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A Total Synthesis of Norhalichondrin B**

*Katrina L. Jackson, James A. Henderson, Hajime Motoyoshi, and Andrew J. Phillips**

Dedicated to Professors Daisuke Uemura, John Blunt, Murray Munro, George R. Pettit, and Yoshito Kishi

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 approximately 15 compounds.[1] The structures of the halichondrins, as exemplified by norhalichondrin B (Figure 1), are characterized by a 53–55 carbon atom backbone which is defined by two domains: the spiroketal containing the C31–C53/55 region and a C1–C30 macrolactone which 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 and co-workers in 1992,[4,5] and the current efforts of Eisai Pharmaceuticals to establish E7389,[6] a truncated analogue of the macrolactone, as an anti-cancer therapeutic. Herein we describe our studies which culminated in the total synthesis of norhalichondrin B.

Our approach is 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 the C1–C13 domain **5** and C12–C38 domain **4**. We envisioned that these two domains would be connected by a combination of cross-metathesis and macrolactonization as the key reactions. Compound **4** could be additionally dissected to arrive at pyranopyran **6** and the C14–C26, tetrahydrofuran (THF)-containing domain **7**.[7] Pyran **2** and pyranopyran **6** would ultimately be prepared by using 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]

The synthesis of **5** commenced with the Davies Rh-catalyzed addition of diazo ester **8** to a 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: 1) methanolysis and then hydrolysis to the acid; 2) Curtius rearrangement/enamine hydrolysis; 3) L-Selectride reduction of the ketone; and 4) acetal formation with acrolein dimethylacetal. Gratifyingly, when **10** was exposed to 3 mol% of Grubbs' second generation catalyst,[12] conversion of the bridged bicyclic structure into pyranopyran **11** smoothly occurred in 71% yield. Hydroboration of the terminal olefin with Sia_2BH gave **12** in 73% yield, and exposure of **12** to the Jones reagent resulted in simultaneous oxidation to the lactone and the acid, which was methylated with $TMSCHN_2$ to give **13** in 68% yield. Advancement of **13** to **5** followed our earlier reported six-step sequence.[10]

Compound **7** was prepared by a sequence beginning with a Noyori hydrogenation of β-ketoester **14** (62% yield,

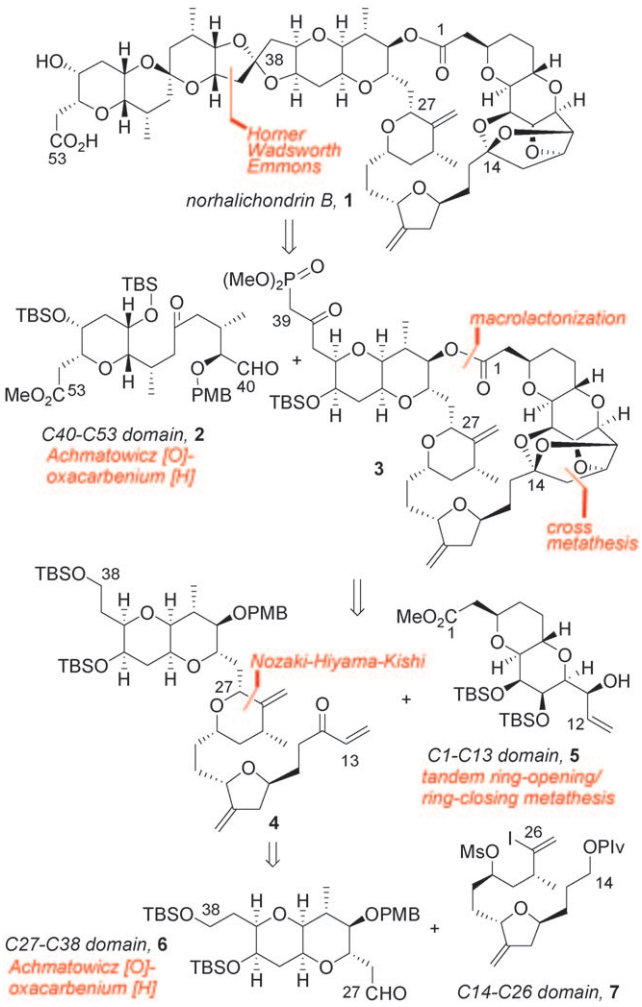

Figure 1. Norhalichondrin B and strategy-level analysis showing key disconnections.

[*] Dr. K. L. Jackson, Dr. J. A. Henderson, Dr. H. Motoyoshi, Prof. Dr. A. J. Phillips
Department of Chemistry and Biochemistry
University of Colorado, Boulder, CO 80309-0215 (USA)
Fax: (+1) 303-492-0439
E-mail: andrew.phillips@colorado.edu

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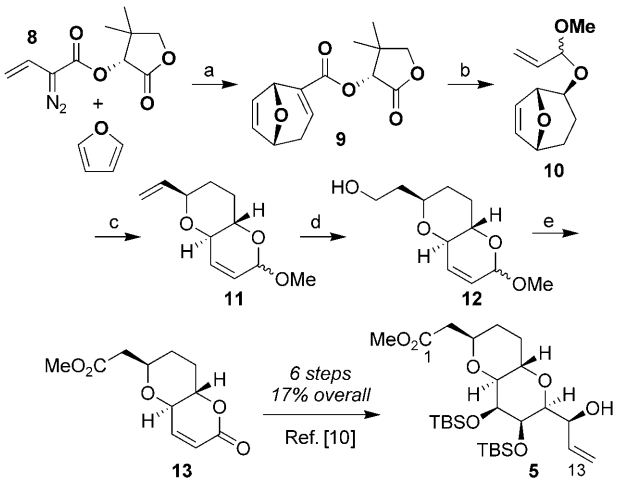
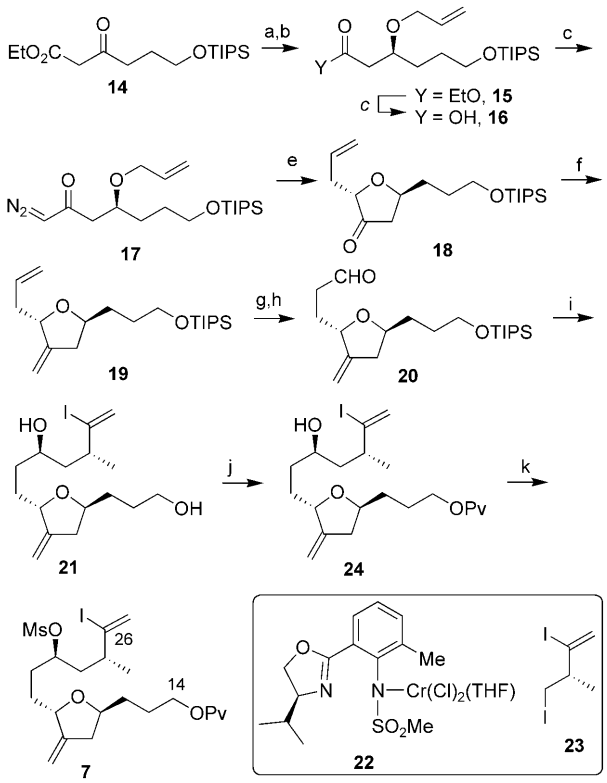


Scheme 1. A tandem ring-opening/ring-closing metathesis approach to **5**. Reagents and conditions: a) $[Rh_2(OOct)_4]$ (1 mol%), hexane, reflux, 59% (d.r. = 94:6); b) 1. NaOMe, MeOH then LiOH, MeOH/H_2O (2:1); 2. DPPA, Et_3N, PhMe/CH_3CN (2:1) then H_2O, reflux; 3. L-Selectride, THF, −78 °C → RT (d.r. = 10:1); 4. $H_2C{=}CHCH(OMe)_2$, PPTS, PhMe, 45 °C, 16% (4 steps); c) Grubbs II (3 mol%), $H_2C{=}CH_2$, PhMe, RT, then EVE, 71%; d) Sia_2BH, THF then $NaBO_3$, H_2O, 73%; e) Jones reagent, acetone then $TMSCHN_2$, MeOH/PhMe (1:3), 68% (2 steps). DPPA = diphenylphosphoryl azide, PPTS = pyridinium *para*-toluenesulfonate, EVE = ethylvinyl ether, TMS = trimethylsilyl.



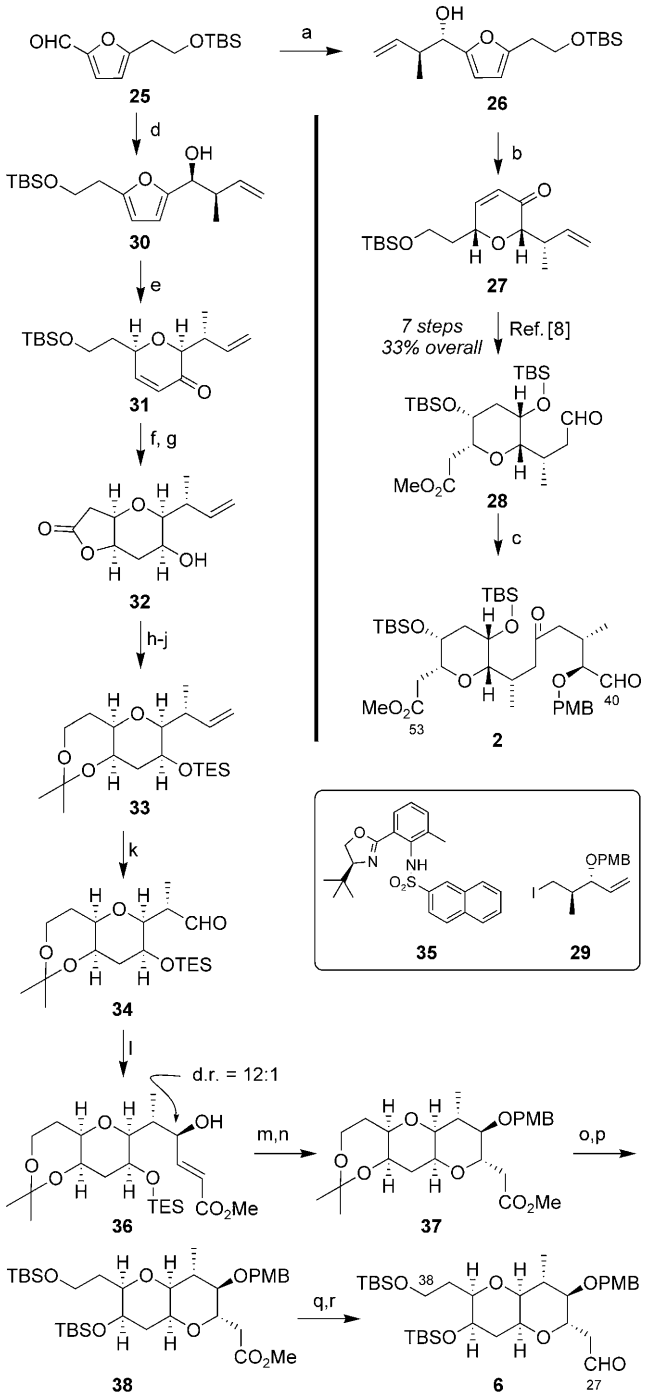
Scheme 2. Synthesis of **7**. Reagents and conditions: a) [(*S*)-binapRuBr$_2$] EtOH, 50 °C, H_2, 62%; b) allyl ethylcarbonate (2.5 mol%), $[Pd_2(dba)_3]$, dppb, THF, 60 °C, 80%; c) LiOH, MeOH/THF (2:3), 99%; d) 1. $(COCl)_2$, DMF, THF; 2. CH_2N_2, Et_3N, Et_2O, 60%; e) $[Cu(acac)_2]$, THF, reflux, 91%; f) $MePPh_3Br$, *t*BuOK, THF, RT, 99%; g) Sia_2BH, THF then NaOH, H_2O_2, 84%; h) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 99%; i) **23** (2 equiv), **22** (0.5 equiv), Co–phthalocyanine, Mn, $Et_3N{\cdot}HCl$, LiCl, TMSCl, DME, RT then TBAF, 52% (d.r. = 6:1); j) PvCl, DMAP, pyridine, CH_2Cl_2, 87%; k) Ms_2O, Et_3N, DMAP, CH_2Cl_2, 99%. binap = 2,2-bis(diphenylphosphanyl)-1,1-binaphthyl, dba = dibenzylideneacetone, dppb = bis(diphenylphosphanyl)butane), DMF = *N*,*N*-dimethylformamide, acac = acetylacetonate, DME = 1,2-dimethoxyethane, Ms = methanesulfonyl, Pv = pivaloyl, DMAP = 4-(dimethylamino)pyridine.

Scheme 2), and subsequent Pd-mediated allylation to give *O*-allyl ester **15** in 80% yield. Hydrolysis of the ester and conversion into the diazoketone **17** set the stage for a [2,3]-sigmatropic rearrangement to form the THF ring.[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. A Wittig olefination led to diene **19** (99% yield), which was selectively hydroborated with Sia_2BH, and subsequent oxidation of the primary alcohol with Dess–Martin periodinane gave aldehyde **20** (83% yield, 2 steps). The introduction of the remaining two stereocenters was achieved by using 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 produced **24** (87% yield), and the secondary alcohol was then mesylated to give **7** (99% yield).

The syntheses of both **6** and **2** were patterned on our previously reported Achmatowicz oxidation and subsequent ionic hydrogenation process for the conversion of furans into pyranones (Scheme 3).[8] For **2**, furfural **25** was subjected to the Brown crotylation using (−)-Ipc$_2$-(*E*)-crotylborane to give **26** in 71% yield. The Achmatowicz oxidation[15] with *t*BuOOH and $[VO(acac)_2]$ produced an intermediate pyranone hemiacetal which was immediately subjected to trifluoroacteic acid-mediated ionic hydrogenation, using Et_3SiH, to yield the desired pyranone **27** as a single diastereomer (d.r. > 20:1 by ^1H NMR analysis) in 86% yield. This material could be converted into aldehyde **28** in seven steps following the sequence described in reference [8].

The addition of the lithium anion derived from iodide **29** with subsequent Dess–Martin oxidation (62% over 2 steps), and then quantitative ozonolysis of the olefin gave fully functionalized **2**.

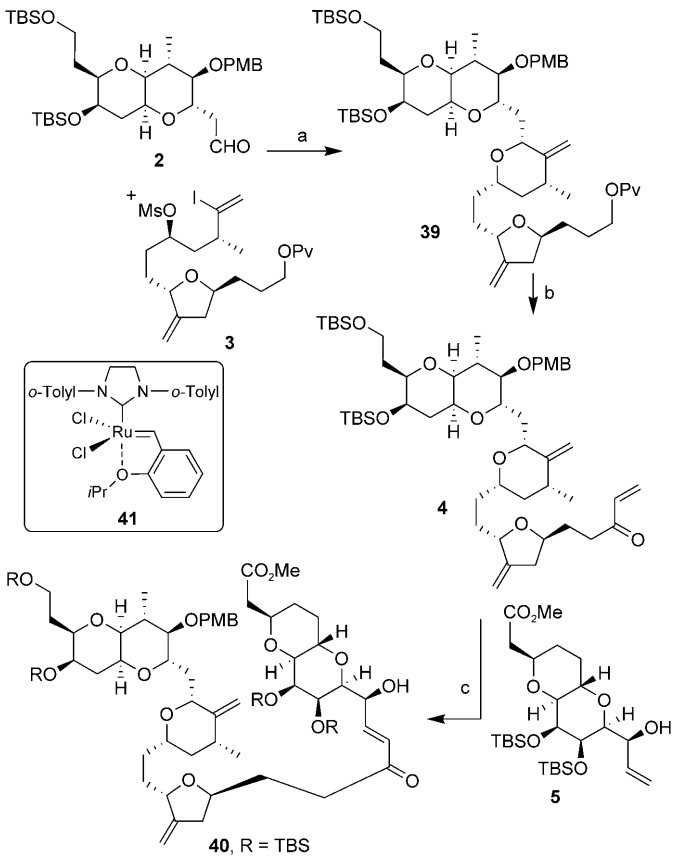
Furfural **25** also served as the departure point for **6** (see also Scheme 3).[9] Brown crotylation of **25** with (−)-(Ipc)$_2$-(*Z*)-crotylborane gave **30** in 75% yield. The two-step protocol of Achmatowicz oxidation and ionic hydogenation (*t*BuOOH, $[VO(acac)_2]$, then TFA and Et_3SiH), produced 90% of pyranone **31** as a single diastereomer (d.r. > 20:1). Conversion of **31** into lactone **32** was achieved by a three-step sequence consisting of: 1) removal of the TBS ether using aqueous TFA, 2) tandem Jones oxidation of the alcohol into the acid and hetero-conjugate addition of the acid to the enone, and 3) $NaBH_4$ reduction of the pyranone (80% yield, d.r. = 5:1). Reduction of the lactone in **32** into the diol with $LiBH_4$ in THF, with subsequent selective formation of the seven-membered ketal, and then protection of the secondary alcohol as the TES ether gave **33** in 75% overall yield.



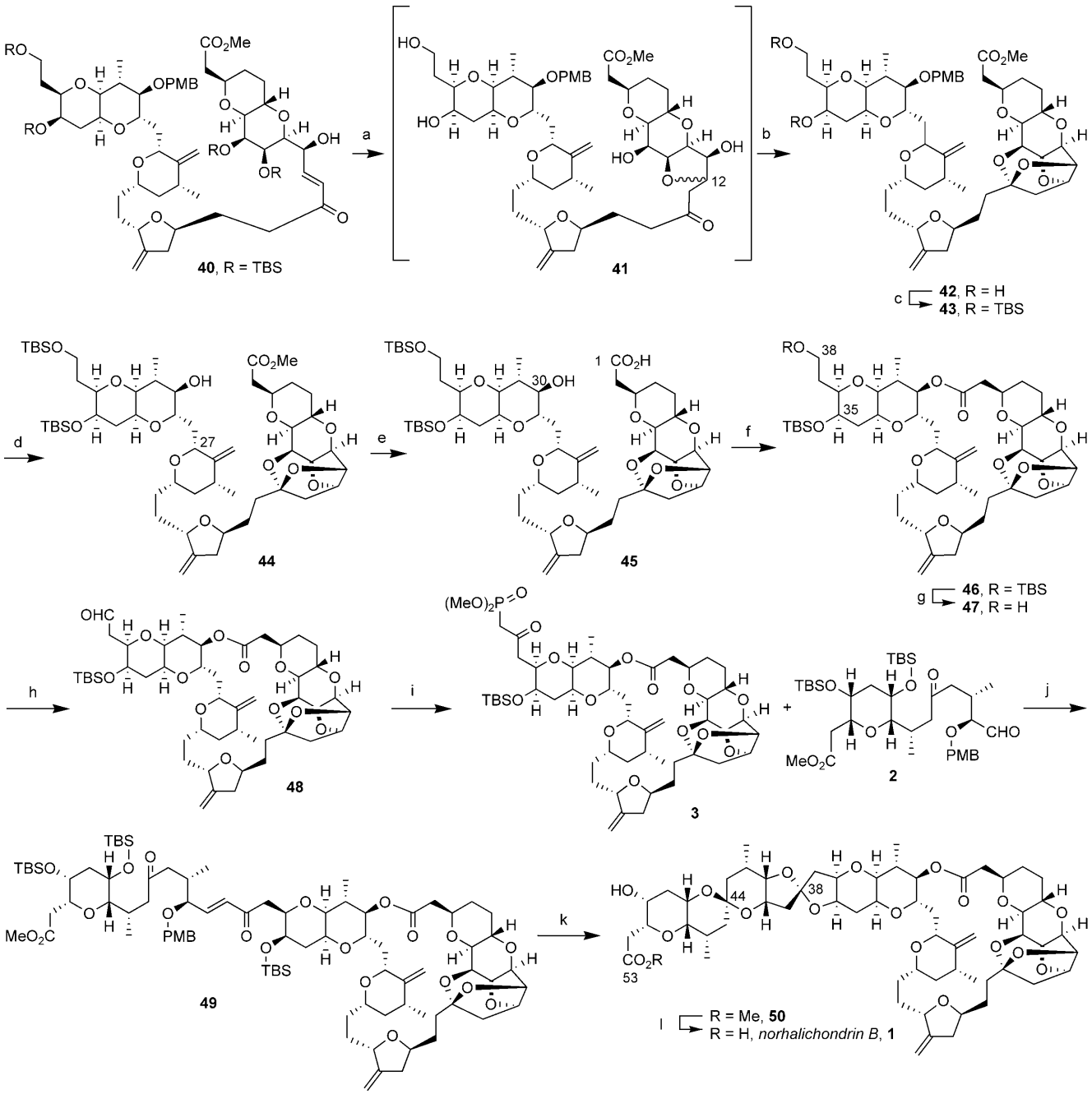
Scheme 3. Syntheses of **6** and **2**. Reagents and conditions: a) (−)-Ipc_2-(*E*)-crotylborane then H_2O_2, NaOH, 71%; b) *t*BuOOH, $[VO(acac)_2]$, CH_2Cl_2 then Et_3SiH, TFA, CH_2Cl_2, −40°C, 86%; c) 1. **29**, *t*BuLi, Et_2O, −78°C; 2. Dess–Martin periodinane, CH_2Cl_2, RT, 62%; 3. O_3, MeOH, pyridine then Me_2S, quant.; d) (−)-Ipc_2-(*Z*)-crotylborane then H_2O_2, NaOH, 75%; e) *t*BuOOH, $[VO(acac)_2]$, CH_2Cl_2 then Et_3SiH, TFA, CH_2Cl_2, −40°C, 90%; f) 1. TFA, H_2O, CH_2Cl_2, −37°C; 2. Jones reagent, acetone, 0°C→RT, 63%; g) $NaBH_4$, MeOH, −10°C, 80%; h) $LiBH_4$, THF, RT; i) 2,2-DMP, PPTS, CH_2Cl_2, j) TESCl, imidazole, DMF, 75% (3 steps); k) O_3 then Me_2S, 95%; l) methyl-β-iodoacrylate, 0.22 mol% **35**, Cr_2Cl_2, proton sponge, LiCl, Mn°, $[NiCl_2(dppp)]$, 2,6-lutidine, Cp_2ZrCl_2, MeCN, RT, 75%; m) $PMBOC(=NH)CCl_3$, $BF_3{\cdot}OEt_2$; n) TBAF, MeOAc, THF, 50% (2 steps); o) PPTS, MeOH; p) TBSOTf, Et_3N, CH_2Cl_2, 87% (2 steps); q) LAH, Et_2O, 0°C; r) Dess–Martin periodinane, CH_2Cl_2, 90% (2 steps). TFA = trifluoroacetic acid, 2,2-DMP = 2,2-dimethoxypropane, TES = triethylsilyl, Cp = cyclopentadienyl, PMB = *para*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, LAH = lithium aluminum hydride.

Ozonolysis of the olefin gave aldehyde **34** (95% yield), 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 $BF_3{\cdot}OEt_2$ was followed by removal of TES group using TBAF. This desilylation was accompanied by a hetero-Michael addition, producing the desired pyranopyran **37** in 50% yield over two steps. The removal of the acetonide 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 fully functionalized **6** in 90% yield over the two steps.

In advance of the key cross-metathesis for the introduction of **5**, pyranopyran **2** and tetrahydrofuran **3** were unified



Scheme 4. Reagents and conditions: a) 1. 1% $NiCl_2/CrCl_2$, THF/DMF (4:1) , RT; 2. KHMDS, THF, 0°C, 59% (d.r. = 3.7:1); b) 1. LAH, Et_2O, 0°C; 2. Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, RT; 3. H_2C=CHMgBr, THF, 0°C; 4. Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, RT, 70% (4 steps); c) **5** (2 equiv), **41** (20 mol%), PhMe, 80°C, 62%. KHMDS = potassium 1,1,1,3,3,3-hexamethyldisilazane.



Scheme 5. Reagents and conditions: a) TBAF, AcOH, THF, RT; b) $CaCO_3$, DOWEX 50WX8-400, MeOH as workup, 64% (2 steps); c) TBSOTf, Et_3N, CH_2Cl_2, 0°C, 78%; d) DDQ, CH_2Cl_2, pH 7 phosphate buffer, 65% (+16% of C27 epimer); e) 1 M LiOH, THF, RT, quantitative; f) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, RT then DMAP, PhMe, 80°C, 92%; g) PPTS, MeOH, 97% (brsm); h) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, RT, 89%; i) dimethyl(diazomethyl)phosphonate (20 equiv), $SnCl_2$ (3 equiv), CH_2Cl_2, RT, 74%; j) **18** (1 equiv), K_2CO_3, 18-crown-6, PhMe, 60°C, 83%; k) 1. TBAF, AcOH, MeOAc/THF (2:1), RT; 2. DDQ, CH_2Cl_2/MeOH (10:1), 65% (2 steps); l) LiOH, THF/H_2O (3:1), 60%. Ac = acetyl, DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, brsm = based on recovered starting material.

by the well-established combination of Nozaki–Hiyama–Kishi reaction and the pyran ring formation[4] by S_N2 reaction to give **39** in 59% yield (Scheme 4). A straightforward sequence of 1) $LiAlH_4$-mediated pivalate removal, 2) Dess–Martin periodinane oxidation, 3) addition of vinylmagnesium bromide, and 4) Dess–Martin periodinane oxidation provided enone **4** in 70% overall yield. Gratifyingly, it was possible to engage **4** and allylic alcohol **5** in a 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 the removal of the silyl protecting groups and concomitant hetero-Michael addition to provide tetrahydro-

furan **41** as a mixture of diastereoisomers. This transformation could be readily monitored by TLC, and subjecting the reaction to non-aqueous workup conditions ($CaCO_3$, DOWEX 50WX8-400, MeOH)[17] resulted in the 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. Protection of the alcohols as TBS ethers provided **43** in 78% yield, and subsequent removal of the PMB ether with buffered aqueous DDQ led to **44** (65% yield). At this juncture it was possible to remove the minor C27 diastereoisomer by column chromatography (16% yield). Hydrolysis of the methyl ester 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 approximately 45% conversion. Oxidation of alcohol **47** using Dess–Martin periodinane yielded aldehyde **48** (89% yield) and set the stage for a daring two-step sequence consisting of 1) Roskamp reaction[19] for the introduction of the desired β-ketophosphonate, and 2) coupling to the final fragment by a 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, and 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 the 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, the ^{1}H 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.

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