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LETTERS

## A short synthesis of *trans*-(+)-laurediol

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### Abstract

A highly convergent and short synthesis of *trans*-(+)-laurediol is presented. The synthesis features a highly efficient construction of a *cis*-3-hydroxy- $\gamma$ -butyrolactone through a Sharpless AD reaction of a  $\beta,\gamma$ -unsaturated ester. © 2000 Elsevier Science Ltd. All rights reserved.

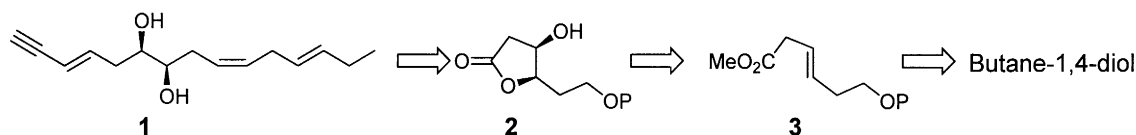
**Keywords:** marine metabolites; Sharpless asymmetric dihydroxylation reaction; asymmetric synthesis.

An important group of marine natural products named *lauroxanes* has been isolated from the red algae of the genus *Laurencia* and from the herbivorous opisthobranch molluscs that consume them.<sup>1</sup> These compounds are characterized by the presence in their structure of polysubstituted cyclic ethers of different sizes. Irie and co-workers reported the isolation from *Laurencia nipponica* Yamada of the enantiomers of (3*E*,9*Z*,12*E*)-pentadeca-3,9,12-trien-1-yne-6,7-diol (*trans*-laurediol) and (3*Z*,9*Z*,12*E*)-pentadeca-3,9,12-trien-1-yne-6,7-diol (*cis*-laurediol).<sup>2</sup> These compounds have been repeatedly proposed as biosynthetic precursors of *lauroxanes* by electrophilic cyclization.<sup>1</sup>

To the best of our knowledge, until now only two syntheses of laurediols have been reported. Masamune et al. accomplished a synthesis of **1** in 21 steps from (2*R*,3*R*)-(+)-tartaric acid.<sup>3</sup> Almost simultaneously, from our laboratory was published an enantioselective synthesis of both *cis*- and *trans*-laurediol in 28 steps from propargylic alcohol.<sup>4</sup> We have been focusing our attention on the synthesis of the above-mentioned cyclic compounds by intramolecular cyclization of hydroxyalkenes induced by a bromonium ion.<sup>5</sup> Prompted by the necessity of having a more efficient synthesis of **1**, we describe here a shorter and highly convergent synthesis of *trans*-laurediol (**1**) that permits us to scale up the preparation of the final products to perform cyclization studies. Our approach to **1** is based on the retrosynthetic analysis, Scheme 1, in which we disconnect to the  $\gamma$ -lactone **2** with the correct stereochemical requirements that could be fulfilled by an asymmetric dihydroxylation of **3**.<sup>6</sup>

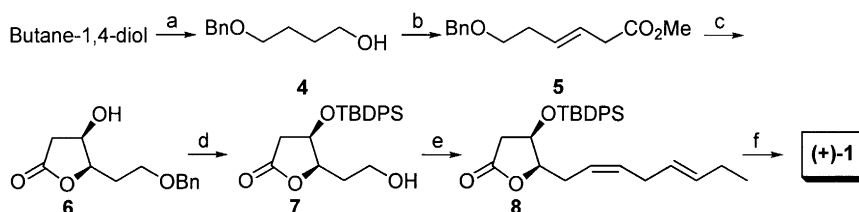
Selective monobenylation of commercially available butane-1,4-diol provided **4** that was oxidized to the corresponding aldehyde. Modified Knoevenagel condensation with malonic acid under nonpolar conditions<sup>7</sup> and further esterification provided the *E*-unsaturated- $\beta,\gamma$ -ester **5**. The application of the

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Scheme 1.

Sharpless asymmetric dihydroxylation reaction provided exclusively the disubstituted- $\gamma$ -lactone **6** (93% ee),<sup>8</sup> permitting us also to differentiate between the two hydroxy groups. Protection of the free secondary alcohol as a silyl ether and cleavage of the benzyl ether afforded the  $\gamma$ -lactone **7** (Scheme 2).



Scheme 2. (a) NaH, BnBr, *n*-Bu<sub>4</sub>NI (cat.), THF, 0°C, 3 h, 78%; (b) (i) SO<sub>3</sub>·Py, DMSO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 2 h, (ii) malonic acid, piperidine (cat.), xylene, reflux, 5 h, (iii) TMSCl, MeOH, rt, 2 h, 58% from **4**; (c) AD-mix- $\beta$ , CH<sub>3</sub>SO<sub>2</sub>NH<sub>2</sub>, *t*-BuOH: H<sub>2</sub>O (1:1), 0°C, 20 h, 90%; (d) (i) TBDPSCl, imidazole, CH<sub>2</sub>Cl<sub>2</sub>, rt, overnight, (ii) H<sub>2</sub>, 10% Pd-C/AcOEt, overnight, 93% from **6**; (e) (i) PCC, NaOAc, CH<sub>2</sub>Cl<sub>2</sub>, 4 Å MS, 2 h, (ii) (*E*)-EtCH=CHCH<sub>2</sub>CH<sub>2</sub>PPh<sub>3</sub><sup>+</sup>I<sup>-</sup>,<sup>9</sup> KN(TMS)<sub>2</sub>, THF, -78°C, 4 Å MS, 3 h, 36% from **7**; (f) (i) DIBAL-H (1 equiv.), Et<sub>2</sub>O, -78°C, 5 min, (ii) TMS≡CCH<sub>2</sub>PPh<sub>3</sub><sup>+</sup>Br<sup>-</sup>, KOBu-*t*, Et<sub>2</sub>O, 0°C to rt, 4 h, (iii) *n*-Bu<sub>4</sub>NF, THF, rt, 1 h, 78% from **8**

At this stage of the synthesis we were ready to homologate in both directions to build the carbon framework. Thus, oxidation of **7** produced an aldehyde that was converted to the corresponding (*Z*)-olefin **8** through a stereoselective Wittig reaction. For the completion of the synthesis, the  $\gamma$ -lactone was reduced with one equivalent of DIBAL-H, and the lactol submitted to Wittig-olefination with the ylide derived from commercially available [3-(trimethylsilyl)-2-propynyl]triphenylphosphonium bromide to yield the *trans*-enyne. Fluoride-induced cleavage of the silyl-protecting groups furnished (+)-*trans*-laurediol (**1**) [ $\alpha$ ]<sub>D</sub><sup>25</sup> +19.8 (*c* 1.2, CCl<sub>4</sub>).<sup>10</sup>

In summary, we have described a convergent and enantioselective short synthesis of (+)-*trans*-laurediol (**1**) with an 11% overall yield (12 steps), which will be useful for studies on biomimetic synthesis of *lauroxanes*. Although the presented methodology has been described only for one enantiomeric series, the alternative choice of the AD-mix in the Sharpless asymmetric dihydroxylation reaction for **5** permits us to control the absolute configuration in the final product.

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  10. [α] reported in the literature for (+)-*trans*-laurediol (Ref. 2) was 27.2, but no concentration data were provided.