Published in final edited form as:

Angew Chem Int Ed Engl. 2009 ; 48(13): 2346–2350. doi:10.1002/anie.200806111.

A Total Synthesis of Norhalichondrin B**

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Keywords

natural products; pyrans; polyethers; metathesis

The halichondrin family of marine polyethers, first defined by the isolation and structure elucidation of norhalichondrin A by Uemura and co-workers in 1985, now numbers ~ 15 compounds.[1] The structures of the halichondrins, as exemplified by norhalichondrin B (Figure 1) are characterized by a 53–55 carbon backbone that is defined by two domains: the spiroketal containing C31–C53/55 region and a C1–C30 macrolactone that also contains a 2,6,9-trioxatricyclo[3.3.2.0^{3,7}]decane. The structures, in conjunction with impressive levels of cytotoxicity, have attracted significant scientific attention[2,3] highlighted by the total syntheses of halichondrin B and norhalichondrin B by Kishi in 1992,[3,5] and the current efforts of Eisai Pharmaceuticals to establish E7389,[6] a truncated analog of the macrolactone, as an anti-cancer therapeutic. In this communication we describe our studies that have culminated in the total synthesis of norhalichondrin B.

Our overall plans are defined in Figure 1, and involve a late stage Horner-Wadsworth-Emmons coupling of C40–C53 domain, **2** with phosphonate **3**. Phosphonate **3** can be traced back to C1–C13 domain **5** and C12–C38 domain **4**. In the forward sense, we envisioned that these two domains would be connected by a combination of cross-metathesis and macrolactonization as the key reactions. The C12–C38 domain **4** could be further dissected to arrive at pyranopyran **6** and the C14–C26 THF-ring containing domain **7**. [7] Pyran **2** and pyranopyran **6** would ultimately be prepared by the application of our recently reported furan→pyranone conversion, [8] and pyranopyran **5** would arise from a tandem ring-opening-ring-closing metathesis of an oxabicyclo[3.2.1]octene.[9]

This research was supported by the National Cancer Institute (NCI CA110246), Eli Lilly & Co under the auspices of the Lilly Awardee Program (to AJP), and in part by The American Chemical Society Petroleum Research Fund (ACS PRF# 38856-G1). We thank Professor R. H. Grubbs and Dr I. C. Stewart (Caltech) and Materia Inc. for catalyst **41, and Professor Yoshito Kishi (Harvard), and Professors John Blunt and Murray Munro (Canterbury) for copies of spectra

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Dedicated to Professors Uemura, Blunt, Munro, Pettit, and Kishi in recognition of their research on the halichondrins.

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The synthesis of the C1-C13 domain **5** commenced with the Davies Rh-catalyzed addition of diazo ester **8** to furan to give oxabicyclo[3.2.1]octene **9** in 59% yield (Scheme 1).[10,11] This ester was advanced to **10** in 16% overall yield by a sequence consisting of: (i) methanolysis and then hydrolysis to the acid; (ii) Curtius rearrangement/enamine hydrolysis; (iii) L-Selectride reduction of the ketone; and (iv) acetal formation with acrolein dimethylacetal. Gratifyingly, when **10** was exposed to 3 mol% of Grubbs' 2nd generation catalyst[12] conversion of the bridged bicyclic structure to pyranopyran **11** smoothly occurred in 71% yield. Hydroboration of the terminal olefin with Sia₂BH gave **12** in 73% yield. Exposure of **12** to Jones reagent resulted in simultaneous oxidation to the lactone and the acid, which was methylated with TMSCHN₂, to give **13** in 66% yield. Advancement of **13** to **5** followed our earlier reported 6 step sequence.[10]

Tetrahydrofuran-containing domain **7** was prepared by a sequence that began with Noyori hydrogenation of β -keto ester **14** (62%, Scheme 2), and subsequent Pd-mediated allylation to give *O*-allyl ester **15** in 80% yield. Hydrolysis of the ester and conversion to the diazoketone **17** ((COCl)₂, DMF then CH₂N₂, Et₃N, 60% after chromatography) set the stage for a [2,3]-sigmatropic rearrangement to form the tetrahydrofuran.[13] To this end, when diazoketone **17** was exposed to Cu(acac)₂ in THF under reflux, the expected rearrangement occurred to yield 2,5-*anti*-tetrahydrofuran **18** in 91% yield. Wittig olefination led to diene **19** (99%), which was selectively hydroborated with Sia₂BH, and subsequent oxidation of the primary alcohol with Dess-Martin periodinane gave aldehyde **20** (83% yield, 2 steps). Introduction of the remaining two stereocenters was achieved by application of the Kishi protocol.[14a] Aldehyde **20** was reacted with **23** in the presence of oxazoline-sulfonamide ligand **22**, to give diol **21** in 52% yield (after desilylation with TBAF). Selective acylation of the primary alcohol with pivaloyl chloride (DMAP, pyridine, 87%) produced **24** and the secondary alcohol was mesylated (Ms₂O, Et₃N, DMAP, 99%) to give **7**.

The syntheses of both the C27-C38 domain and the C40-C53 domain were patterned on our previously reported Achmatowicz oxidation and subsequent ionic hydrogenation process for the conversion of furans to pyranones (Scheme 3).[8] In the case of the C40-C53 domain **2**, furfural **25** was subjected to Brown crotylation using (–)-Ipc₂-(*E*)-crotylborane to give **26** in 71% yield. Achmatowicz oxidation[15] with *t*-BuOOH and VO(acac)₂ produced an intermediate pyranone hemiacetal which was immediately subjected to trifluoroacetic acid-mediated ionic hydrogenation using Et₃SiH to yield the desired pyranone **27** in 86% yield and as a single diastereomer (d.r. >20:1 by ¹H NMR analysis). This material could be converted to aldehyde **28** in 7 steps following the sequence described in Ref ⁸. Addition of the lithium anion derived from iodide **29** (*t*-BuLi, Et₂O), followed by Dess-Martin oxidation (62% over 2 steps), and quantitative ozonolysis of the olefin (O₃, MeOH, pyridine) gave the fully functionalized C40-C53 domain, **2**.

Furfural **25** also served as the departure point for the C27-C38 domain **6** (see also Scheme 3). [9] Brown crotylation of **25** with (–)-Ipc₂-(*Z*)-crotylborane gave **30** in 75% yield. The two step protocol of Achmatowicz oxidation and ionic hydrogenation (*t*-BuOOH, VO(acac)₂ then TFA and Et₃SiH), produced 90% of pyranone **31** as a single diastereomer (d.r. >20:1). Conversion of **31** to lactone **32** was achieved by a three step sequence consisting of: (i) removal of the TBS ether with aqueous TFA, (ii) tandem Jones oxidation of the alcohol to the acid and hetero-conjugate addition of the acid to the enone, and (iii) NaBH₄ reduction of the pyranone (80%, d.r. = 5:1). Reduction of the lactone in **32** to the diol with LiBH₄ in THF, followed by selective formation of the 7-membered ketal, and protection of the secondary alcohol as the TES ether gave **33** in 75% overall yield. Ozonolysis of the olefin gave aldehyde **34** (95%), which was subjected to an asymmetric Nozaki-Hiyama-Kishi reaction with methyl-*trans*-3-iodoacrylate in the presence of oxazoline-sulfonamide ligand **35**[14b] to give **36** in 75% yield (d.r. = 12:1). Protection of the alcohol as the PMB ether using *p*-methoxybenzyl

trichloroacetimidate and $\text{BF}_3 \cdot \text{OEt}_2$ was followed by removal of TES group with TBAF. This desilylation was accompanied by hetero-Michael addition and produced the desired pyranopyran **37** in 50% yield for the two steps. Removal of the acetonide (PPTS, MeOH) and reprotection of the diol with TBSOTf gave **38** in 87% yield. Reduction of the ester with LiAlH_4 and oxidation of the alcohol to the aldehyde provided the fully functionalized C27-C38 domain, **6** in 90% yield for the two steps.

In advance of the key cross-metathesis for the introduction of the C1-C13 domain, pyranopyran **2** and tetrahydrofuran **3** were unified by the well-established combination of Nozaki-Hiyama-Kishi reaction and pyran ring formation[4] by $\text{S}_{\text{N}}2$ reaction to give **39** in 59% yield (Scheme 4). A straightforward sequence of (i) LiAlH_4 -mediated pivalate removal, (ii) Dess-Martin periodinane oxidation (iii) addition of vinylmagnesium bromide, and (iv) Dess-Martin periodinane oxidation provided enone **4** in 70% overall yield. Gratifyingly, it was possible to engage **4** and allylic alcohol **5** in productive cross metathesis in the presence of 20 mol% of the recently reported catalyst **41**[16] to give **40** in 62% yield.

The final fragment union and completion of the synthesis is shown in Scheme 5 and commences with the formation of the polycyclic acetal-containing C8-C14 domain. Treatment of cross metathesis product **40** with TBAF buffered by acetic acid resulted in removal of the silyl protecting groups and concomitant hetero-Michael addition to provide tetrahydrofuran **41** as a mixture of diastereoisomers. This transformation could be readily followed by TLC, and subjecting the reaction to non-aqueous workup conditions (CaCO_3 , DOWEX 50WX8-400, MeOH)[17] resulted in formation of the desired 2,6,9-trioxatricyclo[3.3.2.0^{3,7}]decane ring system to give **42** in 64% yield, along with 26% of the intermediate tetrahydrofuran **41** in which the C12 stereocenter is epimeric to the desired stereochemistry. This transformation could also be achieved by subjecting crude **41** to mild acid (PPTS, CH_2Cl_2). Protection of the alcohols as TBS ethers (TBSOTf, Et_3N , 0 °C) provided **43** in 78% yield, and subsequent removal of the PMB ether with buffered aqueous DDQ led to **44** (65%). At this juncture it was possible to remove the minor C27 diastereoisomer by column chromatography (16%). Hydrolysis of the methyl ester (LiOH , THF, quantitative) produced *seco*-acid **45**, which readily lactonized under standard Yamaguchi conditions[18] to give the macrolactone **46** in 92% yield. Although complete removal of the primary TBS group to give **47** could not be achieved without partial loss of the secondary TBS group at C35, it was possible to cleanly obtain the desired primary alcohol **47** in 97% yield based on recovered starting material when **46** was exposed to PPTS in MeOH and the reaction was run to ~45% conversion. Oxidation of alcohol **47** with Dess-Martin periodinane yielded aldehyde **48** (89%) and set the stage for a daring two step sequence consisting of (i) Roskamp reaction[19] for the introduction of the desired β -ketophosphonate, and (ii) coupling to the final fragment by Horner-Wadsworth-Emmons reaction. Despite some concerns about the viability of these reactions on highly complex substrates that could prove sensitive to Lewis acids[20] or basic conditions, both reactions proceeded without event: reaction of **48** with dimethyl(diazomethyl) phosphonate and SnCl_2 gave **3** in 74% yield, then reaction with aldehyde **2** in the presence of K_2CO_3 and 18-crown-6 in warm toluene produced enone **49** in 83% yield. Treatment of enone **49** with TBAF resulted in removal of the silyl protecting groups over the course of 12 hours to give an intermediate that contained the C44 spiroketal. Removal of the PMB ether proved to be slightly problematic, however recourse to the use of DDQ in CH_2Cl_2 -MeOH (10:1) was successful and resulted in clean removal of the PMB group to yield norhalichondrin B methyl ester, **50** in 65% yield over the two steps. Subsequent hydrolysis of the methyl ester with LiOH yielded norhalichondrin B, **1** in 60% yield and completed the synthesis. Gratifyingly, ^1H NMR data for both of the final two compounds matched data provided by Professor Yoshito Kishi and Professors John Blunt and Murray Munro.

In conclusion, we have described a total synthesis of norhalichondrin B that proceeds in 37 steps from β -furylethanol. Key features of the synthesis are the use of the Achmatowicz oxidation-ionic hydrogenation for the synthesis of pyrans and pyranopyrans, and the application of tandem metathesis for the synthesis of pyranopyrans. The synthesis also provides an example of a cross metathesis reaction on highly functionalized intermediates and establishes the utility of the Roskamp reaction in a complex setting.

Supplementary Material

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Figure 1. Norhalichondrin B and strategy-level analysis showing key disconnections.

Scheme 1.

A tandem ROM-RCM approach to the C1-C13 domain. Reagents and conditions: 1. 1 mol% $\text{Rh}_2(\text{OOct})_4$, hexane, reflux, 59% (*d.r.* = 94:6); 2. (a) NaOMe, MeOH then LiOH, MeOH- H_2O ; (b) DPPA, Et_3N , PhMe- CH_3CN then H_2O , reflux; (c) L-Selectride, THF, -78°C to rt (*d.r.* = 10:1); (d) $\text{H}_2\text{C}=\text{CHCH}(\text{OMe})_2$, PPTS, PhMe, 45°C , 16% (4 steps); 3. 3 mol% Grubbs II, $\text{H}_2\text{C}=\text{CH}_2$, PhMe, rt, then EVE, 71%; 4. Si_2BH , THF then NaBO_3 , H_2O , 73%; 5. Jones reagent, acetone then TMSCHN_2 , MeOH-PhMe, 68% (2 steps).

Scheme 2.

Synthesis of the C14-C26 domain. Reagents and conditions: 1. (*S*)-BINAPRuBr₂, EtOH, 50 °C, H₂, 62%; 2. 2.5 mol% allyl ethylcarbonate, Pd₂(dba)₃, dppb, THF, 60 °C, 80%; 3. LiOH, MeOH-THF, 99%; 4. (i) (COCl)₂, DMF, THF; (ii) CH₂N₂, Et₃N, Et₂O, 60%; 5. Cu(acac)₂, THF, reflux, 91%; 6. MePPh₃Br, *t*-BuOK, THF, rt, 99%; 7. Sia₂BH, THF then NaOH, H₂O₂, 84%; 8. Dess-Martin periodinane, NaHCO₃, CH₂Cl₂, 99%; 9. **23** (2 equiv), **22** (0.5 equiv), Co phthalocyanine, Mn, Et₃N.HCl, LiCl, TMSCl, DME, rt then TBAF, 52% (d.r. = 6:1); 10. PvCl, DMAP, pyr, CH₂Cl₂, 87%; 11. Ms₂O, Et₃N, DMAP, CH₂Cl₂, 99%.

Scheme 3.

Synthesis of the C27-C38 domain and the C40-C53 domain. Reagents and conditions: 1. (–)-Ipc₂-(*E*)-crotylborane then H₂O₂, NaOH, 71%; 2. *t*-BuOOH, VO(acac)₂, CH₂Cl₂ then Et₃SiH, TFA, CH₂Cl₂, –40 °C, 86%; 3. (a) **29**, *t*-BuLi, Et₂O, –78 °C; (b) Dess-Martin periodinane, CH₂Cl₂, rt, 62%; (c) O₃, MeOH, pyr. then Me₂S, quant.; 4. (–)-Ipc₂-(*Z*)-crotylborane then H₂O₂, NaOH, 75%; 5. *t*-BuOOH, VO(acac)₂, CH₂Cl₂ then Et₃SiH, TFA, CH₂Cl₂, –40 °C, 90%; 6. (a) TFA, H₂O, CH₂Cl₂, –37 °C; (b) Jones reagent, acetone, 0 °C to rt, 63%; 7. NaBH₄, MeOH, –10 °C, 80%; 8. LiBH₄, THF, rt; 9. 2,2-DMP, PPTS, CH₂Cl₂, 10. TESCl, imid., DMF, 75% (3 steps); 11. O₃ then Me₂S, 95%; 12. methyl-β-iodoacrylate, 0.22 mol% **35**, Cr₂Cl₂, proton sponge, LiCl, Mn⁰, NiCl₂(dppp), 2,6-lutidine, Cp₂ZrCl₂, MeCN, rt, 75%;

13. PMBOC(=NH)CCl₃, BF₃ OEt₂; 14. TBAF, MeOAc, THF, 50% (2 steps); 15. PPTS, MeOH; 16. TBSOTf, Et₃N, CH₂Cl₂, 87% (2 steps); 17. LAH, Et₂O, 0 °C; 18. Dess-Martin periodinane, CH₂Cl₂, 90% (2 steps).

Scheme 4.

Reagents and conditions: 1. (a) 1% NiCl₂/CrCl₂, 4:1 THF-DMF, RT; (b) KHMDS, THF, 0 °C, 59% (*dr* = 3.7:1); 2. (a) LAH, Et₂O, 0 °C; (b) Dess-Martin periodinane, NaHCO₃, CH₂Cl₂, RT; (c) H₂C=CHMgBr, THF, 0 °C; (d) Dess-Martin periodinane, NaHCO₃, CH₂Cl₂, RT, 70% (4 steps); 3. **6** (2 equiv), 20 mol% **8**, PhMe, 80 °C, 62%.

Scheme 5.

Reagents and conditions: 1. TBAF, AcOH, THF, RT; 2. CaCO_3 , DOWEX 50WX8-400, MeOH as workup, 64% (2 steps); 3. TBSOTf, Et_3N , CH_2Cl_2 , 0 °C, 78%; 4. DDQ, CH_2Cl_2 , pH 7 phosphate buffer, 65% (+16% of C27 epimer); 5. 1M LiOH, THF, rt, quantitative; 6. 2,4,6-trichlorobenzoyl chloride, Et_3N , THF, RT then DMAP, PhMe, 80 °C, 92%; 7. PPTS, MeOH, 97% (brsm); 8. Dess-Martin periodinane, NaHCO_3 , CH_2Cl_2 , RT, 89%; 9. dimethyl (diazomethyl)phosphonate (20 equiv), SnCl_2 (3 equiv), CH_2Cl_2 , RT, 74%; 10. **18** (1 equiv), K_2CO_3 , 18-crown-6, PhMe, 60 °C, 83%; 11. (a) TBAF, AcOH, MeOAc-THF, RT; (b) DDQ, CH_2Cl_2 -MeOH, 65% (2 steps); 12. LiOH, THF- H_2O , 60%.