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# Second Generation Synthesis of C27−C35 Building Block of E7389, a Synthetic Halichondrin Analogue

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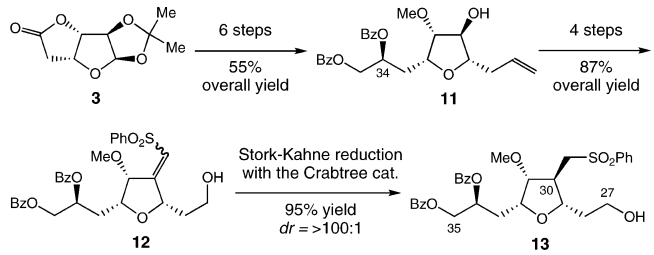
## ABSTRACT




**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) the C30 $PhSO_2CH_2$ 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

(1) For the isolation of the halichondrins from a marine sponge *Halichondria okadai* Kadota, see: (a) Uemura, D.; Takahashi, 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. For isolation of the halichondrins from different species of sponges, see: (c) Pettit, G. R.; Herald, C. L.; Boyd, M. R.; Leet, J. E.; Dufresne, C.; Doubek, D. L.; Schmidt, J. M.; Cerny, R. J.; Hooper, J. N. A.; Rützler, K. C. *J. Med. Chem.* **1991**, *34*, 3339. (d) 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. (e) Litaudon, M.; Hart, J. B.; Blunt, J. W.; Lake, R. J.; Munro, M. H. G. *Tetrahedron Lett.* **1994**, *35*, 9435. (f) 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. (g) Hickford, S. J. H.; Blunt, J. W.; Munro, M. H. G. *Bioorg. Med. Chem.* **2009**, *17*, 2199.

(2) For the synthetic work on the marine natural product halichondrins from this laboratory, see: (a) 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. (b) Stamos, D. P.; Chen, S. S.; Kishi, Y. *J. Org. Chem.* **1997**, *62*, 7552. (c) Choi, H.-W.; Demeke, D.; Kang, F. A.; Kishi, Y.; Nakajima, K.; Nowak, P.; Wan, Z.-K.; Xie, C. *Pure Appl. Chem.* **2003**, *75*, 1. (d) Namba, K.; Jun, H.-S.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7770. (e) Namba, K.; Kishi, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15382. (f) Kaburagi, Y.; Kishi, Y. *Org. Lett.* **2007**, *9*, 723. (g) Zhang, Z.; Huang, J.; Ma, B.; Kishi, Y. *Org. Lett.* **2008**, *10*, 3073. (h) Chen, C.-L.; Namba, K.; Kishi, Y. *Org. Lett.* **2009**, *11*, 409, and references cited therein.

(3) For synthetic work by Salomon, Burke, Yonemitsu, and Phillips, see: (a) Kim, S.; Salomon, R. G. *Tetrahedron Lett.* **1989**, *30*, 6279. Cooper, A. J.; Pan, W.; Salomon, R. G. *Tetrahedron Lett.* **1993**, *34*, 8193, and references cited therein. (b) Burke, S. D.; Buckanan, J. L.; Rovin, J. D. *Tetrahedron Lett.* **1991**, *32*, 3961. Lambert, W. R.; Hanson, G. H.; Benayoud, F.; Burke, S. D. *J. Org. Chem.* **2005**, *70*, 9382, and references cited therein. (c) Horita, K.; Hachiya, S.; Nagasawa, M.; Hikota, M.; Yonemitsu, O. *Synlett* **1994**, 38. Horita, K.; Nishibe, S.; Yonemitsu, O. *PhytochemPhytopharm.* **2000**, 386, and references cited therein. (d) Henderson, J. A.; Jackson, K. L.; Phillips, A. J. *Org. Lett.* **2007**, *9*, 5299. Jackson, K. L.; Henderson, J. A.; Motoyoshi, H.; Phillips, A. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2346, and references cited therein.

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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, Figure 1) of which is currently in

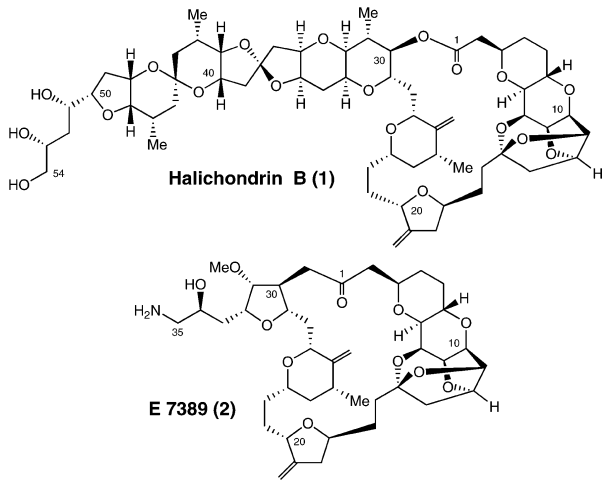
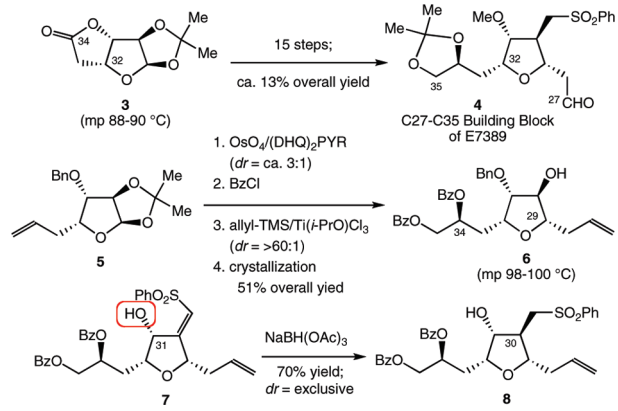



**Figure 1.** Structure of halichondrin B and E7389, an analogue of the right half of halichondrin B.

the late stage of phase III clinical trials.[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 the best of our 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 continued the synthetic studies on the halichondrins.[6] In this paper, 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-deoxy-glucurono-6,3-lactone (**3**) as the starting material.[2c] This synthesis relies on two key processes (Scheme 1). First, the

**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]




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** → **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 paper, 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

(4) Kishi, Y.; Fang, F. G.; Forsyth, C. J.; Scola, P. M.; Yoon, S. K. U.S. Patent 5338866 and International Patent WO93/17650.

(5) (a) Zheng, W.; Seletsky, B. M.; Palme, M. H.; Lydon, P. J.; Singer, L. A.; Chase, C. E.; Lemelin, C. A.; Shen, Y.; Davis, H.; Tremblay, L.; 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*, 5551. (b) Littlefield, B. A.; Palme, M. H.; Seletsky, B. M.; Towle, M. J.; Yu, M. J.; Zheng, W. U.S. Patents 6214865, 6365759, and International Patent WO99/65894. (c) 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, FL, 2005; pp 241−265. (d) E7389 website: http://www.drugs.com/nda/e7389_080201.html.

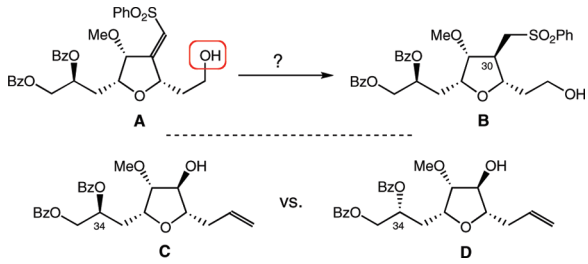
(6) One of the research focuses has been the development and application of catalytic asymmetric Cr-mediated coupling reactions. Recent results on this subject will be reported in separate papers.

(7) For a review on this subject, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(8) Asymmetric dihydroxylation of terminal olefins often suffers from a low degree of asymmetric induction. Replacement of the terminal olefin in **5** for the (*E*)-TMS-CH=CH− resulted in much-improved asymmetric induction (dr = 16:1) in the presence of $(DHQ)_2PYR$.

(9) For a review on substrate-directable chemical reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

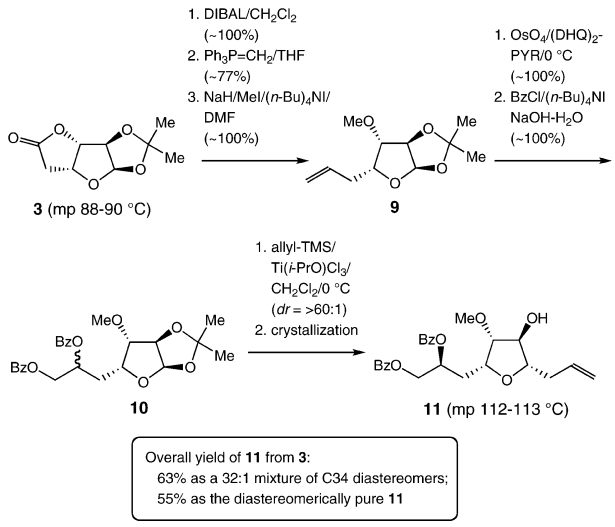
**Scheme 2.** Two Key Questions in the New Synthesis




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 three steps (Scheme 3). As with the benzyl

**Scheme 3.** Second-Generation Synthesis of E7389 C27−C35 Building Block




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 benzoylation and then *C*-allylation. It should be noted that this *C*-allylation is closely related to an example reported in the literature[11] and that, under the specified conditions, the α-/β-selectivity was estimated to be at least 60:1 ($^1$H 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 $^1$H NMR spectra included in Supporting Information illustrate the exceptional effectiveness to isolate **11**.[12] Although the major part of the 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** on a 20 g scale without chromatographic purification, except for filtration through a silica gel pad (one to two times 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.

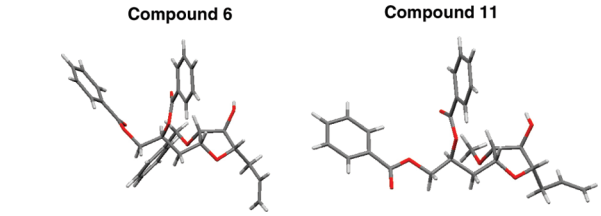



**Figure 2.** X-ray structures of **6** and **11**. For their crystal-packing mode, see the Supporting Information.

Dess−Martin oxidation[15] of **11**, followed by Horner−Emmons reaction with $PhSO_2CH_2P(O)(OEt)_2$/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

(10) (a) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (c) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1992**, *58*, 3785. (d) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 448.

(11) Garcia-Tellado, F.; Armas, P.; Marrero-Tellado, J. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2727.

(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 $OsO_4$/NMO (22% overall yield from **3**).

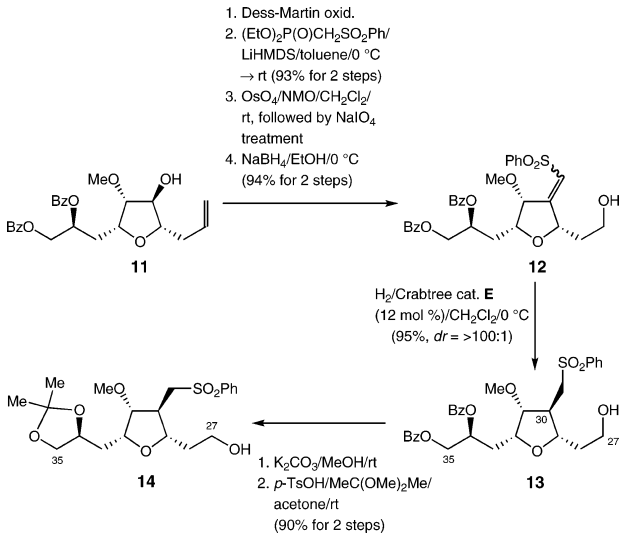
(13) In the new synthesis, the overall yield of **3** → **13** was 45%, whereas that of **3** → the intermediate synthetically equivalent to **13** was 13% in the previous synthesis. The over three-time improvement in overall yield is primarily attributed to (1) higher overall yield from **3** to **11**, (2) elimination of the benzylation (90%)/debenzylation (75%) steps, and (3) higher efficiency of the hydroxyl-directed reduction (vide infra).

(14) The C31 BnO-deprotection required $FeCl_3$ or TMS-I under the carefully monitored conditions. In addition, *only* (*Z*)-α,β-unsaturated phenylsulfone was efficiently reduced under the hydroxyl-directed $NaBH(OAc)_3$ in the previous synthesis, whereas *both* (*Z*)- and (*E*)-α,β-unsaturated phenylsulfones were smoothly reduced in the new synthesis (vide infra).

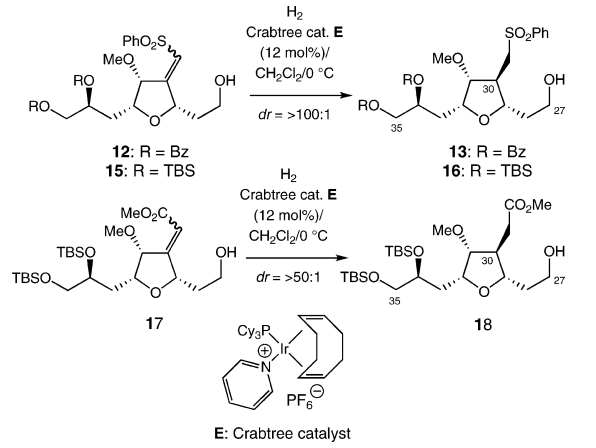
(15) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(16) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072.

**Scheme 4.** Second-Generation Synthesis of the E7389 C27−C35 Building Block




**Scheme 5.** Three Substrates Studied for the C27-Hydroxyl Group Directed Hydrogenation in the Presence of Crabtree Catalyst **E**




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 ($^1$H 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 two 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**.

(17) Crabtree, R. H.; Felkin, H.; Fellebeen-Khan, T.; Morris, G. E. *J. Organomet. Chem.* **1979**, *168*, 183.

(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 (ref 6).

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 high stereoselectivity (>100:1) via the Stork−Kahne hydrogenation of **12** in the presence of Crabtree catalyst **E**. Except for filtration through a silica gel pad (one to two times the substrate weight), this synthesis is practically free from chromatographic separation.

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**Supporting Information Available:** Experimental details and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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