An Expeditious Synthesis of the C(38)−C(54) Halichondrin B Subunit

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Halichondrin B (Figure 1) is the most potent of a class of polyether macrolides isolated in low yield (1.8×10^{-8} to 4.0×10^{-5} %) from a variety of sponge genera.[1] With a tubulin-based mechanism of action as an antimitotic agent, halichondrin B displays an in vitro IC_{50} value of 0.3 nM against L1210 leukemia and remarkable in vivo activities against various chemoresistant human solid tumor xenografts.[2] Despite its extremely limited supply from natural sources, halichondrin B has been recommended by the National Cancer Institute for stage A preclinical development.[2c,d] Synthetic efforts have been described by several groups,[3] and one total synthesis of halichondrin B has been reported.[3d] Our earlier synthetic work toward halichondrin B focused on the C(1)−C(15) and C(20)−C(36) segments of the natural product.[3g−i] In this paper, we report the synthesis of the C(38)−C(54) subunit **1** (Scheme 3) in its natural configuration. Efficient construction of the K, L, M, and N rings, including 10 asymmetric centers, was accomplished by exploiting the local C_2-symmetry about the C(44)-spiroketal carbon.

The known (*S*)-epoxide **2**, available from *(S)*-malic acid[4a−c] or by hydrolytic kinetic resolution of racemic **2**,[4d,e] was opened with the ethylenediamine complex of lithium acetylide (Scheme 1).[5] Isomerization of the crude terminal alkyne with KO*t*-Bu afforded the thermodynamically favored internal alkyne **3** as the sole product. Reduction of **3** with LAH in THF resulted in the *E*-allylic alcohol **4** as a single geometrical isomer.[6] Allylic alcohol **4** was subjected to Johnson ortho ester Claisen rearrangement conditions[7] to provide the ethyl ester **5**.

Claisen self-condensation of **5** (Scheme 2) was effected by slow addition of LHMDS (2.5 equiv) and TMEDA (5.0 equiv) to the ester in THF over 4.5 h at 0 °C, affording the *β*-keto ester in good yield. Decarboalkoxylation under Krapcho conditions[8] cleanly provided the C_2-symmetric ketone **6** as a viscous oil (96%). Asymmetric dihydroxylation[9] with Sharpless's AD-mix-α at 0 °C afforded the C_2-symmetric tetraol, as virtually a single diastereomer, thus setting the C(40), C(41), C(47), and C(48) stereocenters in one step. Acid-catalyzed spiroketalization[10] of the tetraol with camphorsulfonic acid in PhH/MeOH (1:1) yielded the thermodynamic ratio (1.1:1.0) of the C_2-symmetric 1,7-dioxaspiro[5.5]undecane

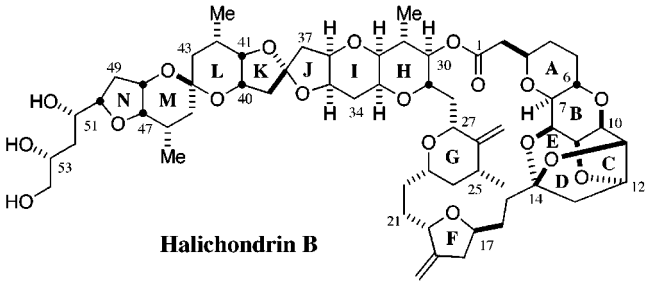
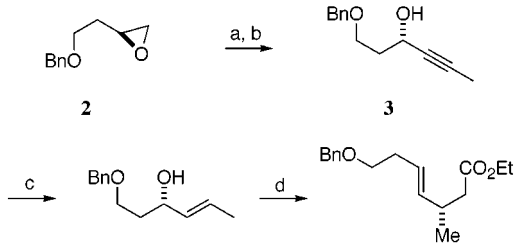


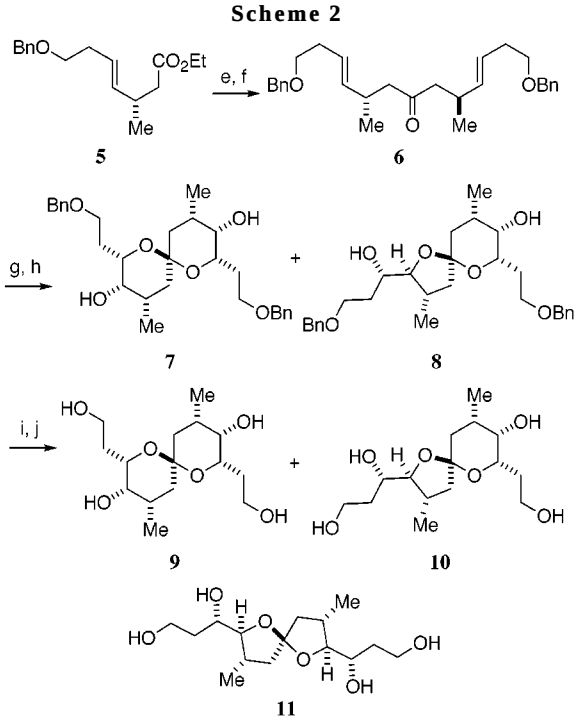
Figure 1.

Scheme 1



(a) LiCCH·$H_2NCH_2CH_2NH_2$, DMSO, 15 °C → rt; (b) KO*t*-Bu, DMSO,15 °C, 85% two steps; (c) LAH, THF, ↓↑, 96%; (d) $CH_3C(OEt)_3$, $CH_3CH_2CO_2H$ (1%),140 °C, 96%.

Scheme 2



(e) LHMDS, TMEDA, THF, 0 °C, 84% + 8% SM; (f) LiCl, DMSO, H_2O, 190 °C, 96%; (g) AD-mix-α, 0 °C,*t*-BuOH/H_2O (1:1); (h) CSA, MeOH/PhH (1:1), ↓↑, 85-92% two steps; (i) H_2(g), $Pd(OH)_2$ on carbon, EtOH, 100 %; (j) TFA, MeOH, ↓↑, 98-100%.

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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, M. 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*, 2271−2281. (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) Duan, J. J.- W.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 7541. (c) Stamos, D. P.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8643. (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 cited 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 cited therein. (g) Burke, S. D.; Buchanan, J. L.; Rovin, J. D. *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.

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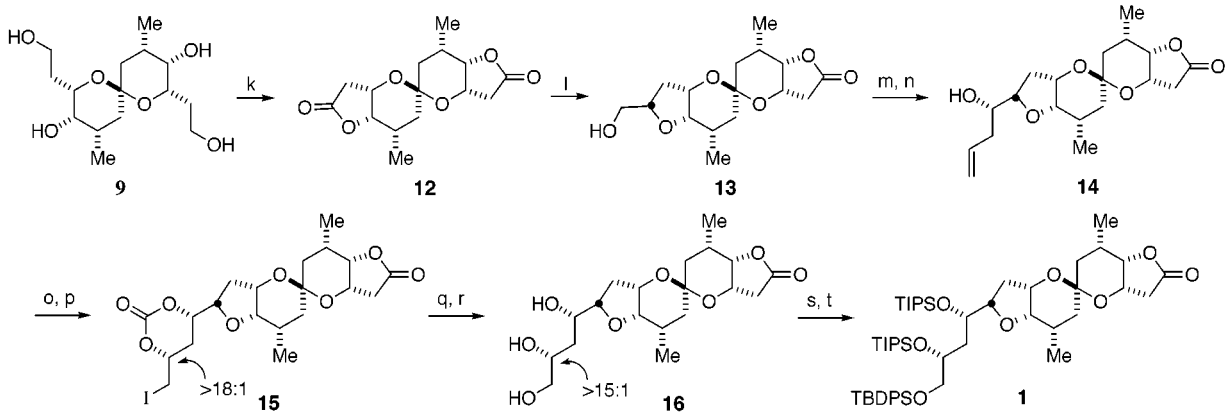
Scheme 3



(k) TPAP, NMO, 4-Å sieves, *t*-BuOH/CH_3CN, rt, 75%; (l) Tebbe reagent (Cp_2TiCH_2•$AlMe_2Cl$), pyr, $PhCH_3$/THF, -78 °C to rt; 9-BBN; $NaBO_3$·$4H_2O$, H_2O, 33-41% + 45% rec. SM; (m) Dess-Martin, CH_2Cl_2, rt; (n) $TiCl_4$, (Allyl)$SnBu_3$, CH_2Cl_2, -78 °C, 77-96%; (o) $(BOC)_2O$, DMAP, pyr, CH_2Cl_2, rt,91-98%; (p) IBr, $PhCH_3$, -80 °C, 96-99%; (q) 0.5 M LiOH(aq), DME, 60-70 °C; (r) CSA, PhH, Δ, 80-94%; (s) TBDPSCl, DMAP, CH_2Cl_2, pyr, rt, 90%; (t) TIPSOTf, pyr, DMAP, rt, 99%.

7, and the isomeric, undesired 1,6-dioxaspiro[4.5]decane **8** as a separable mixture of isomers. Operationally, the mixture of ketals **7** and **8** was debenzylated via hydrogenolysis and then equilibrated with catalytic trifluoroacetic acid in refluxing methanol to the more favorable thermodynamic mixture of desired **9**, plus **10** and **11** (5:2:1). After separation, ketals **10** and **11** were recycled to **9** by reexposure to the equilibrating conditions.

Selective oxidation of the primary alcohol groups in tetrol **9** (Scheme 3) with tetrapropylammonium perruthenate (VII) (TPAP)[11] afforded the C_2-symmetric bislactone **12** as a white crystalline solid, and confirmation of relative and absolute stereochemistry was secured by X-ray crystal structure determination. Monofunctionalization at one end of the C_2-symmetric bislactone was required to desymmetrize **12** and introduce the C(51)−C(54) side chain.[12] To avoid an unfavorable statistical mixture of recovered starting material and mono- and difunctionalized products, partial conversion of **12** to **13** was executed by lactone olefination[13] to the vinyl ether with 0.7 equivalents of the Tebbe reagent, followed by hydroboration/oxidation[14] with 9-BBN/aq $NaBO_3$. Oxidation of primary alcohol **13** with the Dess−Martin periodinane[15] provided the corresponding aldehyde, which was taken crude into a chelation-controlled allylation.[16] $TiCl_4$ promoted reaction with allyltributylstannane[17] at −78 °C provided the homoallylic alcohol **14** as a single diastereomer, within the detection limits of ^1H NMR.

The facial selectivity for the AQN-mediated Sharpless asymmetric dihydroxylation[9,18] of the terminal alkene in **14** proved unsatisfactory for establishing the C(53)−C(54) diol. Alternatively, homoallylic alcohol **14** was converted to the corresponding BOC carbonate with excess $(BOC)_2O$ and DMAP. Treatment of the BOC carbonate with iodine monobromide at −80 °C afforded the iodo carbonate **15** in excellent yield (96%) and diastereoselectivity (>18:1).[19] The conversion of **15** to triol **16** was best accomplished with 0.5 M aqueous LiOH in DME. After 15 h, the reaction contents were neutralized and concentrated. The resulting solids were treated with CSA in refluxing benzene, which accomplished the reclosure of the lactone ring and provided triol **16** in excellent yields from **15**. With the global protecting group scheme for the synthesis of halichondrin B in mind, the primary alcohol in **16** was selectively protected as a TBDPS ether, and the two secondary alcohols were then protected with TIPSOTf and DMAP to afford the desired C(38)−C(54) segment **1**, suitable for subunit coupling.

The synthesis of lactone **1** was accomplished in 18 steps from the known epoxide **2** in an overall 8% yield (based on recovered starting materials). Work toward the total synthesis of halichondrin B is ongoing and will be described as developments merit.

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Supporting Information Available: Experimental procedures, characterization data, and ^1H and/or ^{13}C NMR spectra for compounds **3**−**16**, **1**, and unnumbered intermediates and X-ray data for **12** (63 pages).

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(4) (a) Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fujii, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, 1389. (b) Masamune, S.; Ma, P.; Okumoto, H.; Ellingboe, J. W.; Ito, Y. *J. Org. Chem.* **1984**, *49*, 2834. (c) Hannessian, S.; Ugolini, A.; Dube, D.; Glamyan, A. *Can. J. Chem.* **1984**, *62*, 2146. (d) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (e) Brandes, B. D.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **1997**, *8*, 3927.

(5) Takano, S.; Sekiguchi, Y.; Sato, N.; Ogasawara, K. *Synthesis* **1987**, 139.

(6) Granitzer, W.; Stutz, A. *Tetrahedron Lett.* **1979**, *34*, 3145.

(7) Johnson, W. S.; Werthmann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

(8) Krapcho, A. P.; Weimaster, J. F. *J. Org. Chem.* **1980**, *45*, 4105.

(9) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. Partial spontaneous spiroketalization made precise diastereoselectivity determination difficult.

(10) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617.

(11) (a) Bloch, R.; Brillet, C. *Synlett* **1991**, 829. (b) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, *7*, 639.

(12) For a recent review of desymmetrization tactics for C_2-symmetric compounds, in the context of two-directional synthesis, see: Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167.

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

(14) (a) Carling, R. W.; Clark, J. S.; Holmes, A. B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 83. (b) Brown, H. C.; Ramachandran, P. V.; Vara Prasad, J. V. N. *J. Org. Chem.* **1985**, *50*, 5583. (c) Brown, H. C.; Vara Prasad, J. V. N.; Zee, S. *J. Org. Chem.* **1985**, *50*, 1582.

(15) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(16) Fleming, I. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 2, p 563.

(17) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.

(18) (a) Crispino, G. A.; Jeong, K.; Hartmuth, C. K.; Wang, Z.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785. (b) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448.

(19) (a) Duan, J. J. W.; Sprengeler, P. A.; Smith, A. B., III *Tetrahedron Lett.* **1992**, *33*, 6439. (b) Duan, J. J. W.; Smith, A. B., III *J. Org. Chem.* **1993**, *58*, 3703. (c) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626.