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A synthesis of the C1–C15 domain of the halichondrins

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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 8 stereocenters.

In the context of the development of new reactions and strategies, the halichondrin class of marine macrolides¹ 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**; Figure 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 polyoxyegnated pyranopyrans and furopyranes.

We recently initiated studies directed toward the development of a total synthesis of the halichondrins,⁴ and in this paper we describe a concise synthesis of the 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 (eg **8**→**7**) which would serve as template for the synthesis of the fully functionalized C1–C11 pyranopyran, **4**.

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 oxidant and VO(acac)₂ as catalyst to produce an intermediate pyranone hemiacetal in 83% yield. This pyranone hemiacetal was immediately subjected to O'Doherty's benzylation conditions⁹ to yield **9** (50%). Reduction of ketone **9** with NaBH₄ gave alcohol **10** in 92% yield. Cross metathesis with methyl acrylate using 5 mol% of the Grubbs-Hoveyda catalyst in CH₂Cl₂ produced enoate **11** (82%), which was readily cyclized to pyranopyran **12** in 70% yield upon exposure to TBAF in THF. Subsequent Grieco oxidation¹⁰ of **12** with *m*-CPBA in the presence of BF₃•OEt₂ produced lactone **13** (85%). Dihydroxylation with catalytic OsO₄ 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 reagent¹¹ in 71% yield, and the enol ether was subjected to hydroboration with BH₃•THF and subsequent oxidation with basic H₂O₂ to give the desired alcohol **15** in 48% yield. 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

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stereochemistry we resorted to the preparation of an authentic sample of this compound using Kishi's reported route.¹² 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 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%). 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. 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 and coworkers,¹⁴ global desilylation, followed by hetero-Michael addition and acetalization gave the desired structure **X** in 36% yield.¹⁵ This yield could be dramatically improved by application of Kishi's recently reported non-aqueous desilylation workup protocol¹⁶ 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.

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Position	Burke ^1H δ (CDCl_3)	Phillips ^1H δ (CDCl_3)
CO ₂ Me	3.61–3.66 (m)	3.64 (s, 3H)
1a	2.41 (dd, $J=15.8, 5.0$)	2.41 (dd, $J=15.8, 5.1$)
2a	2.41 (dd, $J=15.8, 8.1$)	2.48 (dd, $J=15.8, 7.9$)
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)	1.25–1.45 (m)
4b	1.73 (m)	1.73 (m)
5a	1.41 (m)	1.25–1.45 (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, $J=6.6, 4.5$)

Position	Burke ^1H δ (CDCl_3)	Phillips ^1H δ (CDCl_3)
1	4.65 (dd, $J=4.5, 4.4$)	4.64 (dd, $J=4.5, 4.4$)
2	4.71 (dd, $J=5.0, 4.4$)	4.71 (dd, $J=4.8, 4.6$)
3	1.98 (d, $J=13.4$)	1.97 (d, $J=13.4$)
5a	3.61–3.66 (m)	3.60–3.67 (m)
5b	3.61–3.66 (m)	3.60–3.67 (m)
PhCH ₂	4.69 (d, $J=12.2$)	4.69 (d, $J=12.1$)
PhCH ₂	4.71 (dd, $J=5.0, 4.4$)	4.71 (dd, $J=4.8, 4.6$)
Ph	7.25–7.36 (m)	7.23–7.36 (m)

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17. See ref 3(a)

Figure 1.
Halichondrin B.

Figure 2.
Overall synthesis plan for C1–C14.

Scheme 1. Reagents and conditions

1. a) VO(acac)₂, TBHP, CH₂Cl₂, 83%; b) BzCl, Et₃N, DMAP, -78 °C, 50%; 2) NaBH₄, CeCl₃·7H₂O, CH₂Cl₂, MeOH, 92%; 3. methyl acrylate, 5 mol% Hoveyda-Blechert catalyst **16**, CH₂Cl₂, 82%; 4. TBAF, THF, 70%; 5. *m*-CPBA, BF₃·OEt₂, CH₂Cl₂, -10 °C to rt, 85%; 6. a) OsO₄, NMO, *t*-BuOH-Me₂CO-H₂O; b) TBSOTf, 2,6-lutidine, CH₂Cl₂, -78 to 0 °C, 58% (2 steps); 7. a) Cp₂TiMe₂, THF-PhMe, 65 °C, 2 days, 71%; b) BH₃·THF, THF, then H₂O₂-NaOH, 48%.

Scheme 2. Reagents and conditions

1. Dess-Martin periodinane, CH_2Cl_2 , 99%; 2. vinyl iodide, 1% $\text{NiCl}_2/\text{CrCl}_2$, THF, 40 °C, 85% (*d.r.* = 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%.