Stereoselective total synthesis of 4-((3S,5R)-3,5-dihydroxynonadecyl)phenol

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Abstract

A stereoselective total synthesis of 4-((3S,5R)-3,5-dihydroxynonadecyl)phenol has been accomplished in two different synthetic approaches. In the first approach, Prins cyclization has been successfully utilized to produce the anti-1,3-diol unit, which was further converted into a required syn-1,3-diol through Mitsunobu reaction. The side chain was constructed through cross metathesis and hydrogenation sequence. In the second approach, the chiral syn-1,3-diol was prepared by a sequence of reactions such as alkylation of 1,3-dithiane with \((R)\)-epichlorohydrin, ring opening of the epoxide with vinylmagnesium bromide, and 1,3-syn-reduction of the \(\beta\)-hydroxyketone with NaBH\(_4\) in the presence of diethylmethoxyborane.

The gingerols are known to exhibit potent antioxidant properties. They are also used in the traditional medicine as anti-inflammatory, antitumor and chemopreventive, bacteriostatic, and nematocida agents. Recently, a novel class of 4-((3S,5R)-3,5-dihydroxynonadecyl)phenol (1) was isolated from the resinous exudates of Chilean desert plants (Fig. 1). It also shows a promising anti-oxidant behavior. The absolute stereochemistry of (1) was determined by Gao and co-workers through its total synthesis.

Inspired by its fascinating structural features and biological activity, we attempted the total synthesis of (1) employing our own strategy to construct the 1,3-diol system. Following our interest on the total synthesis of biologically active natural products, we herein report the total synthesis of 4-((3S,5R)-3,5-dihydroxynonadecyl)phenol (1) in two different synthetic approaches (Scheme 1).

In the first strategy, we assumed that the target molecule (1) could be synthesized from syn-1,3-diol 2, which can be accessed from tetrahydropyranyl derivative 3. In our second strategy, the syn-1,3-diol 2 was proposed to be obtained from \(\beta\)-hydroxy ketone 0040-4039/$ - see front matter © 2014 Elsevier Ltd. All rights reserved.

http://dx.doi.org/10.1016/j.tetlet.2013.12.056

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Figure 1. Naturally occurring 4-((3S,5R)-3,5-dihydroxynonadecyl)phenol (1).

Scheme 1. Retrosynthetic analysis of 4-((3S,5R)-3,5-dihydroxynonadecyl)phenol (1).
6, which in turn could be prepared by alkylation of 1,3-dithiane 8 with (R)-epichlorhydrin 7 (Scheme 1).

According to our first strategy, the (S)-homoallyl alcohol 4\textsuperscript{a} was treated with p-methoxyhydrocinnamaldehyde 5\textsuperscript{a} in the presence of TFA in DCM. The resulting trifluoroacetate was then hydrolyzed with K\textsubscript{2}CO\textsubscript{3} in MeOH to afford the tetrahydropyranol 9,\textsuperscript{11} Tosylation of the primary alcohol of 9 with 1.1 equiv of tosyl chloride in the presence of TEA in DCM gave the corresponding tosylate 10. Mitsunobu inversion\textsuperscript{12} of the secondary hydroxyl group of 10 using DEAD, TPP, and p-nitrobenzoic acid in THF afforded the corresponding benzoate 3 in 94\% yield. Further treatment of 3 with NaI in refluxing acetone gave the corresponding iodide derivative, which was then subjected to reductive elimination using zinc metal in refluxing E\textsubscript{t}OH to furnish the homoallylic benzoate 11 in 85\% yield (over two steps). Cleavage of the benzoate 11 with K\textsubscript{2}CO\textsubscript{3} in methanol gave the required syn-1,3-diol 2\textsuperscript{b} in 92\% yield. Cross-metathesis of the terminal olefin 2 with a readily available tridec-1-ene, using Grubbs’ 2nd generation catalyst in DCM under reflux conditions afforded the olefinic derivative 12 in 85\% yield.\textsuperscript{14} Reduction of the olefin 12 using palladium on carbon on ethyl acetate under hydrogen atmosphere gave the saturated syn-1,3-diol 13 in 94\% yield. Finally, the demethylation of 13 using sodium hydride in the presence of ethanethiol and Al\textsubscript{2}Cl\textsubscript{3} in DCM afforded the target molecule (1) in 95\% yield (28\% overall yield) (Scheme 2). The spectral data of 4-((3S,5R)-3,5-dihydroxynonadecyl)phenol (1) are in good agreement with the reported values.\textsuperscript{15}

As per our second strategy, the readily available alcohol 14 was treated with 2-iodoxybenzoic acid (IBX) to give the corresponding aldehyde, which was then protected with 1,3-propanedithiol using a catalytic amount of boron trifluoride–diethyl ether at room temperature to furnish the 1,3-dithiane 8 in 90\% overall yield in two steps. Alkylation of the dithiane 8 with (R)-epichlorhydrin 7 using n-BuLi in THF at −78 °C gave the epoxy dithiane 15 in 80\% yield.\textsuperscript{16} Ring opening of the epoxide 15 with vinylmagnesium bromide in THF using a catalytic amount of CuCN gave the homoallylic alcohol 6 in 84\% yield. Removal of the dithiane group with CuCl\textsubscript{2}/CuO in aqueous acetone furnished the β-hydroxy ketone 16 in 82\% yield. Treatment of the β-hydroxy ketone 16 with NaN\textsubscript{3} in the presence of diethyl(methoxy)borane in THF/MEOH afforded the syn-1,3-diol 2 in 80\% yield (Scheme 3).\textsuperscript{17} The remaining transformations were similar to Scheme 2. The spectral data of the molecule (1) are in good agreement with the reported values.\textsuperscript{15}

In conclusion, we have demonstrated a stereoselective total synthesis of 4-((3S,5R)-3,5-dihydroxynonadecyl)phenol (1) employing two alternative strategies. The first route involves Prins cyclization as a key step affording the desired molecule in 28\% overall yield whereas the second strategy involves mainly 1,3-syn reduction of the β-hydroxy ketone with an overall yield of 30\%.

Acknowledgments

P.A.N.R. and A.S. thank CSIR, New Delhi for the award of fellowships. J.S.Y. thanks CSIR for the award of Bhatnagar Fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.056.
References and notes