Bioorganic & Medicinal Chemistry Letters 22 (2012) 4678–4680

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Total synthesis and antifungal activity of (2*S*,3*R*)-2-aminododecan-3-ol

T. Vijai Kumar Reddy [a], B. L. A. Prabhavathi Devi [a,*], R. B. N. Prasad [a], M. Poornima [b], C. Ganesh Kumar [b]

[a] *Centre for Lipid Research, CSIR-Indian Institute of Chemical Technology, Uppal Road, Hyderabad 500 607, India*
[b] *Chemical Biology Laboratory, CSIR-Indian Institute of Chemical Technology, Uppal Road, Hyderabad 500 607, India*

ARTICLE INFO

Article history:
Received 14 February 2012
Revised 11 May 2012
Accepted 22 May 2012
Available online 30 May 2012

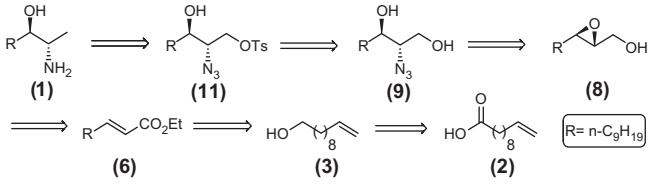
Keywords:
10-Undecenoic acid
Wittig reaction
Sharpless asymmetric epoxidation
Miyashita's azidolysis
Antifungal

ABSTRACT

We report the total synthesis of (2*S*,3*R*)-2-aminododecan-3-ol has been achieved starting from commercially available 10-undecenoic acid. The key steps involved are Sharpless asymmetric epoxidation, Miyashita's boron-directed C-2 regioselective azidolysis, generated the asymmetric centers and in situ detosylation and reduction of azido tosylate. The antifungal activity of the synthesized (2*S*,3*R*)-2-aminododecan-3-ol was evaluated on several *Candida* strains and was comparable to miconazole, a standard drug

Natural products have played an important role in the history of drug discovery and development process by providing novel, clinically useful medicines having various biological activities such as anticancer, anathematic, antifungal, anti-protozoal and antimicrobial activities, among others.[1,2] In the last decades, natural products having antifungal activity received increased attention from chemists since fungal infections are very common. So there is always an ever increasing requirement of safe and effective antifungal agents to control fungal infections. The importance of antifungal chemotherapy continues to evolve rapidly because invasive fungal infections in immuno-compromised patients have become increasingly significant. Recently, new antifungal agents, such as voriconazole and caspofungin,[3] have entered the clinical arena. Ongoing efforts towards the search for new natural antifungal agents from marine organisms have been recently reviewed.[4] (2*S*,3*R*)-2-Aminododecan-3-ol (1), is a natural product isolated from the ascidian *Clavelina oblonga*,[1] which showed strong activity against *Candida albicans* (MIC of 0.7 μg mL^{-1}) and moderately active against Candida *glabrata* (MIC of 30 μg mL^{-1}). Marine-derived long chain 2-amino-3-alkanols, are commonly encountered in tunicates and some sponges.[5] Structurally, these compounds are related to the sphingosine derivatives (e.g., sphinganine, 4-sphinganine, phytosphingosine), long known as central structural element of sphingolipids, which are important constituents of the lipid portion of cell membranes in living organisms. The carbon chain length of these sphingolipid derivatives vary from C_{12} to C_{30}.[6,7] Sphingolipids[8] and 2-amino-3-alkanols such as (2*S*,3*R*)-2-aminododecan-3-ol isolated from *C. oblonga* were found to have (2*S*,3*R*)-configuration. Due to the unusual stereochemical configuration of these natural products and the potent biological activity, we were interested in developing an efficient route for their synthesis. Owing to its structural simplicity, the title compound **1** has been less investigated in terms of its total synthesis. Sutherland reported the total synthesis of **1** from (*S*)-glycidol in 14 steps with an overall yield of 29%.[9] Very recently, Huang reported an improved four-step approach for the stereoselective synthesis of long-chain anti-2-amino-3-alkanols from L-alanine derivatives.[10] In this context, we report a new synthetic approach involving 10 steps for the synthesis of (2*S*,3*R*)-2-aminododecan-3-ol from a cheaper and readily available 10-undecenoic acid, which is being produced from a renewable feedstock, castor oil. The synthesized (2*S*,3*R*)-2-aminododecan-3-ol (**1**) was evaluated for antifungal activity on a series of *Candida* strains.

The retrosynthetic strategy for the total synthesis of the target molecule **1** is delineated in Scheme 1. We envisaged that the target molecule **1** could be obtained from azido tosylate **11** which in turn could be derived from azido diol **9**. The compound **9** could be



Scheme 1. Retrosynthetic analysis of (2*S*,3*R*)-2-aminododecan-3-ol.

* Corresponding author. Tel.: +91 40 27191515; fax: +91 40 27193370.
E-mail address: prabhavathi@iict.res.in (B.L.A. Prabhavathi Devi).

0960-894X/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2012.05.082

obtained from enantiomerically pure epoxy alcohol **8** by the trialkyl borate mediated C-2 selective azidolysis under Miyashita's condition. The fragment **8** could be prepared from the intermediate **6** by involving Sharpless asymmetric epoxidation reaction. The intermediate **6** could in turn be prepared from the intermediate **3** by involving ozonolysis followed by Wittig reaction.

Thus as per the retrosynthesis shown above, the first sub-target for the synthesis of **1** was to synthesize enantiomerically pure epoxy alcohol **8**. Our strategy for the synthesis of **1** started with readily available fatty acid namely, 10-undecenoic acid **2**. According to Scheme 2, the fatty acid **2** was treated with $LiAlH_4$ to afford the alcohol **3** in high yield (97%).[11] The free hydroxymethyl group at C_1 in compound **3** was converted into methyl group by tosylation[12] of the primary alcohol **3** in the presence of triethylamine and subsequent treatment of the tosyloxy derivative **4** with $LiAlH_4$ to afford the desired olefin **5** with 84% yield.[13,14]

Ozonolysis of **5** provided 1-decanal and was used directly in the subsequent Wittig reaction without further purification to avoid decomposition.[15] According to Barrett,[19a] 1-decanal was treated with $Ph_3P{=}CHCO_2Et$ in dry THF gave exclusively *E*-α,β-unsaturated ester **6** in 86% yield (over two steps).[16] Reduction of **6** with DIBAL-H in dry DCM furnished the desired *E*-α,β-unsaturated alcohol **7** in high yield (90%).[14,16–18] Sharpless asymmetric epoxidation[19b] of **7** with D-(−)-diethyl tartrate afforded enantiomerically pure epoxy alcohol **8** in 90% yield with >98% ee by ^1H NMR analysis of the corresponding Mosher ester derivative. C-2 selective azidolysis[20] of enantiomerically pure epoxide **8** by sodium azide in dry DMF in the presence of trimethylborate furnished mixture of azido diols **9** (major) and **10** (minor). These two regioisomers did not show any separation on TLC, and an attempt to purify by column chromatography was also unsuccessful. However, the corresponding tosylates **11** and **12**, which were obtained by tosylation of a mixture of **9** and **10** with 1.1 equiv of tosyl chloride in dry CH_2Cl_2 in the presence of triethylamine at 0 °C, were completely separable by silica gel column chromatography. Amounts of isolated **11** and **12** suggested that in the azidolysis reaction compounds **9** and **10** were formed in a ratio of 84:16. The synthesis of (2*S*,3*R*)-2-aminododecan-3-ol **1** was completed by one-pot reduction of azido tosylate[17] **11** with $LiAlH_4$ involving simultaneous reduction of $-N_3$ to $-NH_2$ and detosylation with 68% yield. The overall yield of the (2*S*,3*R*)-2-aminododecan-3-ol **1** was found to be 17.1% after 10 steps. Spectral data of some selected compounds namely, 8, 11 and 1 are given in Ref. 23.

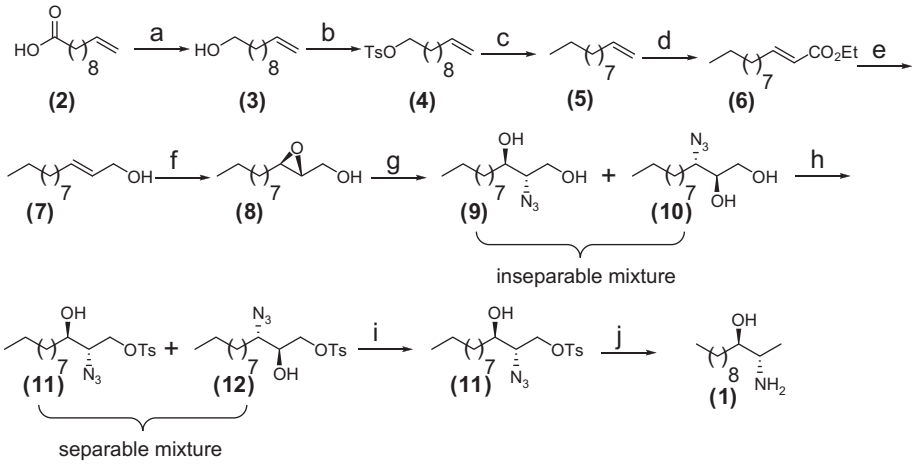
Table 1
Antifungal activity of (2*S*,3*R*)-2-aminododecan-3-ol

Test strains	MIC (μg mL^{-1})				
	C (**1**)[a]	M[b]	F[c]	N[d]	A[e]
Candida parapsilosis MTCC 1744	4.9	9.9	18.8	150	300
Candida aaseri MTCC 1962	9.9	9.9	75.0	150	300
Candida glabrata MTCC 3019	9.9	9.9	75.0	150	300
Candida albicans MTCC 183	9.9	9.9	37.5	150	300
Candida albicans MTCC 7315	9.9	9.9	37.5	150	300
Candida albicans MTCC 3958	19.8	9.9	75.0	150	300
Candida albicans MTCC 854	37.5	9.9	37.5	150	300

[a] C (**1**): compound (**1**).
[b] M: miconazole.
[c] F: fluconazole.
[d] N: nystatin.
[e] A: amphotericin B.

Antifungal activity: In the present study, the antifungal activity (Table 1) of the synthesized (2*S*,3*R*)-2-aminododecan-3-ol (**1**) was carried out using well diffusion method.[21,22]

As shown in Table 1, the synthesized (2*S*,3*R*)-2-aminododecan-3-ol **1** exhibited moderate activity towards *C. albicans* MTCC 854 and *C. albicans* MTCC 3958, while it showed good activity (MIC of 9.9 μg mL^{-1}) towards *C. albicans* MTCC 7315, *C. albicans* MTCC 183, *C. glabrata* MTCC 3019 and *C. aaseri* MTCC 1962 and very high inhibitory activity (MIC of 4.9 μg mL^{-1}) towards *C. parapsilosis* MTCC 1744, demonstrating that the amine and hydroxyl groups present in this target molecule **1** plays a key role in the structure–function relationship in exhibiting this bioactivity. Further, the antifungal activity exhibited by (2*S*,3*R*)-2-aminododecan-3-ol **1** against these strains is comparatively better than the antifungal activity exhibited by different clinically used antifungal drugs like miconazole (MIC of 9.9 μg mL^{-1}), fluconazole (MIC values ranging between 18.8 and 75 μg mL^{-1}), nystatin (MIC of 150 μg mL^{-1}) and amphotericin B (MIC of 300 μg mL^{-1}). While, in an earlier study[1] it was reported that the naturally derived (2*S*,3*R*)-2-aminododecan-3-ol **1** exhibited strong activity against *C. albicans* (MIC of 0.7 μg mL^{-1}) and moderate activity against *C. glabrata* (MIC of 30 μg mL^{-1}). This activity was comparable to the antifungal activity of standard antifungal drugs like nystatin (MIC values ranging between 1.0 and 4.0 μg mL^{-1}) and ketoconazole (MIC between 0.01 and 1 μg mL^{-1}).



Scheme 2. Reagents and conditions: (a) $LiAlH_4$, dry THF, 0 °C to rt, 30 min, 97%; (b) TsCl, Et_3N, DMAP, dry CH_2Cl_2, 0 °C, 2 h, 89.6%; (c) $LiAlH_4$, dry THF, 0 °C-reflux, 3 h, 84%; (d) (i) O_3, CH_2Cl_2, $(CH_3)_2S$, −78 °C, 6 h, (ii) $Ph_3P{=}CHCO_2Et$, dry THF, rt, 12 h, 86% over two steps; (e) DIBAL-H, dry CH_2Cl_2, −78 °C to rt, 0.5 h, 90%; (f) D-(−)-DET, $Ti(OiPr)_4$, TBHP, dry CH_2Cl_2, −25 °C, 24 h, 90%; (g) NaN_3, (MeO)3B, dry DMF, 50 °C, 3 h, 92%; (h) TsCl, Et_3N, DMAP, dry CH_2Cl_2, 0 °C, 5 h, 64%; (i) Silica gel column chromatography; (j) $LiAlH_4$, dry THF, 0 °C to rt, 8 h, 68%.

In conclusion, the total synthesis of (2*S*,3*R*)-2-aminododecan-3-ol **1** was efficiently synthesized from commercially available 10-undecenoic acid. Key steps in the developed route were Wittig reaction and Sharpless asymmetric epoxidation to synthesize the enantiomerically pure epoxy alcohol and regioselective epoxide azidolysis for the synthesis of target molecule **1**. The proposed route constitutes a valuable alternative to the established methodologies, as the raw material comes from renewable sources and most followed steps are operationally simple and high yielding. The antifungal activity of the title compound **1** was found to be comparable to miconazole towards all the tested *Candida* strains.

Acknowledgements

One of the authors T.V.K. Reddy thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, India, for financial support as Junior Research Fellowship (JRF).

Supplementary data

Supplementary data (all of the full procedures and chemical compound information) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.05.082.

References and notes

1. Kossuga, M. H.; Macmillan, J. B.; Rogers, E. W.; Molinski, T. F.; Nascimento, G. G. F.; Rocha, R. M.; Berlinck, R. G. S. *J. Nat. Prod.* **1879**, *2004*, 67.
2. Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461.
3. Hospenthal, D. R.; Murray, C. K.; Rinaldi, M. G. *Diagn. Microbiol. Infect. Dis.* **2004**, *48*, 153.
4. (a) Mayer, A. M. S.; Hamann, M. T. *Mar. Biotechnol.* **2004**, *6*, 37; (b) Mayer, A. M. S.; Hamann, M. T. *Comp. Biochem. Physiol.* **2002**, *132C*, 315.
5. Molinski, T. F. *Curr. Med. Chem. Anti-Infect. Agents* **2004**, *3*, 197.
6. Clark, R. J.; Garson, M. J.; Hooper, J. N. A. *J. Nat. Prod.* **2001**, *64*, 1568.
7. (a) Makarieva, T. N.; Denisenko, V. A.; Stonik, V. A.; Milgrom, J. M.; Rashkes, Y. V. *Tetrahedron Lett.* **1989**, *30*, 6581; (b) Molinski, T. F.; Makarieva, T. N.; Stonik, V. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 4076; (c) Nicholas, G. M.; Hong, T. W.; Molinski, T. F.; Lerch, M. L.; Cancilla, M. T.; Lebrilla, C. B. *J. Nat. Prod.* **1999**, *62*, 1678; (d) Nicholas, G. M.; Molinski, T. F. *J. Am. Chem. Soc.* **2000**, *122*, 4011.
8. For reviews, see: (a) Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075; (b) Howell, A. R.; So, R. C.; Richardson, S. K. *Tetrahedron* **2004**, *60*, 11327.
9. Zaed, A. M.; Sutherland, A. *Org. Biomol. Chem.* **2011**, *9*, 8030.
10. Chen, B. S.; Yang, L. H.; Ye, J. L.; Huang, T.; Ruan, Y. P.; Fu, J.; Huang, P. Q. *Eur. J. Med. Chem.* **2011**, *46*, 5480.
11. (a) Jiang, S.; WU, Y. L.; Yao, Z. J. *Chinese J. Chem.* **2002**, *20*, 692; (b) Sharma, A.; Sankaranarayanan, S.; Chattopadhyay, S. *J. Org. Chem.* **1814**, *1996*, 61; (c) Lu, S. F.; O'yang, Q. Q.; Guo, Z. W.; Yu, B.; Hui, Y. Z. *J. Org. Chem.* **1997**, *62*, 8400; (d) Lu, S. F.; O'yang, Q. Q.; Guo, Z. W.; Yu, B.; Hui, Y. Z. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2344; (e) Smith, J. A.; Brzezinska, K. R.; Valenti, D. J.; Wagener, K. B. *Macromolecules* **2000**, *33*, 3781.
12. (a) Nishio, T.; Niikura, K.; Matsuo, Y.; Ijiro, K. *Chem. Commun.* **2010**, *46*, 8977; (b) Mori, K.; Harada, H.; Zagatti, P.; Cork, A.; Hall, D. R. *Liebigs Ann. Chem.* **1991**, 259; (c) Liu, Y.; Patricelli, M. P.; Cravatt, B. F. *Proc. Natl. Acd. Sci.* **1999**, *96*, 14694.
13. Ghosal, P.; Shaw, A. K. *Tetrahedron Lett.* **2010**, *51*, 4140.
14. Sabitha, G.; Yadagiri, K.; Bhikshapathi, M.; Chandrashekar, G.; Yadav, J. S. *Tetrahedron: Asymm.* **2010**, *21*, 2524.
15. (a) Prabhavathi Devi, B. L. A.; Gangadhar, K. N.; Vijaya Lakshmi, K.; Ramakrishna, S.; Madhusudan, K.; Rao, P. V.; Prasad, R. B. N.; Patent No: WO 2010/079514 A1.; (b) Kurashina, Y.; Miura, A.; Enomoto, M.; Kuwahara, S. *Tetrahedron* **2011**, *67*, 1649; (c) Ishmuratov, G. Y.; Yakovleva, M. P.; Kharisov, R. Y.; Botsman, O. V.; Izibarov, O. I.; Mannapov, A. G.; Tolstikov, G. A. *Chem. Nat. Compounds* **2001**, *37*, 190.
16. (a) Fernades, R. A.; Kumar, P. *Tetrahedron* **2002**, *58*, 6685; (b) Piva, O. *Tetrahedron* **1994**, *50*, 13687.
17. Dinda, S. K.; Das, S. K.; Panda, G. *Tetrahedron* **2010**, *66*, 9304.
18. Zhang, Z. B.; Wang, Z. M.; Wang, Y. X.; Liu, H. Q.; Lei, G. X.; Shi, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 53.
19. (a) Barrett, A. G. M.; Head, J.; Smith, M. L.; Stock, N. S.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1999**, *64*, 6005; (b) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
20. Sasaki, M.; Tanino, K.; Hirai, A.; Miyashita, M. *Org. Lett.* **2003**, *5*, 1789.
21. Amsterdam, D. Susceptibility testing of antimicrobials in liquid media. In *Antibiotics in Laboratory Medicine*; Loman, V., Ed., 4th Ed.; Williams and Wilkins: Baltimore, MD, 1996; pp 52–111.
22. *Assay for antifungal activity:* The antifungal activity of the synthesized (2*S*,3*R*)-2-aminododecan-3-ol was determined using well diffusion method[21] against different pathogenic *Candida* reference strains procured from the Microbial Type Culture Collection (MTCC), CSIR-Institute of Microbial Technology, Chandigarh, India. The *Candida* reference strains were seeded on the surface of the media petri plates, containing Muller-Hinton agar with 0.1 mL of previously prepared microbial suspensions individually containing 1.5×10^8 cfu mL^{-1} (equal to 0.5 McFarland). Wells of 6.0 mm diameter were prepared in the media plates using a cork borer and the synthesized (2*S*,3*R*)-2-aminododecan-3-ol at a dose range of 300–1.4 μg $well^{-1}$ was added in each well under sterile conditions in a laminar air flow chamber. Standard antibiotic solutions of fluconazole, miconazole, nystatin and amphotericin B at a dose range of 300–1.4 μg $well^{-1}$ and the well containing methanol served as positive and negative controls, respectively. The plates were incubated for 24 h at 30 °C and the well containing the least concentration showing the inhibition zone is considered as the minimum inhibitory concentration. All experiments were carried out in duplicates and mean values are represented.
23. *The spectral data of some selected compounds are given below:*
Compound **8:** $[\alpha]_D^{28}$ +30.9 (*c* 1.05, $CHCl_3$.); mp 57.0-59.0 °C; IR (KBr) υ_{max}: 3440, 2925, 2854, 1596, 1215, 1086 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 6.9 Hz, H-12), 1.24–1.36 (12H, m, H-6, H-7, H-8, H-9, H-10, H-11), 1.40–1.47 (2H, br m, H-5), 1.52–1.59 (2H, br m, H-4), 2.83–2.85 (1H, td, *J* = 5.93, 1.97 Hz, H-3), 2.88–2.92 (1H, td, *J* = 5.93, 1.97 Hz, H-2), 3.55–3.62 (1H, m, H-1_b), 3.82–3.89 (1H, m, H-1_a); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.0 (CH_3), 22.6 (CH_2), 25.9 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 31.5 (CH_2), 31.8 (CH_2), 55.9 (CH), 58.3 (CH), 61.7 (CH_2); *m*/*z* (EI) 169 [M-CH_2OH]$^+$.
Compound **11:** $[\alpha]_D^{28}$ +15.1 (*c* 0.85, $CHCl_3$); IR (neat) υ_{max}: 3519, 2925, 2854, 2100, 1598, 1459, 1364, 1189, 1176, 981, 666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 6.9 Hz, H-12), 1.20–1.35 (14H, m, H-5, H-6, H-7, H-8, H-9, H-10, H-11), 1.37–1.57 (2H, m, H-4), 2.17 (1H, br s, -OH), 2.46 (3H, s, $ArCH_3$), 3.52–3.58 (1H, br m, H-2), 3.63–3.70 (1H, br m, H-3), 4.17 (1H, dd, *J* = 10.7, 7.3 Hz, H-1_b), 4.31 (1H, dd, *J* = 10.5, 3.2 Hz, H-1_a), 7.36 (2H, d, *J* = 8.1 Hz, ArH), 7.82 (2H, d, *J* = 8.3 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.0 (CH_3), 21.6 (CH_3), 22.6 (CH_2), 25.4 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 31.8 (CH_2), 33.2 (CH_2), 64.6 (CH_2), 68.9 (CH), 70.9 (CH), 127.9 (2×CH), 129.9 (2×CH), 132.5 (C), 145.2 (C); *m*/*z* (ESI) 420 (MNa^+. $C_{19}H_{31}N_3O_4NaS$ requires 420.1932).
Compound **1:** $[\alpha]_D^{29}$ +4.5 (*c* 0.22, CH_3OH), lit.[1] $[\alpha]_D^{29}$ +4.6 (*c* 0.5, CH_3OH); mp 106.8–109 °C, lit.[9] mp 107–109 °C; IR (KBr) υ_{max}: 3384, 2927, 2855, 1647, 1370, 1216, 1120, 976, 758, 666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+CD_3OD) δ: 0.88 (3H, t, *J* = 6.7 Hz, H-12), 1.19 (3H, d, *J* = 6.7 Hz, H-1), 1.22–1.32 (16H, m, H-4, H-5, H-6, H-7, H-8, H-9, H-10, H-11), 3.18–3.27 (1H, br m, H-2), 3.57–3.76 (1H, br m, H-3); ^{13}C NMR (75 MHz, $CDCl_3$+CD_3OD) δ: 11.7 (CH_3),14.5 (CH_3), 23.2 (CH_2), 26.4 (CH_2), 29.8 (CH_2), 30.1 (2×CH_2), 30.1 (CH_2), 32.4 (CH_2), 33.4 (CH_2), 51.8 (CH), 70.6 (CH); *m*/*z* (ESI) 202 (MH^+. $C_{12}H_{28}NO$ requires 202.2170).