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Enantioselective synthesis of (–)-Bifurcadiol: a natural antitumor marine product

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Abstract

The enantioselective synthesis of natural antitumor (–)-Bifurcadiol involving an alkylation key-step reaction is reported.

Keywords: marine natural product; (–)-Bifurcadiol; alkylation; asymmetric reduction.

In the course of our investigations on the brown alga *Bifurcaria bifurcata*, we have recently isolated a new class of di-functionalized oxygenated linear diterpenes.[1] Numerous biological activities such as antiulcer, antimitotic or cytotoxic properties have been found among the linear diterpenes. *Bifurcaria bifurcata*, in particular, is a source of potent active compounds such as [12(*S*)-hydroxy-geranylgeraniol] ((–)-Bifurcadiol) exhibiting cytotoxicity against cultured human tumor cell lines (A549, SK-OV-3, SK-MEL-2, XF 498 and HCT 15).[2]

In this paper, we report the first enantioselective synthesis of (–)-Bifurcadiol **6** involving an alkylation key-step reaction between a cyanohydrin and an allyl bromide (Scheme 1).

trans trans Farnesol **1** was converted into the corresponding ether **2** by treatment with dihydropyran and subsequently oxidized using a mixture of pyridine, selenium dioxide and PDC to afford the expected aldehyde **3** in 34% yield.[4] Compound **3** was added to a solution of trimethylsilyl cyanide in the presence of a catalytic amount of sodium cyanide and 18-crown-6 ether complex to lead, after addition to a solution of $LiN(SiMe_3)_2$ in anhydrous THF (–78°C) and condensation with 1-bromo-3-methylbut-2-ene, to the silyl cyanide derivative **4**[5] (52% yield). Subsequent treatment with triethylamine trihydrofluoride salt afforded the expected ketone **5** in 70% yield.[6]

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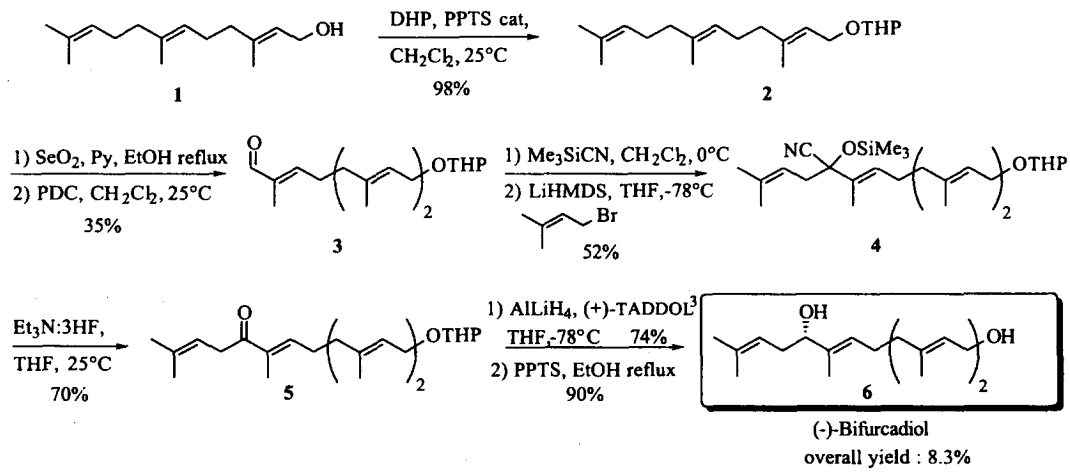

Scheme 1.

The synthesis of natural (−)-Bifurcadiol was achieved involving an asymmetric reduction of ketone **5**. In a first attempt, an enantioselective borane reduction using Corey's oxazaborolidine catalyst (prepared from (*S*)-(−)-(diphenylhydroxymethyl)pyrrolidine and methylboronic acid) has been performed.[7] Nevertheless, more than 95% of **5** has been recovered whatever the experimental conditions applied. The asymmetric reduction of **5** has been successfully realized using a stoichiometric $AlLiH_4$/(+)-TADDOL[3,8] mixture affording, after removal of the protective group, (−)-Bifurcadiol **6** in 66% yield and 92% enantiomeric excess as determined by chiral HPLC analysis and measurement of optical deviation on a sample of the natural and synthetic corresponding diacetate.[9] The same procedure has been applied using (−)-TADDOL[10] to prepare the nonnatural (+)-Bifurcadiol in 73% yield and up to 99% enantiomeric excess.

Further studies involving this general method for the preparation of new linear di-functionalized oxygenated diterpenes with a potent biological interest, are in progress.

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2. (a) ED_{50} values ranging from 4.1–8.3 μg mL^{-1}. See: Zee, O. P.; Kim, D. K.; Choi, S. U.; Lee, C. O.; Lee, K. R. *Arch. Pharmacal. Res.* **1999**, 22, 225–227.
3. The (+)-TADDOL used is the (4*S*,5*S*)-2,2-dimethyl-α,α,α′,α′-tetraphenyldioxolane-4,5-dimethanol.
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9. The enantiomeric excesses were determined using a Daicel Merck LichroCART column 250-4 (*S,S*) Whelk-O1, refractometric detector, using a mixture of 2-propanol:hexane (5:95, v/v), flow rate 0.5 mL min^{-1} and retention time of 10.2 min.
10. The (−)-TADDOL used is the (4*R*,5*R*)-2,2-dimethyl-α,α,α′,α′-tetraphenyldioxolane-4,5-dimethanol.