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Highly Functionalized Pyranopyrans from Furans: A Synthesis of the C27–C38 and C44–C53 Subunits of Norhalichondrin B

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ABSTRACT

A synthesis of highly functionalized pyranopyrans based on an Achmatowicz oxidation followed by a remarkably diastereoselective Kishi reduction is described in the context of studies directed toward norhalichondrin B.

Since the initial discovery of norhalichondrin A (**1**, Figure 1) by Uemura and co-workers,[1a,] and subsequent reports detailing the structures of related halistatins and halichondrins from the groups of Uemura,[1b] Pettit,[1c] and Blunt and Munro,[1d] there has been substantial interest from both chemists and biologists in this family of compounds.[2] Much of the biological interest is due to their extraordinary in vitro and in vivo antitumor activities, and the current pinnacle of this interest is the advancement of Eisai's halichondrin-derived E7389, **2**, into phase III clinical trials for the treatment of breast cancer.[3]

From a chemistry perspective, the halichondrins present a daunting challenge for chemical synthesis. The structures are characterized by a 53−55 carbon backbone that is

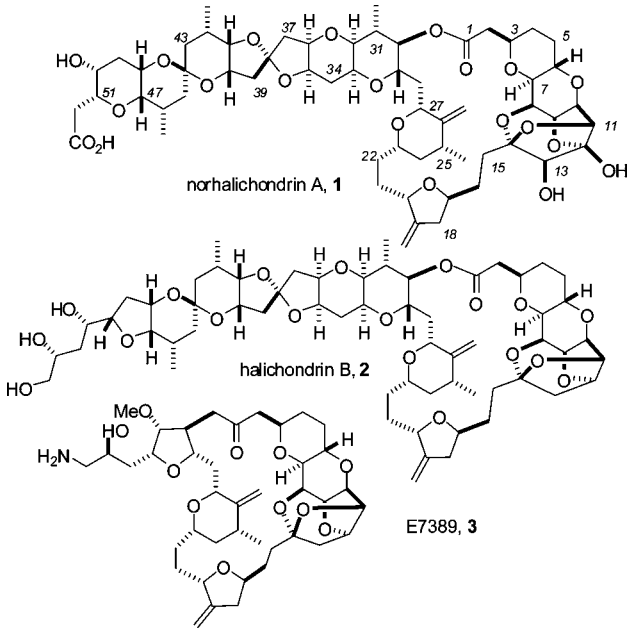

Figure 1. Norhalichondrin A, halichondrin B, and E7389.

decorated by a 2,6,9-trioxatricyclo[3.3.2.0^{3,7}] decane, a 22-membered macrolactone, and an array of polyoxygenated

(1) (a) Uemura, D.; Takahashi, K.; Yamamoto, K.; Yamamoto, T.; Katayama, C.; Tanaka, J.; Okumura, Y.; Hirata, Y. *J. Am. Chem. Soc.* **1985**, *107*, 4796. (b) Hirata, Y.; Uemura, D. *Pure Appl. Chem.* **1986**, *58*, 701. (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. Hickford, S. J. H.; Lill, R. E.; Lake, R. J.; Blunt, J. W.; Munro, M. H. G. *J. Org. Chem.* **1997**, *62*, 1868.

(2) For a review, see: Hart, J. B.; Lill, R. E.; Hickford, S. J. H.; Blunt, J. W.; Munro, M. H. G. *Drugs Sea* **2000**, 134−153.

(3) (a) Seletsky, B. M.; Wang, Y.; Hawkins, L. D.; Palme, M. H.; Habgood, G. J.; DiPietro, L. V.; Towle, M. J.; Salvato, K. A.; Wels, B. F.; Aalfs, K. K.; Kishi, Y.; Littlefield, B. A.; Yu, M. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5547. (b) Yu, M. J.; Kishi, Y.; Littlefield, B. A. In *Anticancer Agents from Natural Products*; Cragg, G. M., Kingston, D. G. I., Newman, D. J., Eds.; CRC Press: Boca Raton, 2005; pp 241−265.

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pyran and furan rings. To date, only the Kishi group has been successful in this domain, reporting total syntheses of halichondrin B, **2**, and norhalichondrin B (**4**, Figure 2) in

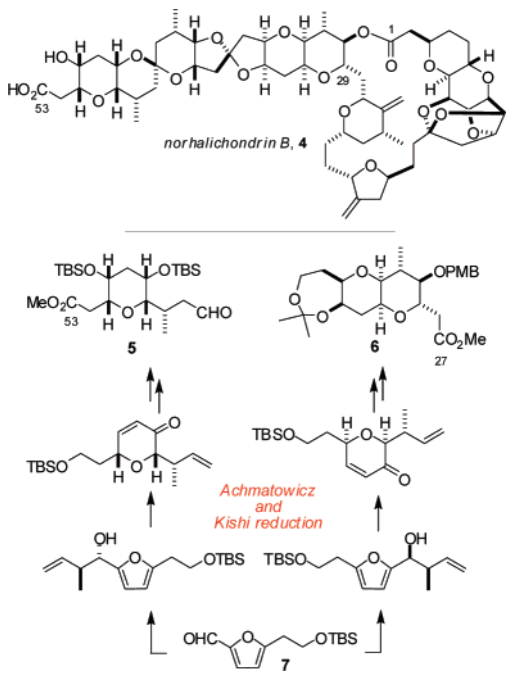


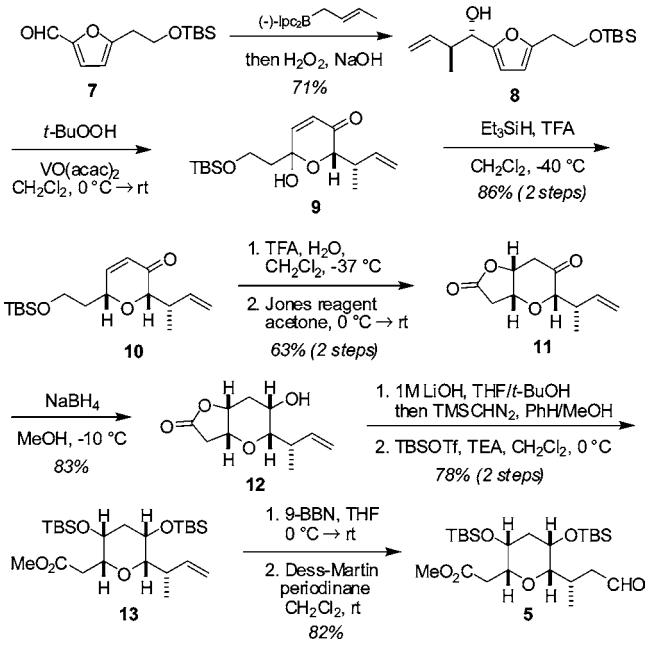
Figure 2. Overview of the synthesis strategy.

1992.[4,5] Aside from further illustrating the value of the Nozaki−Hiyama−Kishi coupling for complex molecule synthesis, it is noteworthy that the lead compound for the program that led to E7389 came from the ability to test materials prepared as part of the Kishi total synthesis.[6] A substantial body of work has also accumulated from the groups of Burke,[7] Horita and Yonemitsu,[8] and Salomon.[9] In this paper, we describe our approach to the pyranopyran-containing C27−C38 and C44−C53 domains (**5** and **6**, Figure 2) of the norhalichondrins.

An overview of the plans for the synthesis of complex pyranopyrans **5** and **6** is shown in Figure 2. The genesis of these two compounds can be traced back to a common starting material, known furan **7**,[10] and the overarching feature in the assembly of these structures is the key role of the Achmatowicz furan → furanone conversion[11] and subsequent Kishi reduction.

The synthesis of the C44−C53 pyranopyran **5** commences with Brown crotylation of furfural **7** using (−)-$(Ipc)_2$-(*E*)-crotylborane to produce **8** in 71% yield (Scheme 1).

Scheme 1



Achmatowicz oxidation of **8** was best performed using the conditions reported by Ho,[12] and upon subjection of **8** to TBHP in the presence of $VO(acac)_2$ as catalyst, smooth

(4) 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.

(5) For early studies from the Kishi group, see: (a) Aicher, T. D.; Kishi, Y. *Tetrahedron Lett.* **1987**, *28*, 3463. (b) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Scola, P. M. *Tetrahedron Lett.* **1992**, *33*, 1549. (c) Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Scola, P. M.; Yoon, S. K. *Tetrahedron Lett.* **1992**, *33*, 1553. (d) Fang, F. G.; Kishi, Y.; Matelich, M. C.; Scola, P. M. *Tetrahedron Lett.* **1992**, *33*, 1557. For recent work, see: Namba, K.; Jun, H.-S.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7770 and references cited therein.

(6) (a) Kishi, Y.; Fang, F. G.; Forsyth, C. J.; Scola, P. M.; Yoon, S. K. U.S. Patent 5338866, International Patent WO93/17650. (b) See also ref 3b.

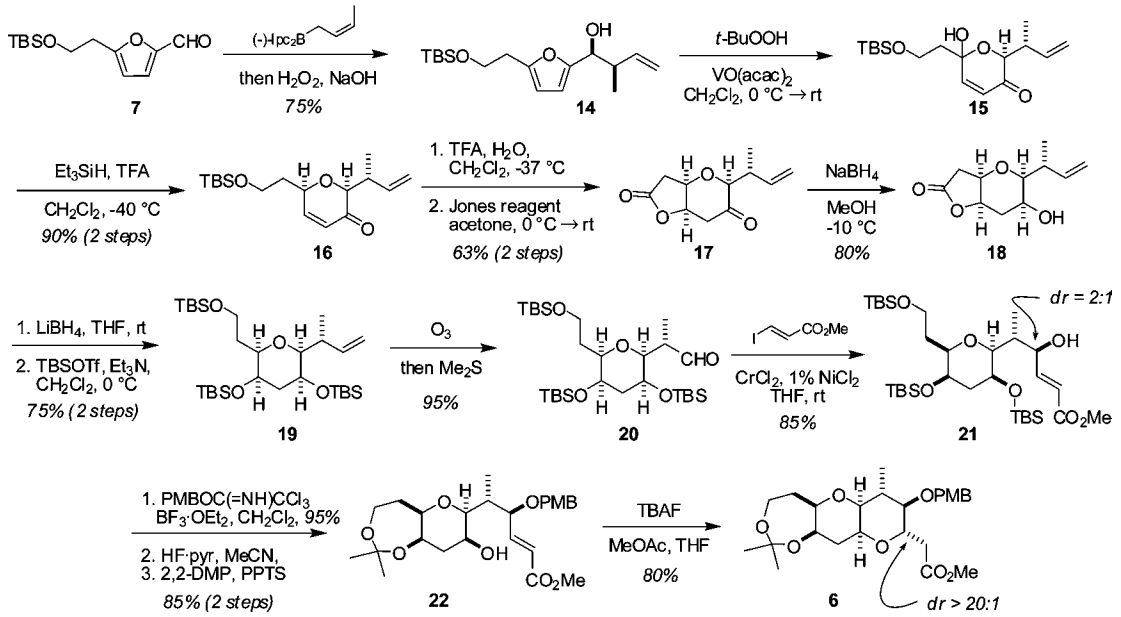
(7) (a) Burke, S. D.; Buchanan, J. L.; Rovin, J. D. *Tetrahedron Lett.* **1991**, *32*, 3961. (b) Burke, S. D.; Jung, K. W.; Phillips, J. R.; Perri, R. E. *Tetrahedron Lett.* **1994**, *35*, 703. (c) Burke, S. D.; Zhang, G.; Buchanan, J. L. *Tetrahedron Lett.* **1995**, *36*, 7023. (d) Burke, S. D.; Austad, B. C.; Hart, A. C. *J. Org. Chem.* **1998**, *63*, 6770. (e) Burke, S. D.; Quinn, K. J.; Chen, V. J. *J. Org. Chem.* **1998**, *63*, 8626. (f) Burke, S. D.; Jung, K. W.; Lambert, W. T.; Phillips, J. R.; Klovning, J. J. *J. Org. Chem.* **2000**, *65*, 4070. (g) Austad, B. C.; Hart, A. C.; Burke, S. D. *Tetrahedron* **2002**, *58*, 2011. (h) Jiang, L.; Burke, S. D. *Org. Lett.* **2002**, *4*, 3411. (i) Lambert, W. T.; Burke, S. D. *Org. Lett.* **2003**, *5*, 515. (j) Jiang, L.; Martinelli, J. R.; Burke, S. D. *J. Org. Chem.* **2003**, *68*, 1150. (k) Keller, V. A.; Kim, I.; Burke, S. D. *Org. Lett.* **2005**, *7*, 737.

(8) (a) Horita, K.; Hachiya, S.; Nagasawa, M.; Hikota, M.; Yonemitsu, O. *Synlett* **1994**, 38. (b) Horita, K.; Nagasawa, M.; Hachiya, S.; Yonemitsu, O. *Synlett* **1994**, 40. (c) Horita, K.; Sakurai, Y.; Nagasawa, M.; Hachiya, S.; Yonemitsu, O. *Synlett* **1994**, 43. (d) Horita, K.; Sakurai, Y.; Nagasawa, M.; Maeno, K.; Hachiya, S.; Yonemitsu, O. *Synlett* **1994**, 46. (e) Horita, K.; Hachiya, S.-i.; Ogihara, K.; Yoshida, Y.; Nagasawa, M.; Yonemitsu, O. *Heterocycles* **1996**, *42*, 99. (f) Horita, K.; Nagasawa, M.; Hachiya, S.-i.; Sakurai, Y.; Yamazaki, T.; Uenishi, J.; Yonemitsu, O. *Tetrahedron Lett.* **1997**, *38*, 8965. (g) Horita, K.; Hachiya, S.-i.; Yamazaki, T.; Naitou, T.; Uenishi, J.; Yonemitsu, O. *Chem. Pharm. Bull.* **1997**, *45*, 1265. (h) Horita, K.; Sakurai, Y.; Nagasawa, M.; Yonemitsu, O. *Chem. Pharm. Bull.* **1997**, *45*, 1558. (i) Yonemitsu, O.; Yamazaki, T.; Uenishi, J.-i. *Heterocycles* **1998**, *49*, 89. (j) Horita, K.; Nagasawa, M.; Sakurai, Y.; Yonemitsu, O. *Chem. Pharm. Bull.* **1998**, *46*, 1199. (k) Horita, K.; Nishibe, S.; Yonemitsu, O. *Phytochem. Phytopharm.* **2000**, 386;

(9) 10. (a) Kim, S.; Salomon, R. G. *Tetrahedron Lett.* **1989**, *30*, 6279−6282. (b) Cooper, A. J.; Salomon, R. G. *Tetrahedron Lett.* **1990**, *31*, 3813. (c) DiFranco, E.; Ravikumar, V. T.; Salomon, R. G. *Tetrahedron Lett.* **1993**, *34*, 3247. (d) Cooper, A. J.; Pan, W.; Salomon, R. G. *Tetrahedron Lett.* **1993**, *34*, 8193.

(10) Readily obtained on a large scale from β-furylethanol by silylation with TBSCl (imidazole, DMF, rt) and then DoM (*n*-BuLi, THF) with DMF as electrophile. See: Kolb, H. C.; Hoffmann, H. M. R. *Tetrahedron* **1990**, *46*, 5127.

Scheme 2



conversion to intermediate pyranone hemiacetal **9** was observed. This crude hemiacetal was then immediately treated to Kishi reduction[13] with Et_3SiH in TFA−CH_2Cl_2[14] to produce the desired 2,6-*syn*-pyranone **10** in 86% yield over these two steps and with greater than 20:1 diastereoselectivity.[15] Careful removal of the TBS group with trifluoroacetic acid in wet CH_2Cl_2 at −37 °C was followed by tandem Jones oxidation and heteroconjugate addition of the acid to the enone to produce pyranolactone **11** in 63% overall yield from **10**. Installation of the final pyran stereocenter was achieved by reduction of the ketone with $NaBH_4$ to produce alcohol **12** (85%, dr ∼ 5:1). Basic hydrolysis of the lactone, followed by immediate conversion to the methyl ester with (trimethylsilyl)diazomethane (86%),[16] and finally silylation of the alcohols with TBSOTf, gave pyran **13** (91%; 78% yield from **12**). Hydroboration with 9-BBN and oxidation of the resulting primary alcohol with Dess−Martin periodinane produced the expected aldehyde (82% over two steps), completing the synthesis of the targeted pyranone **5**.

Our synthesis of the C27−C38 domain **6** also began with a Brown crotylation of furfural **7**—in this case, use of the (−)-$(Ipc)_2$-(*Z*)-crotylborane gave **14** in 75% yield (Scheme 2). Achmatowicz oxidation using $VO(acac)_2$ and *tert*-butyl hydroperoxide gave the expected intermediate pyranone **15**, which was immediately subjected to reduction with Et_3SiH in the presence of TFA to produce pyranone **16** in 90% yield for the two steps. As was the case with the sequence described above, careful removal of the TBS group with trifluoroacetic acid in wet CH_2Cl_2 at −37 °C was followed by tandem Jones oxidation and heteroconjugate addition of the acid to the enone to yield pyranolactone **17 (**63% overall from **16)**. Reduction of the pyranone to the alcohol with $NaBH_4$ yielded **18** (80%, dr 5:1) and was followed by reduction of the lactone to the diol with $LiBH_4$ in THF and subsequent silylation with TBSOTf to produce alkene **19** in 75% yield (two steps). Careful ozonolysis of the olefin to gave aldehyde **20** (95%), and set the stage for the introduction of the remaining carbons required for the C27−C38 subunit. Following Kishi's lead,[5c] Nozaki−Hiyama−Kishi reaction of this aldehyde with methyl *trans*-3-iodoacrylate gave **21** in 85% yield (dr 2:1).[17] Protection of the alcohol as the PMB ether, removal of TBS ethers, and conversion to the isopropylidene acetal was achieved in 80% yield (**21** → **22**) by a three-step sequence consisting of (1) $PMBOC(=NH)CCl_3$, $BF_3{\cdot}OEt_2$, (2) HF·pyridine, and (3) 2,2-dimethoxypropane, cat. PPTS. Finally, when **22** was treated with TBAF, heteroconjugate addition proceeded as expected to give the pyranopyran **6** in 80% yield and in greater than 20:1 diastereoselectivity.

(11) For reviews of the use of the Achmatowicz reaction in the synthesis of oxygen-containing heterocycles, see: (a) Georgiadis, M. P.; Albizati, K. F.; Georgiadis, T. M. *Org. Prep. Proced. Int.* **1992**, *24*, 95. (b) Harris, J. M.; Li, M.; Scott, J. G.; O'Doherty, G. *Strategies Tactics Org. Synth.* **2004**, *5*, 221.

(12) Ho, T. −L.; Sapp, S. G. *Synth. Commun.* **1983**, *13*, 267.

(13) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.

(14) For the initial use of TFA in Kishi reductions, see: Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Chem. Soc., Chem. Commun.* **1986**, *21*, 1568.

(15) To the best of our knowledge, highly diastereoselective reductions of simple pyranones of this type are without precedent. Studies to elucidate the underlying source of the remarkable diastereoselectivity of the Kishi reduction are ongoing and will be reported in due course.

(16) (a) Seyferth, D.; Menzel, H.; Dow, A. W.; Flood, T. C. *J. Am. Chem. Soc.* **1968**, *90*, 1080. (b) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475. (c) For a detailed mechanism, see: Kühnel, E.; Laffan, D. D. P.; Lloyd-Jones, G. C.; Martínez del Campo, T.; Shepperson, I. R.; Slaughter, J. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7075.

(17) Recent advancements from the Kishi laboratory include the ability to perform this reaction in the presence of chiral sulfonamide ligands. Reported diastereoselectivties for substrates similar to **20** are on the order of 12:1−15:1. See: Namba, K.; Kishi, Y. *Org. Lett.* **2004**, *6*, 5031.

In summary, we have described concise routes to two key pyranopyran subunits of norhalichondrin B. The synthesis of the C44−C53 domain **5** proceeds in 12 steps from commercially available β-furylethanol, and the synthesis of the C27−C38 domain **6** proceeds in 16 steps from the same starting material. A key feature of the synthesis is the application of an Achmatowicz oxidation followed by oxacarbenium ion reduction for the synthesis of syn-2,6-substituted pyranones. Efforts toward the integration of this chemistry into a synthesis of norhalichondrin B are ongoing and will be reported in due course.

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Supporting Information Available: Procedures for the synthesis of all new compounds, along with characterization data and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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