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3



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



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ABSTRACT

A stereoselective total synthesis of 4-((3*S*,5*R*)-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 β -hydroxyketone with NaBH₄ in the presence of diethylmethoxyborane.

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The gingerols are known to exhibit potent antioxidant properties.¹ They are also used in the traditional medicine as anti-inflammatory, antitumor and chemopreventive,² bacteriostatic,³ and nematocida agents.⁴ Recently, a novel class of 4-((3*S*,5*R*)-3,5-dihydroxynonadecyl)phenol (**1**) was isolated from the resinous exudates of Chilean desert plants (Fig. 1).⁵ It also shows a promising anti-oxidant behavior. The absolute stereochemistry of (**1**) was determined by Gao and co-workers⁶ 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.⁷ Following our interest on the total synthesis of biologically active natural products,⁸ we herein report the total synthesis of 4-((3*S*,5*R*)-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 β -hydroxy ketone

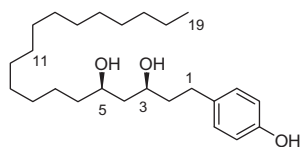
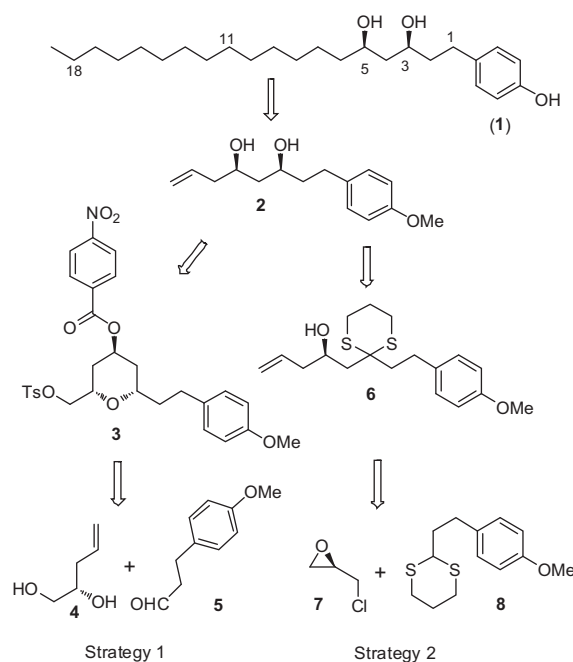


Figure 1. Naturally occurring 4-((3*S*,5*R*)-3,5-dihydroxynonadecyl)phenol (**1**).



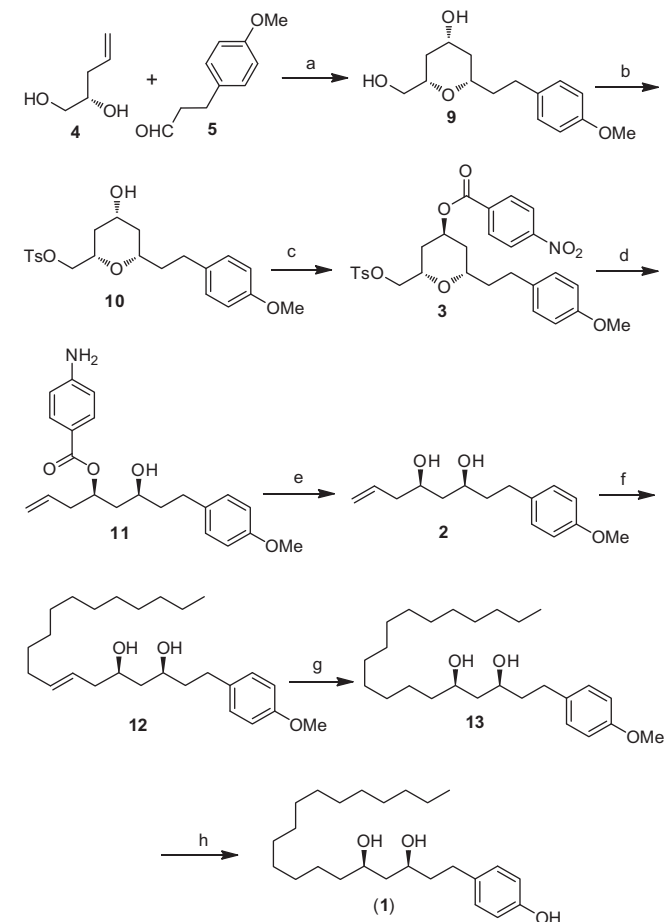
Scheme 1. Retrosynthetic analysis of 4-((3*S*,5*R*)-3,5-dihydroxynonadecyl)phenol (**1**).

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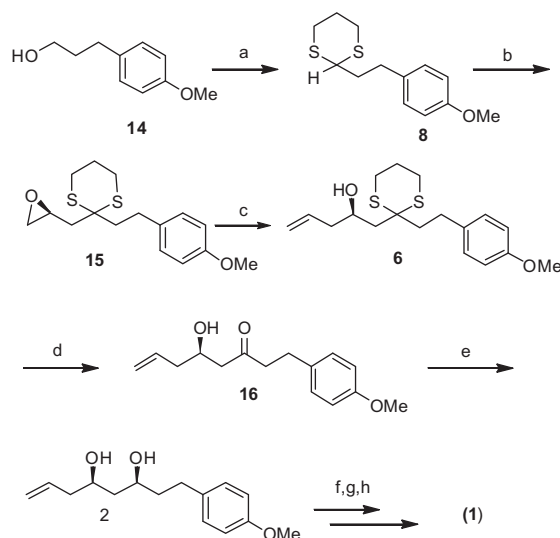
E-mail address: yadavpub@gmail.com (J.S. Yadav).

6, which in turn could be prepared by alkylation of 1,3-dithiane **8** with (*R*)-epichlorohydrin **7** (Scheme 1).

According to our first strategy, the (*S*)-homoallyl alcohol **4**⁹ was treated with *p*-methoxyhydrocinnamaldehyde **5**¹⁰ in the presence of TFA in DCM. The resulting trifluoroacetate was then hydrolyzed with K₂CO₃ in MeOH to afford the tetrahydropyranol **9**.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 primary tosylate **10**. Mitsunobu inversion¹² 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 EtOH to furnish the homoallylic benzoate **11** in 85% yield (over two steps). Cleavage of the benzoate **11** with K₂CO₃ in methanol gave the required *syn*-1,3-diol **2**¹³ in 92% yield. Cross-metathesis of the terminal olefin **2** with a readily available tridec-1-ene, using Grubbs's 2nd generation catalyst in DCM under reflux conditions afforded the olefinic derivative **12** in 85% yield.¹⁴ Reduction of the olefin **12** using palladium on carbon in 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 AlCl₃ in DCM afforded the target molecule (**1**) in 95% yield (28% overall yield) (Scheme 2). The



Scheme 2. Synthesis of 4-((3*S*,5*R*)-3,5-dihydroxynonadecyl)phenol (**1**) through Prins cyclization. Reagents and conditions: (a) (i) TFA, DCM, 6 h, (ii) K₂CO₃, MeOH, 3 h, 60% over two steps; (b) Et₃N, TsCl, DCM, 0 °C to rt, 6 h, 90%; (c) DEAD, TPP, *p*-NO₂-C₆H₄CO₂H, THF, 0 °C to rt, 5 h, 88%; (d) (i) acetone, NaI, reflux, 24 h (ii) zinc dust, EtOH, reflux, 2 h, 85% over two steps; (e) K₂CO₃, MeOH, rt, 3 h, 92%; (f) tridecene (10 equiv), Grubbs-II catalyst (5 mol %), DCM, reflux, 12 h, 85%; (g) 10% Pd/C, EtOAc, H₂, rt, 3 h, 94%; (h) AlCl₃, EtSH, DCM, 0 °C to rt, 1 h, 93%.



Scheme 3. Umpolung route for the synthesis of 4-((3*S*,5*R*)-3,5-dihydroxynonadecyl)phenol (**1**). Reagents and conditions: (a) (i) IBX/DMSO, (ii) 1,3-ethane dithiol, BF₃·OEt₂, DCM, 0 °C to rt, 3 h, 90%; (b) *n*-BuLi, (*R*)-epichlorohydrin, THF, −78 °C, 4 h, 80%; (c) vinylmagnesium bromide, CuCN, −78 °C to −40 °C, 84%; (d) CuCl₂/CuO, Acetone (99% aqueous), 82%; (e) diethyl(methoxy)borane, THF/MeOH (4:1), NaBH₄, −78 °C, 5 h, 80%; (f) tridec-1-ene (10 equiv), Grubbs 2 catalyst (5 mol %), DCM, reflux, 12 h, 85%; (g) 10% Pd/C, EtOAc, H₂, rt, 3 h, 94%; (h) AlCl₃, EtSH, DCM, 0 °C to rt, 1 h, 95%.

spectral data of 4-((3*S*,5*R*)-3,5-dihydroxynonadecyl)phenol (**1**) are in good agreement with the reported values.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*)-epichlorohydrin **7** using *n*-BuLi in THF at −78 °C gave the epoxy dithiane **15** in 80% yield.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 CuCl₂/CuO in aqueous acetone furnished the β-hydroxy ketone **16** in 82% yield. Treatment of the β-hydroxy ketone **16** with NaBH₄ in the presence of diethyl(methoxy)borane in THF/MeOH afforded the *syn*-1,3-diol **2** in 80% yield (Scheme 3).¹⁷ The remaining transformations were similar to Scheme 2. The spectral data of the molecule (**1**) are in good agreement with the reported values.¹⁵

In conclusion, we have demonstrated a stereoselective total synthesis of 4-((3*S*,5*R*)-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%.

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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>.

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