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ENANTIOMERIC SYNTHESES OF 6(R), 7(R) AND 6(S), 7(S) trans- AND cis-LAUREDIOL

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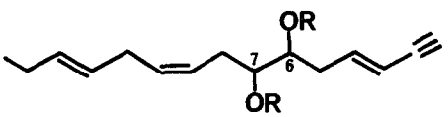
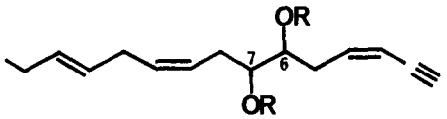
Abstract: The title compounds have been synthesized by using acetylenic coupling procedures, asymmetric epoxidation and stereo- and regio-selective openings of the epoxides.

From the red algae of the genus Laurencia have been isolated a wide variety of halogenated cyclic ethers characterized by a straight-chain C_{15} atom skeleton and a terminal enyne function[1]. Related compounds have also been found in Aplysia[1] probably having a dietary origin in Laurencia. Irie and his coworkers[2] reported the isolation from Laurencia nipponica Yamada of optical isomers with 6(S),7(S) and 6(R),7(R) configurations of 6,7-dihydroxy-3,12-trans-9-cis-pentadeca-3,9,12-trien-1-yne (trans-laurediol) (**1**,**2**) and 6,7-dihydroxy-3,9-cis-12-trans-pentadeca-3,9,12-trien-1-yne (cis-laurediol) (**3**,**4**) as well as their corresponding acetates (**5**-->**8**).



1, R=H, C_6-S, C_7-S
2, R=H, C_6-R, C_7-R
5, R=Ac, C_6-S, C_6-S
6, R=Ac, C_6-R, C_7-R

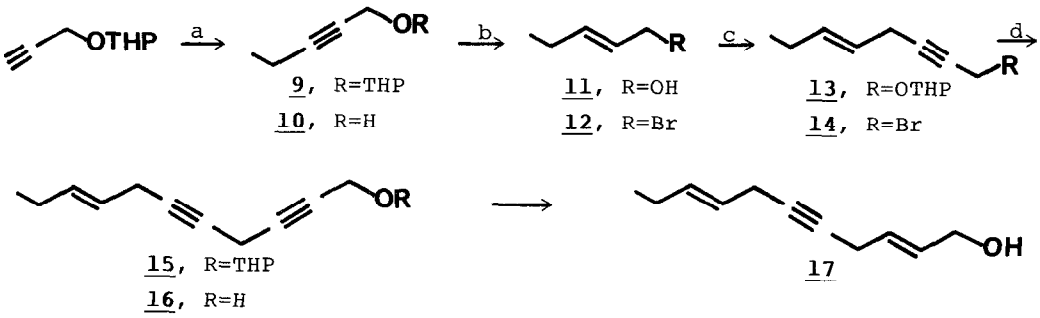


3, R=H, C_6-S, C_7-S
4, R=H, C_6-R, C_7-R
7, R=Ac, C_6-S, C_7-S
8, R=Ac, C_6-R, C_7-R

These compounds have been repeatedly proposed as biosynthetic precursors of the cyclic ethers[1] by electrophilic cyclization[2]. In this communication we report the total syntheses[3] of these metabolites in their enantiomeric natural form by a general methodology based on acetylenic coupling catalyzed by copper[4], asymmetric epoxidation[5] and regio- and stereo-selective openings of the epoxides[6].

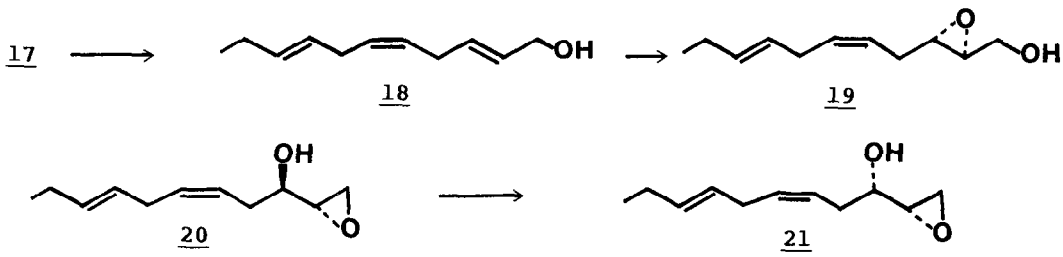
For the synthesis of **1** and its acetate **5** a dienynol **17** was prepared from ethyl bromide and propargyl-O-THP ether by acetylenic coupling catalyzed by copper (I) chloride[4] (Scheme **I**)[7].

17 was selectively hydrogenated using Lindlar's catalyst[8] in 87% yield and submitted to asymmetric epoxidation under the standard conditions[5],



Scheme I

$Ti(OPr^i)_4$, D-(+)-diethyl tartrate, tert-butyl hydroperoxide, CH_2Cl_2, -20°C, 20 hrs., giving the epoxyalcohol **19** in 82% yield with over 95% ee[9], $|\alpha|_D^{25}$ -10.2° (c 3.45, $CHCl_3$) (Scheme **II**).

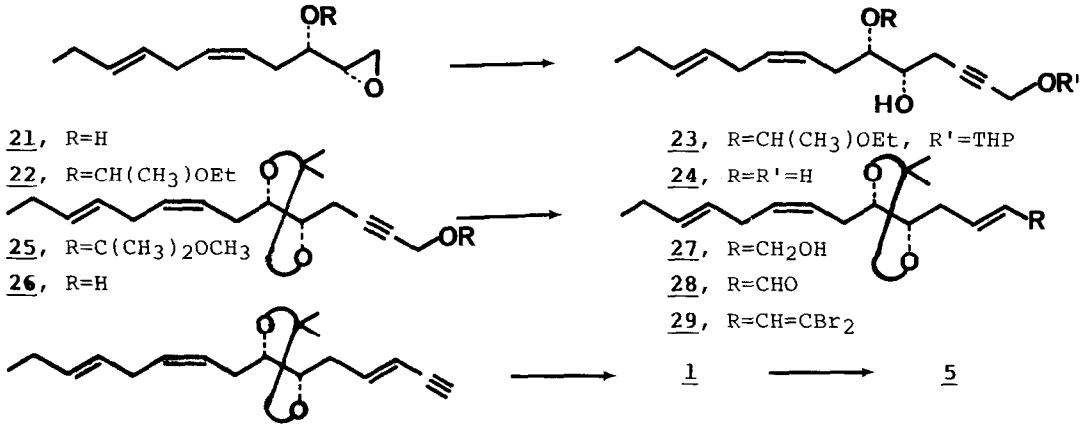


Scheme II

At this point of the synthesis, we need the isomerization of the 2,3- to the threo-1,2-epoxyalcohol to create the right configuration of the diol system by a carbon nucleophile attack to the terminal epoxide at the C-1 position. The described procedure[6] using titanium (IV) isopropoxide assisted opening of chiral 2,3-epoxyalcohols from E-allylic alcohols has proved to be an excellent way to obtain **21** in 65% yield from **19**. The threo-1,2-epoxide **21**, $|\alpha|_D^{25}$ -10.7° (c 2.09, ether), was protected with ethyl vinyl ether, in CH_2Cl_2, using pyridium p-toluenesulphonate as catalyst[10] and was treated with the lithium salt of propargyl-O-THP ether (1.5 equiv.) and $BF_3.OEt_2$[11] (1.5 equiv.) at -78°C for 0.5 hr. to give **23** in 73% yield (Scheme **III**).

The acidic deprotection of **23** in methanol, protection of **24** with 2-methoxypropene in CH_2Cl_2 and deprotection of some **25** formed with methanol and a catalytic amount of acetic acid yielded **26**, 85% yield, $|\alpha|_D^{25}$ -25.4° (c 1.65, $CHCl_3$). Reduction of the yne-function with lithium aluminum hydride[12] in THF at 0°C for 2 hrs. led to **27** in 93% yield $|\alpha|_D^{25}$-25.4° (c 1.65, $CHCl_3$). This compound was oxidised with excess of manganese dioxide in CH_2Cl_2 at room temperature and treated without purification with triphenyl phosphine (5.5 equiv.) and carbon tetrabromide (2.7 equiv.) at 0°C in CH_2Cl_2 for 2 hrs. to yield **29**, $|\alpha|_D^{25}$ -27.9° (c 2.40, $CHCl_3$), in 73% overall yield [13].

Treatment in ether for 10 min. with 2.1 equiv. of n-BuLi[14] gave **30** in 82% yield, $|\alpha|_D^{25}$-25.0° (c 1.32, $CHCl_3$).



Scheme III

The deprotection of **30** with methanol and a catalytic amount of p-toluenesulphonic acid gave **1**, $|\alpha|_D^{25}$ -14.7° (c 1.2, CCl_4) in 85% yield. Acetylation under standard conditions (Ac_2O, Py) gave the diacetate **5**, $|\alpha|_D^{25}$ +5.3° (c 0.7, $CHCl_3$) in 95% yield. According to the optical purity observed in the epoxide **25** these products must have more than 95% ee[14].

The syntheses of the geometrical isomer cis-laurediol **3**, $|\alpha|_D^{25}$ -9.3° (c 0.9, $CHCl_3$)[14] and its corresponding acetate **7**, $|\alpha|_D^{25}$ +3.5 ° (c 0.8, $CHCl_3$), were performed in a totally similar manner, but using Lindlar's hydrogenation of **26** to get the Z-olefin[15]. The syntheses of isomers **2**,**6** and **4**,**8** were carried out following a similar procedure but changing the isomer of the tartaric acid ester used at the asymmetric epoxidation step.

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References and notes:

1) a) Moore, R.E.; Algal Nonisoprenoids in Marine Natural Products, Ed. by P.J. Scheuer, N.Y., 1978, Vol I, 44-121.
b) Faulkner,D.J.; Natural Products Report, 1984, 1, 251-280.
2) Kurosawa, E.; Fukuzawa, A., Irie, T.; Tet. Lett., 1972, 21, 2121.
3) A total synthesis of 6(S), 7(S) trans-laurediol **1** has been recently reported: Fukuzawa, A.; Sato, H.; Miyamoto, M.; Masamune, T.; Tet. Lett., 1986, 27, 2901.
4) Taginachi, H.; Mathai, I.M.; Miller, S.I.; Org. Synth., 1970, 50, 97.
5) a) Katsuki, T.; Sharpless, K.B.; J. Am. Chem. Soc., 1980, 102, 5974.

b) Martín, V.S., Woodard, S.S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K.B.; J. Am. Chem. Soc., 1981, 103, 6237.

c) Hill, P.G.; Rossiter, B.E.; Sharpless, B.B.; J. Org. Chem., 1983, 48, 3603.

6) See the preceding paper.

7) a) i)n-BuLi, THF, HMPA, -78°C, 1 hr.; ii)EtBr, -78°C-->R.T., 14 hrs.; iii)HCl (conc.)(cat.), MeOH, R.T., 10 hrs., 92% overall yield; b) i)$LiAlH_4$, THF, reflux, 2 hrs. 87%; ii)Br_3P, pentane, 0°C, 0.5 hr., 78%; c) i)$BrMgC \equiv CCH_2OTHP$, THF, Cu_2Cl_2 (cat.), 0°C-->reflux, 4 hrs.; ii)$(C_6H_5)_3PBr^+Br^-$, CH_2Cl_2, R.T., 74%; d) $BrMgC \equiv CCH_2OTHP$, THF, Cu_2Cl_2 (cat.), Me_2S, 0°C-->reflux, 4 hrs., 83%; e) i)HCl (conc)(cat.), MeOH, R.T., 5 hrs.; ii)$LiAlH_4$, ether, R.T., 14 hrs., 81% overall yield.

8) **17** must be carefully purified in order to obtain a good rate in Lindlar's hydrogenation.

9) The optical purities of all the epoxides were checked by using NMR on the epoxyalcohol acetates with $Eu(hfbc)_3$ as chiral shift reagent and/or the Mosher's ester.

10) Any attempt to protect the hydroxy group under basic conditions gave a substantial amount of isomerization to the 2,3-epoxyalcohol.

11) Yamaguchi, M.; Hirao, I.; J. Chem. Soc. Chem. Comm., 1984, 202.

12) Magoon, E.F.; Slaugh, L.H.; Tetrahedron, 1967, 23, 4509.

13) Corey, E.J.; Lansburg, P.T.; Cashman, J.R.; Kantner, S.S.; J. Am. Chem. Soc., 1984, 106, 1501.

14) The reported optical rotation for 6(R), 7(R) trans-laurediol **2** obtained from laurencin by Zn-AcOH-EtOH treatment is $|\alpha|_D$ +27.2°. In a similar manner the value for 6(S), 7(S) cis-laurediol is $|\alpha|_D$ -19.5°. See Ref. 2.

15) Corey, E.J.; Ruden, R.A.; Tet. Lett., 1973, 1495. By this procedure a ratio of 1:1 of **30** and the cis isomer was reached. Both products were separated by column chromatography.

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