; Bentley, P. H., O'Hanlon, P. J., Eds.; The Royal Society of Chemistry: Cambridge, **1997**; p 73. (k) Burke, S. D.; Austad, B. C.; Hart, A. C. *J. Org. Chem.* **1998**, *63*, 6770.

(4) (a) Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167. (b) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9. (c) Hoye, T. R.; Peck, D. R.; Trumper, P. K. *J. Am. Chem. Soc.* **1981**, *103*, 5618.

(5) (a) Burke, S. D.; Armistead, D. M.; Schoenen, F. J. *J. Org. Chem.* **1984**, *49*, 4320. (b) Burke, S. D.; Armistead, D. M.; Schoenen, F. J.; Fevig, J. M. *Tetrahedron* **1986**, *42*, 2787.

(6) (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (d) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634. For recent examples of dihydropyran synthesis via ring closing metathesis, see: (e) Miller, J. F.; Termin, A.; Koch, K.; Piscopio, A. D. *J. Org. Chem.* **1998**, *63*, 3158. (f) Burke, S. D.; Ng, R. A.; Morrision, J. A.; Alberti, M. J. *J. Org. Chem.* **1998**, *63*, 3160.

(7) (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875. (b) Bazan, G. C.; Khosravi, E.; Schrock, R. R.; Feast, W. J.; Gibson, V. C.; O'Regan, M. B.; Thomas, J. K.; Davis, W. M. *J. Am. Chem. Soc.* **1990**, *112*, 8378. (c) Bazan, G. C.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899.

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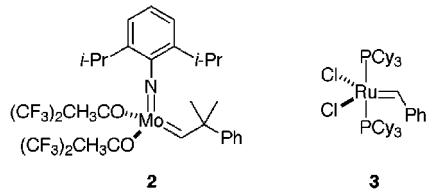
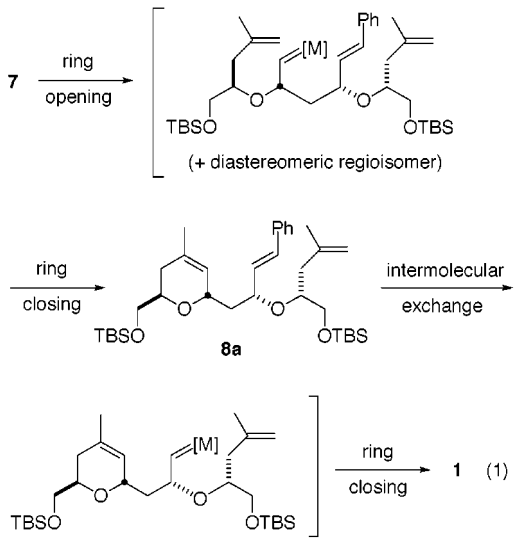


Figure 2.

As before,[3g,i] the synthesis of **1** began with *meso*-2-cyclopentene-1,4-diol (**4**) (Scheme 1).[8] Although **5** could be formed in a single step by bis(*O*-alkylation) of **4** with (4*S*)-3-(bromoacetyl)-4-isopropyl-2-oxazolidinone[9] (e.g., Ag_2O,[10] acetone, 50 °C, 2 days, 47%), these and a variety of other reaction conditions gave only low conversion and forced us to employ an alternative. To this end, treatment of **4** with excess NaH, tetrabutylammonium iodide, and sodium bromoacetate in refluxing THF effected bis(*O*-alkylation) and gave the corresponding meso diacid in 86% yield. Formation of the bis(pivalic anhydride) followed by reaction with *N*-lithio-(4*S*)-4-isopropyl-2-oxazolidinone[11] accomplished desymmetrization and afforded bis(imide) **5** in 80% yield. Treatment of **5** with NaHMDS in THF at −78 °C resulted in bis(*Z*-enolate) formation, and double methallylation gave **6** in 72% yield as a single diastereomer by virtue of the valine-derived Evans chiral auxiliaries.[12] Reductive removal of the chiral auxiliaries with $LiBH_4$[13] and protection of the resulting diol with TBSCl and imidazole gave metathesis substrate **7** in 88% yield for two steps.

Bis(dihydropyran) formation was anticipated to proceed via two distinct olefin metatheses,[6d] initiated by ring opening−ring closing metathesis as shown in eq 1. Initially, we



chose to use the Grubbs ruthenium carbene catalyst **3** (Figure 2).[14] Treatment of a 0.01 M solution of triene **7** with 25 mol % of **3** in refluxing PhH led to the formation of an inseparable mixture of diastereomeric dihydropyrans **8a** and **8b** (Scheme 1) in 21% yield.[15] These products apparently arise from initial ring opening of the cyclopentene with incorporation of the catalyst and intramolecular metathesis of the resulting Ru carbene with the proximal methallyl group. The propagating methylidene carbene $RuCl_2(=CH_2)$-$[P(C_6H_{11})_3]_2$ fails to undergo intermolecular exchange with either the phenyl-substituted olefin formed in the initial ring opening step or the remaining methallyl group, resulting in interruption of the metathesis sequence. The inability of the methylidene carbene to induce a second metathesis is not completely unexpected, as the remaining acyclic olefins (see **8a** in eq 1) have substitution patterns (disubstituted with allylic branching and *gem*-disubstituted) that are known to retard the metathesis reaction.[16] In an attempt to avoid the formation of **8a** and **8b**, the Ru methylidene carbene was preformed from **3** by exposure to an ethylene atmosphere.[14b] Upon addition of **7**, however, TLC analysis of the reaction mixture showed only baseline products, which presumably arise from polymerization. Fortunately, use of the more reactive Schrock catalyst **2** effected the desired transformation of **7** to **1**. Specifically, treatment of a 0.1 M solution of triene **7** with 25 mol % of **2** in dry, degassed PhH[17] at 60 °C gave clean formation of the desired bis(dihydropyran) **1** in 79% yield. Treatment of the mixture of dihydropyrans **8a** and **8b** with 25 mol % of **2** at 60 °C also resulted in conversion to **1** (74%), further demonstrating the greater reactivity of **2** over **3** toward sterically encumbered substrates and supporting the mechanistic sequence proposed in eq 1.

The synthesis of bis(dihydropyran) **1** was therefore achieved in six steps and 35% overall yield from meso diol **4**. This supplants our previous conversion of **4** to **1**,[3g,i] which required 11 steps and proceeded in 14% overall yield. Moreover, the new route is operationally much simpler and serves to further validate the powerful synthetic utility of alkene metathesis.

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Supporting Information Available: Experimental procedures, characterization data, and ^{1}H NMR spectra for compounds **1** and **5**−**8** (15 pages).

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(8) Kaneko, C.; Sugimoto, A.; Tanaka, S. *Synthesis* **1974**, 876.
(9) Canan Koch, S. S.; Chamberlin, R. A. *J. Org. Chem.* **1993**, *58*, 2725.
(10) Martin, S. F.; Rüeger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124.
(11) Evans, D. A.; Mathre, D. J.; Scott, W. L. *J. Org. Chem.* **1985**, *50*, 1830.
(12) (a) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**. *53*, 1109. (b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (c) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23. (d) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldichim. Acta* **1997**, *30*, 3.
(13) (a) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, *20*, 307. (b) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434.
(14) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.
(15) The ratio of diastereomers was found to be 3:1 by ^{1}H NMR; however, it could not be determined which regioisomer was favored.
(16) (a) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942. (b) Furstner, A.; Langemann, K. *Synthesis* **1997**, 792. (c) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.
(17) Benzene used for metathesis reactions was distilled from sodium benzophenone ketyl and degassed by several freeze−pump−thaw cycles. If the solvent was not degassed in this way, reaction yields were low and inconsistent.