Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 2939–2941
Tetrahedron Letters

A synthesis of the C1–C15 domain of the halichondrins

Katrina L. Jackson, James A. Henderson, Jonathan C. Morris [†], Hajime Motoyoshi, Andrew J. Phillips [*]

Department of Chemistry and Biochemistry, University of Colorado, Boulder, CO 80309-0215, USA

Received 29 December 2007; accepted 5 March 2008
Available online 8 March 2008

Abstract

A concise route to the C1–C15 domain of the halichondrins is described. The key reaction is the conversion of a furfuryl alcohol to a pyranone. The stereocenter of this pyranone serves as the starting point for the other eight stereocenters.

In the context of the development of new reactions and strategies, the halichondrin class of marine macrolides[1] has provided a substantial amount of inspiration to the synthesis community.[2,3] The gross structures of these molecules, as exemplified by halichondrin B (**1**, Fig. 1), are characterized by a 2,6,9-trioxatricyclo[3.3.2.0^{3,7}]decane ring system embedded within a 31-membered lactone, and the presence of a number of polyoxygenated pyranopyrans and furopyrans.

We recently initiated studies directed toward the development of a total synthesis of the halichondrins,[4] and in this Letter we describe a concise synthesis of the C1–C15

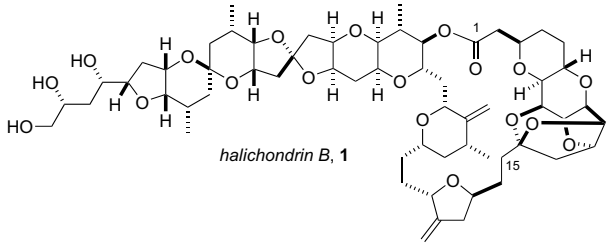


Fig. 1. Halichondrin B.

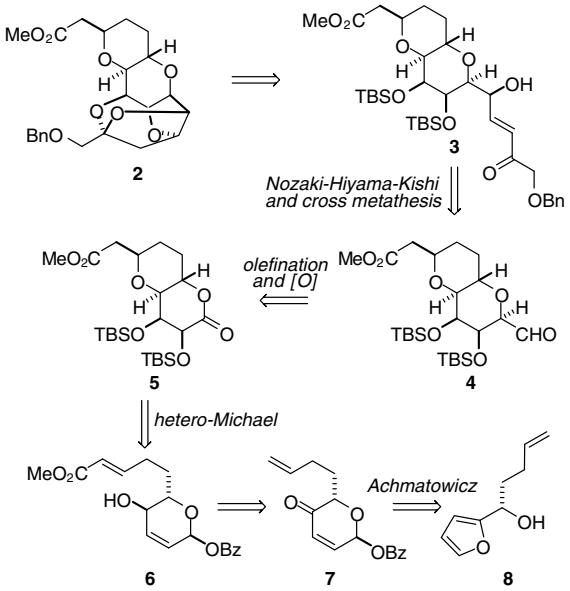


Fig. 2. Overall synthesis plan for C1–C15.

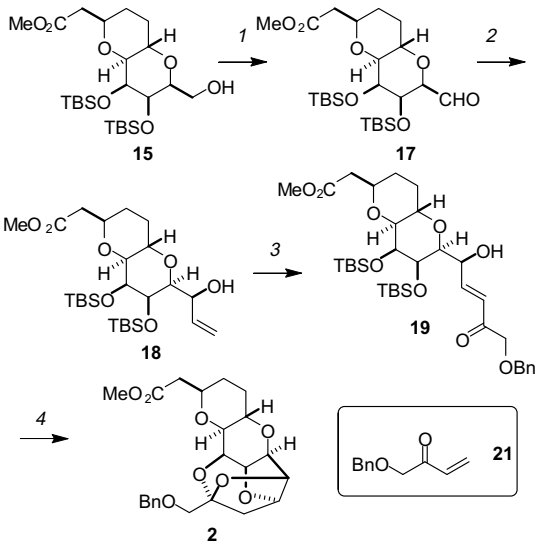
domain of the halichondrins. An overview of the retrosynthesis of the C1–C15 subunit, **2**, is presented in Figure 2. As can be seen, these plans are predicated on the use of the Achmatowicz oxidation for the conversion of a furfuryl alcohol to a pyranone (e.g., **8**→**7**), which would serve as a template for the synthesis of the fully functionalized C1–C11 pyranopyran, **4**.

* Corresponding author. Tel.: +1 303 735 2049; fax: +1 303 492 0439.
E-mail address: Andrew.Phillips@colorado.edu (A. J. Phillips).
† School of Chemistry and Physics, The University of Adelaide, Australia 5005.

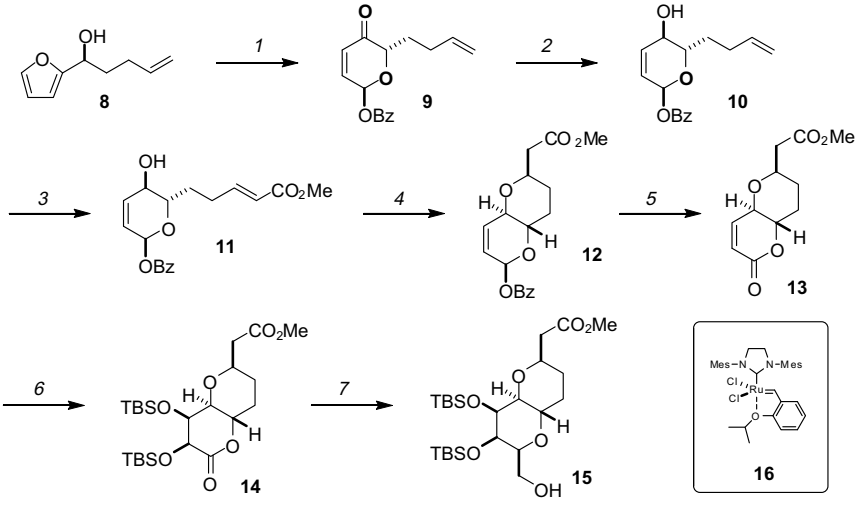
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.03.018

The departure point for our venture was known alcohol **8**[5,6] (Scheme 1), which was subjected to Achmatowicz oxidation[7,8] with *tert*-butylhydroperoxide as an oxidant and $VO(acac)_2$ as a catalyst to produce an intermediate pyranone hemiacetal in 83% yield. This pyranone hemiacetal was immediately subjected to O'Doherty's benzoylation conditions[9] to yield **9** (50%). The reduction of ketone **9** with $NaBH_4$ gave alcohol **10** in 92% yield. Cross metathesis with methyl acrylate using 5 mol % of the Hoveyda-Blechert catalyst in CH_2Cl_2 produced enoate **11** (82%), which was readily cyclized to pyranopyran **12** in 70% yield upon exposure to TBAF in THF. The subsequent Grieco oxidation[10] of **12** with *m*-CPBA in the presence of $BF_3{\cdot}OEt_2$ produced lactone **13** (85%). Dihydroxylation with catalytic OsO_4 and NMO produced a very water-soluble diol that was immediately subjected to TBSOTf in the presence of 2,6-lutidine to give bis-TBS ether **14** in 58% yield over the two steps. At this juncture, we were able to exercise a selective olefination of the lactone carbonyl group using the Petasis reagent[11] in 71% yield, and the enol ether was subjected to hydroboration with $BH_3{\cdot}THF$ and subsequent oxidation with basic H_2O_2 to give the desired alcohol **15** in 48% yield. The assignment of the stereochemistry of this compound proved problematic, primarily due to the compression of $^3J_{H,H}$ coupling constants. Ultimately, in order to unequivocally determine the stereochemistry we resorted to the preparation of an authentic sample of this compound using Kishi's reported route.[12] The comparison of the material obtained by that route, and the material prepared by the route described in Scheme 1 showed that they were identical.

With a route to alcohol **15** secured, we were able to evaluate the utility of cross metathesis for the introduction of the enone required for the formation of the 2,6,9-trioxatricyclo[3.3.2.0^{3,7}]decane ring system (Scheme 2). To this end, alcohol **15** was oxidized to aldehyde **17** (Dess–Martin periodinane, 99%). The introduction of a vinyl group was best achieved using vinyl iodide under Nozaki–Hiyama–Kishi reaction conditions to give a 7:1 ratio of the desired product **18** to the undesired diastereoisomer in 85% combined yield. All other methods for the introduction of this group favored the chelation-controlled addition to produce the undesired diastereoisomer. The cross metathesis of **18** and **21** (10 equiv) to produce enone **19** was possible in 81% yield using 5 mol % of the Hoveyda–Blechert catalyst **16**[13] in toluene at 80 °C. Gratifyingly, when this enone was subjected to the aqueous HF conditions reported by Burke et al.,[14] global desilylation, followed by hetero-Michael



Scheme 2. Reagents and conditions: (1) Dess–Martin periodinane, CH_2Cl_2, 99%; (2) vinyl iodide, 1% $NiCl_2/CrCl_2$, THF, 40 °C, 85% (dr = 7:1); (3) 1-(benzyloxy)but-3-en-2-one (**21**), 5 mol % Hoveyda–Blechert catalyst **16**, PhMe, 80 °C, 81%; (4) (a) 48% aq HF, MeCN, 36% or (b) TBAF, AcOH, then ion-exchange column (see text), 90%.



Scheme 1. Reagents and conditions: (1) (a) $VO(acac)_2$, TBHP, CH_2Cl_2, 83%; (b) BzCl, Et_3N, DMAP, −78 °C, 50%; (2) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, CH_2Cl_2, MeOH, 92%; (3) methyl acrylate, 5 mol % Hoveyda–Blechert catalyst **16**, CH_2Cl_2, 82%; (4) TBAF, THF, 70%; (5) *m*-CPBA, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −10 °C to rt, 85%; (6) (a) OsO_4, NMO, *t*-BuOH–Me_2CO–H_2O; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 to 0 °C, 58% (2 steps); (7) (a) Cp_2TiMe_2, THF–PhMe, 65 °C, 2 days, 71%; (b) $BH_3{\cdot}THF$, THF, then H_2O_2–NaOH, 48%.

addition and acetalization gave the desired structure **X** in 36% yield.[15] This yield could be dramatically improved by the application of Kishi's recently reported non-aqueous desilylation workup protocol[16] followed by ketal formation using Kishi's ion-exchange column system.[17] Under these conditions, the desired compound was obtained in 90% yield.

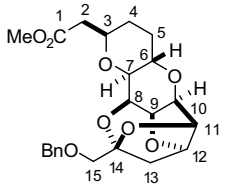
In summary, we have described a concise route to the C1–C15 domain of the halichondrins that is based on an Achmatowicz reaction of a furfuryl alcohol. This oxidation produces a pyranone that serves as the template for the remaining stereocenters. Further applications of this strategy and progress toward the synthesis of the halichondrins will be reported in due course.

Acknowledgments

We thank Eli Lilly and Company (via Lilly Grantee Program), the AP Sloan Foundation, and the National Cancer Institute (CA 110246) for support of this research. We thank Melissa Highfill for preliminary studies.

References and notes

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. 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.
3. For representative examples see the following papers and references cited therein: (a) Namba, K.; Jun, H.-S.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7770; (b) Keller, V. A.; Kim, I.; Burke, S. D. *Org. Lett.* **2005**, *7*, 737; (c) Horita, K.; Nishibe, S.; Yonemitsu, O. *Phytochem. Phytopharm.* **2000**, 386; (d) Cooper, A. J.; Pan, W.; Salomon, R. G. *Tetrahedron Lett.* **1993**, *34*, 8193.
4. Henderson, J. A.; Jackson, K. L.; Phillips, A. J. *Org. Lett.* **2007**, *9*, 5299.
5. Fürstner, A.; Nagano, T. *J. Am. Chem. Soc.* **2007**, *129*, 1906.
6. All new compounds were fully characterized by ^{1}H and ^{13}C NMR, HRMS and IR.
7. The oxidation of furans to butenolides has been known since the mid-1960s. See, for example: Ferland, J. M.; Lefebvre, Y.; Deghenghi, R.; Wiesner, K. *Tetrahedron Lett.* **1966**, 3617 and references cited therein.
8. For early examples of the Achmatowicz oxidation see: (a) Achmatowicz, O., Jr.; Bukowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, 1973; (b) Cavill, G. W.; Laing, D. G.; Williams, P. J. *Aust. J. Chem.* **1969**, 2145; (c) Lefebvre, Y. *Tetrahedron Lett.* **1972**, 133.
9. Harris, J. M.; Keranen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. *Carbohydr. Res.* **2000**, *328*, 17.
10. Grieco, P. A.; Oguri, T.; Yokoyama, Y. *Tetrahedron Lett.* **1978**, 419.
11. Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
12. Aicher, T. D.; Kishi, Y. *Tetrahedron Lett.* **1987**, *28*, 3463.
13. (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168; (b) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973.
14. Burke, S. D.; Jung, K. W.; Phillips, J. R.; Perri, R. E. *Tetrahedron Lett.* **1994**, *35*, 703.
15. The NMR data for the final compounds matched those reported by Burke et al. (coupling constants in Hz):



Position	Burke ^{1}H δ ($CDCl_3$)	Phillips ^{1}H δ ($CDCl_3$)
CO_2Me	3.61–3.66 (m)	3.64 (s, 3H)
2a	2.41 (dd, $J = 15.8$, 5.0)	2.41 (dd, $J = 15.8$ 5.1)
2b	2.49 (dd, $J = 15.8$, 8.1)	2.48 (dd, $J = 15.8$, 7.9)
3	3.81 (m)	3.80 (m)
4a	1.33 (m)	1.26–1.45 (m)
4b	1.73 (m)	1.73 (m)
5a	1.41 (m)	1.26–1.45 (m)
5b	2.04 (m)	2.02 (m)
6	4.25 (ddd, $J = 10.0$, 9.6, 4.4)	4.25 (m)
7	2.97 (dd, $J = 9.6$, 1.8)	2.97 (dd, $J = 9.6$, 1.8)
8	4.39 (dd, $J = 3.9$, 1.8)	4.39 (dd, $J = 3.6$, 1.7)
9	4.14 (dd, $J = 6.5$, 3.9)	4.13 (dd, $J = 6.6$, 3.8)
10	4.20 (dd, $J = 6.5$, 4.5)	4.20 (dd, $J = 6.6$, 4.5)
11	4.65 (dd, $J = 4.5$, 4.4)	4.64 (dd, $J = 4.5$, 4.4)
12	4.71 (dd, $J = 5.0$, 4.4)	4.71 (dd, $J = 4.8$, 4.6)
13	1.98 (d, $J = 13.4$)	1.97 (d, $J = 13.4$)
15a	3.61–3.66 (m)	3.60–3.67 (m)
15b	3.61–3.66 (m)	3.60–3.67 (m)
PhC*H*H	4.69 (d, $J = 12.2$)	4.69 (d, $J = 12.1$)
PhCH*H*	4.71 (dd, $J = 5.0$, 4.4)	4.71 (dd, $J = 4.8$, 4.6)
Ph	7.26–7.36 (m)	7.23–7.36 (m)

16. Kaburagi, Y.; Kishi, Y. *Org. Lett.* **2007**, *9*, 723.
17. See Ref. 3a.