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Second Generation Synthesis of C27-C35 Building Block of E7389, A Synthetic Halichondrin Analog

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Abstract

A practical method is reported to synthesize E7389 C27-C35 building block (13) from 1,2-*O*-isopropylidene-α-D-5-deoxyglucurono-6,3-lactone (3). This synthesis relies on two key processes: (1) C34/C35-diol is introduced via asymmetric dihydroxylation with *dr* = 3:1, with the undesired C34-diastereomer effectively removed by crystallization of 11 and (2) C30 PhSO₂CH₂-group is introduced stereoselectively (>100:1) via hydrogenation of 12 in the presence of the Crabtree catalyst. The reported synthesis is practically free from chromatographic separation.

Halichondrins are polyether macrolides, originally isolated from the marine sponge *Halichondria okadai* by Hirata and Uemura, which have received much attention due to their intriguing structure and extraordinary *in vitro* and *in vivo* antitumor activity.¹ On completion of the total synthesis of halichondrin B, norhalichondrin B, and homohalichondrin B,^{2,3} we asked the late Dr. Suffness at the National Cancer Institute (NCI) and Dr. Littlefield at Eisai Research Institute (ERI) to test the *in vitro* and *in vivo* antitumor activities of the totally synthetic halichondrins as well as several synthetic intermediates. The results were sensational; their experiments clearly demonstrated that the antitumor activity of halichondrin B resides in the right portion of the molecule. With this crucial information,⁴ a massive drug discovery effort was undertaken by ERI, resulting in two exceptional drug candidates, one (E7389) of which is currently at the late stage of Phase III clinical trial.⁵ This is exciting news for us, partly because we have been involved in the chemistry of halichondrins from its infancy, but largely because we believe in the potential that the halichondrins offer to cancer chemotherapy. However, we should point out that, to our best knowledge, the structural complexity of the right half of halichondrin B, or E7389, exceeds by far the structural complexity of synthetic drugs on the market and/or synthetic drug candidates under development. Thus, an economically feasible synthesis of the right half of halichondrin B and/or Eisai's drug candidate will play the key role for ultimate success of this program. With this analysis in mind, we have

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Supporting Information Available. Experimental details and analytical data (38 pages). This material is available free of charge via the Internet at <http://pubs.acs.org>

continued the synthetic studies on the halichondrins.⁶ In this letter we report a second-generation synthesis of the E7389 C27-C35 building block, which has several appealing features, including overall efficiency, operational simplicity, and scalability.

In the first generation synthesis of E7389 C27-C35 building block, we chose 1,2-*O*-isopropylidene- α -D-5-deoxyglucurono-6,3-lactone (**3**) as the starting material.^{2c} This synthesis relies on two key processes (Scheme 1). First, the C34/C35-diol was incorporated via catalytic asymmetric dihydroxylation. Asymmetric dihydroxylation of terminal olefins is known to often proceed with relatively low asymmetric induction; for the case of **5**, asymmetric dihydroxylation was best achieved with Sharpless (DHQ)₂PYR, to yield a 3:1 mixture of the C34 diastereomers.^{7, 8} Fortunately, the undesired C34-diastereomer was effectively removed by crystallization of **6**. Second, the C30 stereocenter was stereospecifically introduced via NaBH(OAc)₃-reduction under the influence of the C31 hydroxyl group, cf., **7** $\rightarrow$ **8**.⁹ For this reason, the synthesis was carried out with the C31 hydroxyl group protected as a benzyl ether.

Although lengthy, the first generation synthesis has attractive features, including the high overall yield and only one required chromatographic purification. In this letter, we report two major modifications that make this synthesis even more practical.

As outlined in Scheme 1, we utilized the C31-hydroxyl group to stereoselectively reduce the α,β -unsaturated phenylsulfone. In principle, either the C27- or C34-hydroxyl group could serve the same purpose, but a molecular model analysis suggested that the C27-hydroxyl group might give a better chance of success. If successful, we could eliminate two steps required for the temporary protection/deprotection of the C31-hydroxyl group (Scheme 1). Then, our concern was how effectively the desired C34-diastereomer could be isolated after the asymmetric dihydroxylation. We made a primitive, and wishful, assumption that, because of their structure similarity, **C** and **D** (Scheme 2) might exhibit the chemical property parallel to that of **6** and its C34-diastereomer (Scheme 1), respectively, thereby allowing us to isolate the desired C34 diastereomer **C** effectively by simple crystallization.

The synthesis began with 1,2-*O*-isopropylidene- α -D-5-deoxyglucurono-6,3-lactone (**3**). Following the previous route, except the *O*-methylation step, **3** was uneventfully converted to **9** in 3 steps. As with the benzyl series, catalytic asymmetric dihydroxylation of **9** was best achieved with Sharpless (DHQ)₂PYR,¹⁰ to give a 3:1 mixture of the C34 diastereomers, which was directly subjected to benzylation and then *C*-allylation. It should be noted that this *C*-allylation is closely related to an example reported in the literature¹¹ and that, under the specified condition, the α - and β -selectivity was estimated to be at least 60:1 (¹H NMR).

Once again, we were delighted to observe that the α -*C*-allylated product **11** derived from the desired, major product formed in the dihydroxylation exhibited an excellent crystallinity, whereas the α -*C*-allylated product derived from the undesired, minor product remained as oil. This remarkable difference in chemical property allowed us to isolate stereochemically homogeneous **11** (mp 112–113 °C; colorless needles) by simple crystallization in >55% overall yield from **3**. The ¹H NMR spectra included in Supporting Information illustrate the exceptional effectiveness to isolate **11**.¹² Although the major part of new synthesis is very similar to the first generation of synthesis, we should note that it has several appealing features, including the overall yield and operational simplicity.^{13,14} We routinely carried out the synthesis of **11** from **3** in a 20 g scale without chromatographic purification, except for filtration through a silica gel pad (1~2 times of the substrate weight).

In order to test the assumption mentioned above, single crystals of **6** and **11** were grown and subjected to X-ray analysis, thereby revealing that their crystal packing is very different from each other (Figure 2). After all, the wishful notion was simply premature and incorrect.

Dess-Martin oxidation¹⁵ of **11**, followed by Horner-Emmons reaction with $\text{PhSO}_2\text{CH}_2\text{P}(\text{O})(\text{OEt})_2/\text{LiHMDS}$ in toluene,^{2c} furnished the corresponding α,β -unsaturated phenylsulfone as a 30:1 mixture of the *Z/E*-isomers (Scheme 4). There are two potentially enolizable sites in the ketone and α,β -unsaturated phenylsulfone, but no epimerized product was detected in this transformation. The terminal olefin was selectively cleaved, followed by reduction, to furnish the primary alcohol **12** as a 30:1 *Z/E*-mixture.

We planned to use the C27-hydroxyl group to reduce the α,β -unsaturated phenylsulfone from the concave face, based on literature precedent reported by Stork and Kahne.¹⁶ Indeed, hydrogenation of **12** in the presence of Crabtree catalyst **E**¹⁷ (Scheme 5) in methylene chloride at 0 °C smoothly proceeded, to furnish the C27-C35 building block **13** in 95% yield with a >100:1 stereoselectivity (¹H NMR). The C30 stereochemistry of **13** was assigned first by nOe studies and later confirmed by X-ray analysis of its 3,5-dinitrobenzoate. We should note that, if needed, the protecting group of **13** can be easily adjusted in 2 steps, cf., **13** → **14**.¹⁸

It is noteworthy that Crabtree catalyst **E** exhibited a high tolerance against the functional groups present in the current system. For example, both *Z*- and *E*-geometric isomers of **12** were smoothly reduced, to furnish **13** with a >100:1 stereoselectivity (Scheme 5).¹⁴ α,β -Unsaturated phenylsulfones with C34/C35 bis-TBS were reduced well, to give the desired, expected product in a high stereoselectivity, cf., **15** → **16**. Similarly, the reduction of α,β -unsaturated esters gave the expected product in a high yield, cf., **17** → **18**.

In summary, a practical route has been developed to synthesize E7389 C27-C35 building block **13** from 1,2-*O*-isopropylidene- α -D-5-deoxyglucurono-6,3-lactone (**3**). This synthesis relies on two key processes: (1) the C34/C35-diol is introduced via asymmetric dihydroxylation with *dr* = 3:1, with the undesired C34-diastereomer effectively removed by crystallization of **11** and (2) the C30 PhSO_2CH_2 -group is introduced with a high stereoselectivity (>100:1) via the Stork-Kahne hydrogenation of **12** in the presence of Crabtree catalyst **E**. Except filtration through a silica gel pad (1~2 times of the substrate weight), this synthesis is practically free from chromatographic separation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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12. This crystallization was also effective to isolate the stereochemically homogeneous **11** from a 1:1 mixture of the C34 diastereomers obtained via osmylation with OsO₄/NMO (22% overall yield from **3**).
13. In the new synthesis, the overall yield of **3** → **13** was 45%, whereas that of **3** → the intermediate synthetically equivalent to **13** was 13% in the previous synthesis. The over 3-time improvement in overall yield was primarily attributed to: (1) higher overall yield from **3** to **11**, (2) elimination of the benzylation (90%)/debenzylation (75%) steps, (3) higher efficiency of the hydroxyl-directed reduction (*vide infra*).
14. The C31 BnO-deprotection required FeCl₃ or TMS-I under the carefully monitored conditions. In addition, *only* Z- α,β -unsaturated phenylsulfonthe was efficiently reduced under the hydroxyl-directed NaBH(OAc)₃ in the previous synthesis, whereas *both* Z- and E- α,β -unsaturated phenylsulfonthes were smoothly reduced in the new synthesis (*vide infra*).
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18. In the previous syntheses, we used **14** and **16** as the C27-C35 building block. However, our recent studies demonstrate that **13** is an ideal C27-C35 building block (reference 6).

Figure 1.
Structure of Halichondrin B and E7389, an analog of the right half of halichondrin B.

Compound 6 **Compound 11**

Figure 2.
X-ray structure of **6** and **11**. For their crystal-packing mode, see Supporting Information.

Scheme 1.

Two key processes used in the first generation synthesis of C27-C35 building block **4** from 1,2-*O*-isopropylidene- α -D-5-deoxyglucurono-6,3-lactone.^{2c}

Scheme 2.
Two key questions in the new synthesis.

Scheme 3.

Second generation synthesis of E7389 C27-C35 building block. Conditions: (a) 1. DIBAL/ CH_2Cl_2 (~100%) 2. $\text{Ph}_3\text{PCH}_2\text{Br}/n\text{-BuLi}/\text{THF}$ (91% with ~85% purity). 3. $\text{NaH}/\text{MeI}/(n\text{-Bu})_4\text{NI}/\text{DMF}$ (~100%). (b). 1. Sharpless asymmetric dihydroxylation, $(\text{DHQ})_2\text{PYR}/0^\circ\text{C}$. 2. $\text{BzCl}/(n\text{-Bu})_4\text{NCl}/\text{NaOH-H}_2\text{O}$ (99% for 2 steps) (c) 1. allyl-TMS/ $\text{Ti}(i\text{-PrO})\text{Cl}_3/\text{CH}_2\text{Cl}_2$ ($dr > 60:1$). 2. crystallization: 1st crop ($dr = 32:1$, 63% overall yield from **3**); recrystallization: 1st crop (opt. pure, 55% overall yield from **3**).

Scheme 4.

Second generation synthesis of the E7389 C27-C35 building block. Conditions: (a) 1. Dess-Martin periodinane/rt. 2. $\text{PhSO}_2\text{CH}_2\text{P}(\text{O})(\text{OEt})_2/\text{LiHMDS}/\text{toluene}/0\text{ }^\circ\text{C} \rightarrow \text{rt}$ (93% yield for 2 steps). 3. $\text{OsO}_4/\text{NMO}/\text{CH}_2\text{Cl}_2/\text{rt}$, followed by NaIO_4 treatment. 4. $\text{NaBH}_4/\text{EtOH}/0\text{ }^\circ\text{C}$ (94% yield for 2 steps). (b) $\text{H}_2/\text{Crabtree catalyst E}$ (Scheme 5; 12 mol%)/ $\text{CH}_2\text{Cl}_2/0\text{ }^\circ\text{C}$ (95%, $dr = >100:1$). (c) 1. $\text{K}_2\text{CO}_3/\text{MeOH}/\text{rt}$. 2. $\text{MeC}(\text{OMe})_2\text{Me}/\text{acetone}/p\text{-TsOH}/\text{rt}$ (90% yield for 2 steps).

Scheme 5.

Three substrates studied for the C27-hydroxyl group directed hydrogenation in the presence of Crabtree catalyst **E**.