Tetrahedron Letters 55 (2014) 1395–1397

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

J. S. Yadav [a,*], P. Adi Narayana Reddy [a], A. Suman Kumar [a], A. R. Prasad [a], B. V. Subba Reddy [a], Ahmad Alkhazim Al Ghamdi [b]

[a] Centre for SemioChemicals, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India
[b] Engineer Abdullah Baqshan for Bee Research, King Saudi University, Saudi Arabia

ARTICLE INFO

Article history:
Received 27 November 2013
Revised 12 December 2013
Accepted 14 December 2013
Available online 21 December 2013

Keywords:
Prins cyclization
Cross metathesis
1,3-*syn* Reduction

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-dithane with (*R*)-epichlorohydrin, ring opening of the epoxide with vinylmagnesium bromide, and 1,3-*syn*-reduction of the β-hydroxyketone with $NaBH_4$ in the presence of diethylmethoxyborane.

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] bactereostatic,[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-workers[6] 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

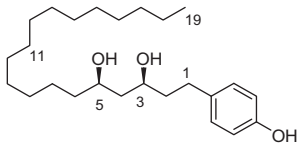
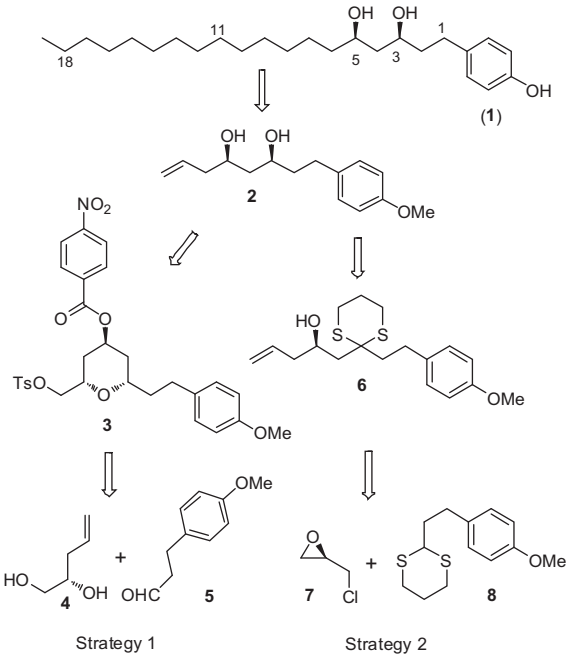


Figure 1. Naturally occurring 4-((3*S*,5*R*)-3,5-dihydroxynonadecyl)phenol (**1**).



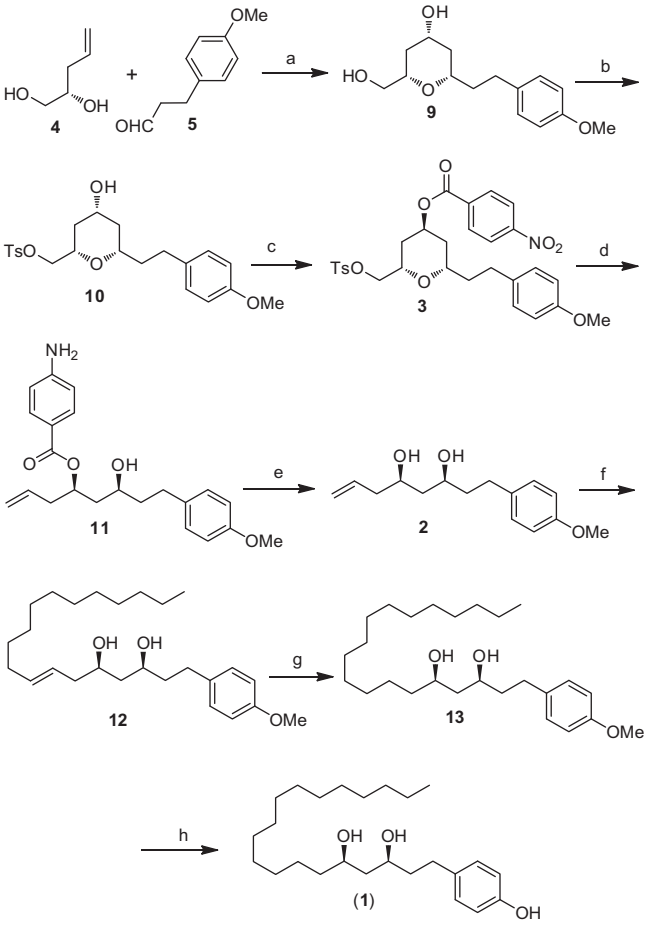
Scheme 1. Retrosynthetic analysis of 4-((3*S*,5*R*)-3,5-dihydroxynonadecyl)phenol (**1**).

* Corresponding author. Tel.: +91 40 27193737; fax: +91 40 27160512.
E-mail address: yadavpub@gmail.com (J.S. Yadav).

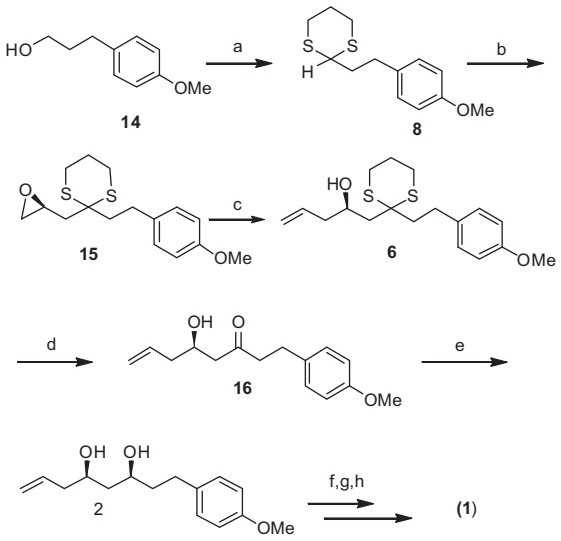
0040-4039/$ - see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.12.056

6, which in turn could be prepared by alkylation of 1,3-dithane **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 K_2CO_3 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 inversion[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 EtOH to furnish the homoallylic benzoate **11** in 85% yield (over two steps). Cleavage of the benzoate **11** with K_2CO_3 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 Grubb'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 $AlCl_3$ 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) K_2CO_3, MeOH, 3 h, 60% over two steps; (b) Et_3N, TsCl, DCM, 0 °C to rt, 6h, 90%; (c) DEAD, TPP, *p*-NO_2–$C_6H_4CO_2H$, 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) K_2CO_3, MeOH, rt, 3 h, 92%; f) tridecene (10 equiv), Grubbs-II catalyst (5 mol %), DCM, reflux, 12 h, 85%; (g) 10% Pd/C, EtOAc, H_2, rt, 3 h, 94%; (h) $AlCl_3$, 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, $BF_3.OEt_2$, 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) $CuCl_2$/CuO, Acetone (99% aqueous), 82%; (e) diethyl(methoxy)borane, THF/MeOH (4:1), $NaBH_4$, −78 °C, 5h, 80%; (f) tridec-1-ene (10 equiv), Grubbs 2 catalyst (5 mol %), DCM, reflux, 12 h, 85%; (g) 10% Pd/C, EtOAc, H_2, rt, 3 h, 94%; (h) $AlCl_3$, 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 $CuCl_2$/CuO in aqueous acetone furnished the β-hydroxyl ketone **16** in 82% yield. Treatment of the β-hydroxy ketone **16** with $NaBH_4$ 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%.

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

1. (a) Chen, H.; Zhou, A. X.; Guo, S. Y. *Chin. J. Exp. Trad. Med. Formulae* **1999**, *5*, 12; (b) Sabitha, G.; Srinivas, C.; Reddy, T. R.; Yadagiri, K.; Yadav, J. S. *Tetrahedron: Asymmetry* **2011**, *22*, 2124.
2. (a) Kunnumakkara, A. B.; Anand, P.; Aggarwal, B. B. *Cancer Lett.* **2008**, *269*, 199; (b) Duvoix, A.; Blasius, R.; Delhalle, S.; Schnekenburger, M.; Morceau, F.; Henry, E.; Dicato, M.; Diederich, M. *Cancer Lett.* **2005**, *223*, 181; (c) Hatcher, H.; Planalp, R.; Cho, J.; Torti, F. M.; Torti, S. V. *Cell. Mol. Life Sci.* **2008**, *65*, 1631.
3. Schraufstatter, E.; Bernt, H. *Nature* **1949**, *164*, 456.
4. Kiuchi, F.; Goto, Y.; Sugimoto, N.; Akao, N.; Kondo, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1993**, *41*, 1640.
5. Modak, B.; Torres, R.; Lissi, E.; Monache, F. D. *Nat. Prod. Res.* **2003**, *17*, 403.
6. Chen, C.-Y.; Zhang, S.-M.; Wu, Y.; Gao, P. *Eur. J. Org. Chem.* **2013**, 348.
7. Yadav, J. S.; Reddy, M. S.; Rao, P. P.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4397.
8. (a) Yadav, J. S.; Reddy, N. M.; Reddy, P. A. N.; Ather, H.; Prasad, A. R. *Synthesis* **2010**, 1473; (b) Yadav, J. S.; Reddy, Y. J.; Reddy, P. A. N.; Reddy, B. V. S. *Org. Lett.* **2013**, *15*, 546; (c) Reddy, B. V. S.; Reddy, B. P.; Pandurangam, T.; Yadav, J. S. *Tetrahedron Lett.* **2011**, *52*, 2306; (d) Reddy, B. V. S.; Reddy, B. P.; Reddy, P. S.; Reddy, Y. J.; Yadav, J. S. *Tetrahedron Lett.* **2013**, *54*, 4960.
9. Yadav, J. S.; Reddy, P. A.; Reddy, Y. J.; Meraj, S.; Prasad, A. R. *Eur. J. Org. Chem.* **2013**, 6317.
10. Daniel, A. B.; Matthias, B. *J. Am. Chem. Soc.* **2012**, *134*, 9890.
11. (a) Yadav, J. S.; Rao, P. P.; Reddy, M. S.; Rao, N. V.; Prasad, A. R. *Tetrahedron Lett.* **2007**, *48*, 1469; (b) Reddy, B. P.; Reddy, B. V. S.; Pandurangam, T.; Yadav, J. S. *Tetrahedron Lett.* **2012**, *53*, 5749; (c) Yadav, J. S.; Lakshmi, K. A.; Reddy, N. M.; Prasad, A. R.; Reddy, B. V. S. *Tetrahedron* **2010**, *66*, 334.
12. (a) Mitsunobu, O. *Synthesis* **1981**, 1; (b) Yadav, J. S.; Rao, P. P.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2008**, *49*, 5427.
13. (a) Yadav, J. S.; Reddy, P. A. N.; Ather, H.; Kumar, A. S.; Prasad, A. R.; Reddy, B. V. S.; Khazim, A. A. *Synthesis* **2012**, 579.
14. (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446; (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.
15. Harbindu, A.; Kumar, P. *Synthesis* **2010**, 1479.
16. Smith, A. B.; Han, H.; Kim, W. S. *Org. Lett.* **2011**, *13*, 3328.
17. (a) Narasaka, K.; Pai, F. C. *Tetrahedron* **1984**, *40*, 2233; (b) Chen, K.-M.; Hardmann, G. E.; Prasada, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.