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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-γ-butyrolactone through a Sharpless AD reaction of a β,γ-unsaturated ester.

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.[1] 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).[2] These compounds have been repeatedly proposed as biosynthetic precursors of *lauroxanes* by electrophilic cyclization.[1]

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.[3] Almost simultaneously, from our laboratory was published an enantioselective synthesis of both *cis*- and *trans*-laurediol in 28 steps from propargylic alcohol.[4] 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.[5] 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 γ-lactone **2** with the correct stereochemical requirements that could be fulfilled by an asymmetric dihydroxylation of **3**.[6]

Selective monobenzylation 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[7] and further esterification provided the *E*-unsaturated-β,γ-ester **5**. The application of the

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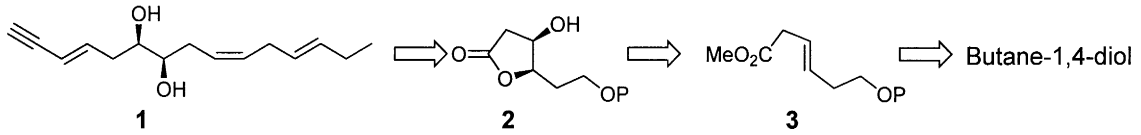
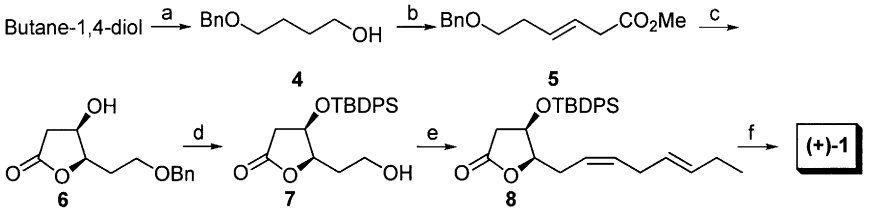


Scheme 1.

Sharpless asymmetric dihydroxylation reaction provided exclusively the disubstituted-γ-lactone **6** (93% ee),[8] 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 γ-lactone **7** (Scheme 2).



Scheme 2. (a) NaH, BnBr, *n*-Bu_4NI (cat.), THF, 0°C, 3 h, 78%; (b) (i) $SO_3 \cdot Py$, DMSO, Et_3N, CH_2Cl_2, 2 h, (ii) malonic acid, piperidine (cat.), xylene, reflux, 5 h, (iii) TMSCl, MeOH, rt, 2 h, 58% from **4**; (c) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH: H_2O (1:1), 0°C, 20 h, 90%; (d) (i) TBDPSCl, imidazole, CH_2Cl_2, rt, overnight, (ii) H_2, 10% Pd–C/AcOEt, overnight, 93% from **6**; (e) (i) PCC, NaOAc, CH_2Cl_2, 4 Å MS, 2 h, (ii) (*E*)-EtCH=$CHCH_2CH_2PPh_3^+I^-$,[9] KN$(TMS)_2$, THF, −78°C, 4 Å MS, 3 h, 36% from **7**; (f) (i) DIBAL-H (1 equiv.), Et_2O, −78°C, 5 min, (ii) TMSC≡$CCH_2PPh_3^+Br^-$, KOBu-*t*, Et_2O, 0°C to rt, 4 h, (iii) *n*-Bu_4NF, 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 γ-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**) $[\alpha]_D^{25}$ +19.8 (*c* 1.2, CCl_4).[10]

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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References

1. (a) Moore, R. E. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. 1, pp. 43–121. (b) Erickson, K. L. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1983; Vol. V, pp. 131–257. (c) Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251. (d) *Ibid* **1986**, *3*, 1. (e) *Ibid* **1987**, *4*, 539. (f) *Ibid* **1988**, *5*, 613. (g) *Ibid* **1990**,

7, 269. (h) *Ibid* **1991**, *8*, 97. (i) *Ibid* **1992**, *9*, 323. (j) *Ibid* **1993**, *10*, 497. (k) *Ibid* **1994**, *11*, 355. (l) *Ibid* **1995**, *12*, 223. (m) *Ibid* **1997**, *14*, 259. (n) *Ibid* **1998**, *15*, 113. (o) *Ibid* **1999**, *16*, 155.

2. Kurosawa, E.; Kukusawa, A.; Irie, T. *Tetrahedron Lett.* **1972**, 2121.
3. Fukusawa, A.; Sato, H.; Miyamoto, M.; Masamune, T. *Tetrahedron Lett.* **1986**, *27*, 2901.
4. Añorbe, B.; Martín, V. S.; Palazón, J. M.; Trujillo, J. M. *Tetrahedron Lett.* **1986**, *27*, 4991.
5. Martín, T.; Soler, M. A.; Betancort, J. M.; Martín, V. S. *J. Org. Chem.* **1997**, *62*, 1570.
6. (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483. (b) Harcken, C.; Brückner, R. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2750.
7. Ragoussis, N. *Tetrahedron Lett.* **1987**, *28*, 93.
8. The enantiomeric excess was determined by the ^{1}H NMR analysis of the corresponding (*R*)- and (*S*)-Mosher esters. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
9. The phosphonium salt was prepared by refluxing $(Ph)_3P$ and (3*E*)-$C_2H_5CH{=}CHCH_2CH_2I$ in CH_3CN. The iodide was synthesized from the commercially available alcohol [$(Ph)_3P$, imidazole, I_2, C_6H_6, rt].
10. [α] reported in the literature for (+)-*trans*-laurediol (Ref. 2) was 27.2, but no concentration data were provided.