

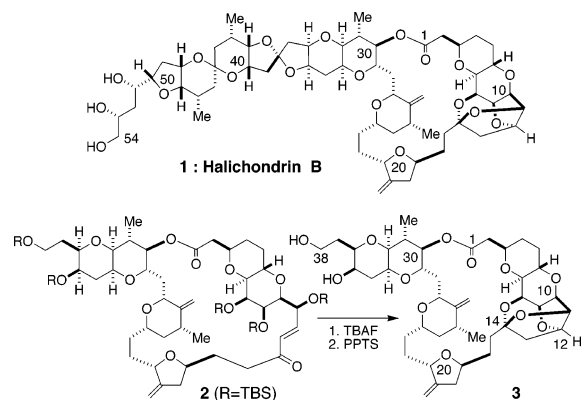
A Simple but Remarkably Effective Device for Forming the C8–C14 Polycyclic Ring System of Halichondrin B

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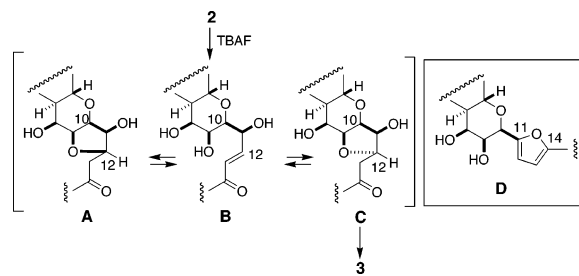
Halichondrins, the polyether macrolides originally isolated from the marine sponge *Halichondria okadai* by Hirata and Uemura, have received much attention due to their intriguing structural architecture and extraordinary in vitro and in vivo antitumor activity.^{1,2} With primary interest being focused on the demonstration of the unique potential the Ni/Cr-mediated coupling reaction offers,^{3,4} we have been engaged in synthetic work on this class of natural products,^{5,6} resulting in the first, and only, total synthesis of halichondrin B (**1**).^{5b}



In the original synthesis,^{5b} the C8–C14 polycyclic ring system was constructed from the enone **2** in two steps, (1) TBAF treatment to remove the TBS groups and promote the oxy-Michael addition to form the O–C12 bond and (2) PPTS treatment to form the ketal between the C14-ketone and the two alcohols at C8 and C11, to furnish a 5–6:1 mixture of the desired polycyclic ketal **3** and the undesired oxy-Michael adduct (cf. **A** in Scheme 1). The undesired oxy-Michael product was recycled, but it was operationally cumbersome; namely, it required the recycle consisting of three steps to be repeated: (1) chromatographic separation of the desired polycyclic ketal **3** and the undesired oxy-Michael adduct, (2) buffered TBAF treatment of the undesired oxy-Michael adduct, and (3) PPTS treatment. In this communication, we report a simple but remarkably effective solution for constructing this unique ring system.

Scheme 1 shows a simplistic picture of the chemistry involved in this transformation. Thus, if both oxy-Michael and retro-oxy-Michael reactions were promoted by an acid, we would expect that the desired polyketal **3** can be accumulated via the ketalization step, i.e., **C** → **3**. Unfortunately, we noticed that both **2** and **3** are not stable in the presence of mineral or Lewis acids, to yield the furan (cf. the partial structure **D** in Scheme 1). Fortunately, **3** was found to be stable in the presence of not only weak acids such as PPTS and AcOH but also quaternary ammonium bases such as Triton B, thereby suggesting a simple device that might allow us to transform **A–C** completely into **3** in a single operation. This device consists of two columns, each of which contains basic and acidic ion-exchange resins or their equivalents, and the substrates **A–C** are

Scheme 1



circulated through these columns. During the circulation, we anticipate that both the oxy-Michael reaction (**B** → **A** + **C**) and the retro-oxy-Michael reaction (**A** + **C** → **B**) are promoted at the surface of basic resins, whereas the ketalization (**C** → **3**) is promoted at the surface of acidic resins. It is important to note that, given sufficient time for the circulation, this device should allow us to convert all of the enone into the polycyclic ketal, regardless of equilibration degree established at each circulation or the stereo-selectivity in the initial oxy-Michael reaction.⁷

Using the crude mixture obtained by TBAF deprotection of **2**,^{5b,8} we first screened solid bases or equivalents for effecting the equilibration between the undesired and desired oxy-Michael products in MeOH, EtOH, *n*-PrOH, *i*-PrOH, THF, and dioxane.^{9,10} Among the basic reagents tested,¹¹ Amberlite IRA 400 (OMe form) was found to be most effective in promoting both oxy-Michael reaction (**B** → **A** + **C**) and retro-oxy-Michael reaction (**A** + **C** → **B**). On the other hand, an acidic ion-exchange resin Rexyn 101 was found to effect the ketalization, i.e., **C** → **3**, without noticeable furan formation (cf. **D**).¹²

With effective basic and acidic resins identified, we then assembled a simple device consisting of two ion-exchange columns, two alumina-based filters between the ion-exchange columns, and a pump (Figure 1). Without the alumina-based filters,¹³ the ion-exchange resins, particularly the basic ion-exchange resin, were found to be less effective. An EtOH solution of the crude mixture obtained by TBAF deprotection of **2**⁸ was placed in this device and circulated through the ion-exchange columns overnight, furnishing the virtually pure desired polycyclic ketal **3**. Trace (if any) amounts of the material(s) breached from the ion-exchange resins were removed by filtration through a silica gel plug, giving the desired product **3** in >95% yield with ≥98% purity.

The effectiveness of this device has been demonstrated for two additional substrates. The first substrate was the undesired oxy-Michael adduct **4** in the synthesis of ER-07639 (**5**).^{14,15} Satisfyingly, we have found that this device is equally effective for the transformation of **4** into **5** (ER-076349; >97% yield with ≥98% purity).

The second substrate tested was the enone **6**,^{5b,8} corresponding to the open form of **2**. For this substrate, the acidic ion-exchange

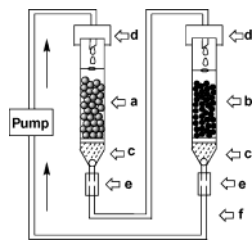
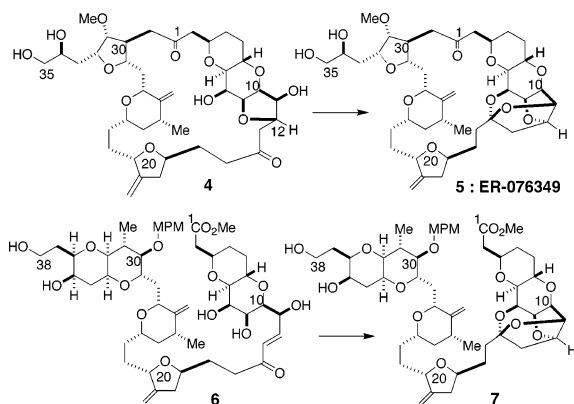


Figure 1. (a) Amberlite IRA 400 (OMe) column (diameter = 5 mm). (b) Rexyn 101 (H⁺) column (diameter = 5 mm). (c) Basic Al₂O₃ (Baker) filter (diameter = 5 mm) with glass wool dividers. (d) Septum. (e) Teflon connector tube. (f) Teflon tubing. Pump: FMI QG50. For a 40 mg-scale experiment, approximately 0.4 cm³ of Amberlite IRA 400, 0.4 cm³ of Rexyn 101, and 0.1 cm³ of alumina were placed in each column. The total volume of solvent was ca. 4 mL (*c* = ca. 0.01 M) and the flow-rate was ca. 2 mL per min.

resin in EtOH was found gradually to lose its effectiveness for the ketalization.⁹ However, when the solvent was changed from EtOH to *n*-PrOH, the ketalization smoothly progressed to completion. Thus, the overall transformation of **6** to **7** was once again realized in *n*-PrOH in >95% yield and ≥98% purity.¹⁶



In conclusion, a simple device has been assembled to form the polycyclic ring system present in the halichondrin B class of natural products. The assembly is based on well-recognized chemistry, but it is remarkably effective and efficient and has many appealing features, including its practicability. Although it is designed specifically for the halichondrin B synthesis, the reported assembly should be applicable, with necessary modification(s), to solve other synthetic problems.

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (7) In the case of **2** → **3**, the ratio of **3** and the undesired oxy-Michael adduct was 5–6:1. Assuming a complete equilibration established on each circulation, two and three cycles should boost the ratio up to 25–36:1 and 125–216:1, respectively.
- (8) ¹H NMR analysis showed that this crude mixture consisted of a ca. 3:1 mixture of the desired and undesired oxy-Michael products **C** and **A** but contained only a trace amount of the enone **B**.
- (9) For experimental convenience, this screening was done by a batch method and the equilibration was followed by ¹H NMR. It is worthwhile noting that the batch method was effective for the overall transformations of **2** → **3**, **4** → **5**, and **6** → **7** for preparative purposes. For example, the transformation of **2** → **3** was effected in ≥95% completion by repeating three times the procedure of (1) **2** in a flask/Amberlite IRA 400 (OMe)/EtOH/rt/overnight, (2) the EtOH solution transferred into a separate flask, and (3) Rexyn 101/EtOH/rt/3 h.
- (10) Among solvents tested, EtOH, *n*-PrOH, *i*-PrOH, EtOH-THF, and THF were found to be usable for the transformation of **2** → **3** and **6** → **7**. However, the lifetimes of the ion-exchange resins were shorter in THF than in EtOH, *n*-PrOH, or *i*-PrOH, i.e., the ion-exchange resins in EtOH and *n*-PrOH can be reused several times. In addition, only a trace (if any) amount of the material(s) breached out from the ion-exchange resins in EtOH, *n*-PrOH, or *i*-PrOH, whereas a more significant amount (ca. 3 mg) breached out in THF.
- (11) These included Amberlite IRA 400 (OH and OR), Amberlyst A-26 (OH), Scavenge Pore (OH), and TBAF absorbed on Al₂O₃. Among them, TBAF absorbed on Al₂O₃ was found to be effective. However, a significant amount of TBAF breached out.
- (12) Interestingly, Dowex 40Wx4 promoted both the processes but also the furan formation.
- (13) These included glass wool, Celite, Florisil, 3 Å molecular sieves, MgSO₄, Na₂SO₄, K₂CO₃, and silica gel. Among them, Florisil and silica gel were partially effective, but the reaction stopped at around 50% conversion. In this connection, it is worthwhile noting that, recognizing that acidic and basic ion-exchange resins can coexist, we tested the possibility of using both resins in a single flask but without much success.
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- (15) We thank Drs. Brian Austad and Frank Fang at Eisai Research Institute for a generous gift of **4**.
- (16) Structure of **7** was established by its conversion into **3** in five steps [(1) TBSCl/imidazole/DMF for the selective protection of the C38–OH alcohol, (2) DDQ, (3) aq LiOH, (4) Yamaguchi macrolactonization, (5) TBAF].

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