Adv. Org. Chem. Lett. 2017, 4(1), 4-6 Article

Advanced
ORGANIC CHEMISTRY LETTERS

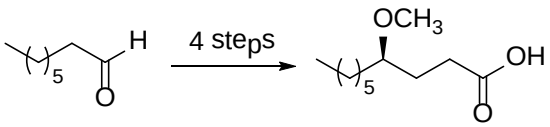
Horner-Wadsworth-Emmons olefination useful for the stereoselective total synthesis of antifungal (R)-4-Methoxydecanoic Acid

Dattatraya N. Bhangare,[1] Mahendra N. Lokhande,[2] Sneha C. Pisolkar,[2] Milind D. Nikalje[2*]

[1]P. G. and Research center, Department of chemistry, Government of Maharashtra's Ismail Yusuf College of Arts, Science and Commerce Jogeshwari (East), Mumbai-400060, Maharashtra, India. [2]Center for advanced studies, Department of Chemistry, Savitribai Phule Pune University, Ganeshkhind Pune-411 007, Maharashtra, India.

Submitted on: 28-Oct-2017, Accepted on: 12-Dec-2017 and Published on 21–Dec-2017

ABSTRACT



The stereoselective total synthesis of novel antifungal (R)-4-methoxydecanoic acid has been accomplished. The chiral centre was developed using D-Proline catalyzed asymmetric α-aminoxylation reaction. Synthesis was completed in four steps with good overall yield 46% and optical purity is up to 95% ee.

Keywords: Stereoselective, antifungal, α-aminoxylation Horner-Wadsworth-Emmons olefination, Nitrosobenzene

INTRODUCTION

Most of the antifungal agents are belonging to classes polyenes, pyrimidines, and azoles. Amphotericin B, conventional antifungal is the standard therapy for many life-threatening fungi, but these polyene drugs have significant toxicity such as chills, fever, headache, nausea, vomiting and dose-limiting nephrotoxicity.[1] Now-a-days hydroxyl alkanoic acids and mid-chainmethoxylated fatty acids have been reported from natural sources and they are known to exhibit excellent antifungal activity.[2,3]

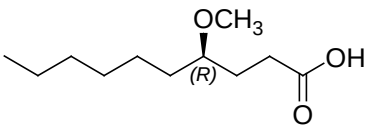
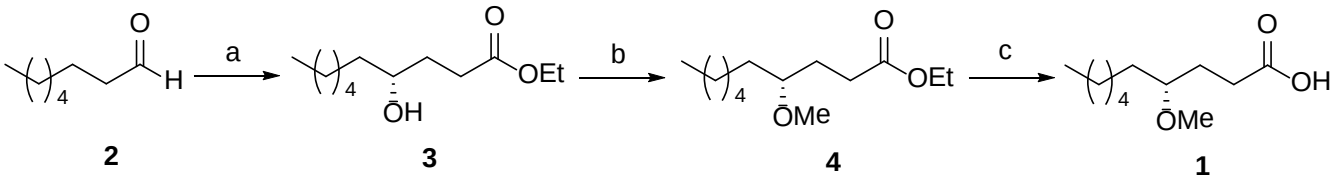


Figure 1. Chemical structure of (R)-4-Methoxydecanoic Acid

However, compounds of this category have not been studied much to evaluate their antifungal property.[4] Biswanath Das first time investigated their antifungal activity and effect of stereochemistry of these compounds on their activity.[5] For that Das group prepared some 4-methoxyalkanoic acids, both in racemic and stereoselective forms, and examined their antifungal activity. While comparing antifungal property of these new group of compounds, the Das group found that (R)-4-methoxydecanoic acid shows good antifungal activity. Thus, considering the biological value of (R)-4-methoxydecanoic acid, we achieved stereoselective short route synthesis of this intermediate. Only two liturature reports are available for the synthesis of 4-methoxydecanoic acid, out of which one is racemic synthesis and other is stereoselective; but these methods are very lengthy.[6] Normally many aliphatic fatty acids are used as antifunal agent and efficiency increases with increase in chain length. These also show vasodilator activity. Now we can see that fatty acids has shown great potential as environmentally friendly leads for novel antifungal drugs. 4-Methoxy decanoic acid was found to be an inhibitor of the growth of bacteria such as Bacillus subtilis, Fusarium oxysporum and Trichothecium roseum at different concentrations.

*Corresponding Author: Dattatraya N. Bhangare
Tel: +91-020-25601395,Fax:+020-25601728
Email:dnbhangare@gmail.com

Cite as: *Adv. Org. Chem. Lett, 2017, 4(1), 4-6.*



Scheme 1. a) i) Nirosobenzene, D-proline, CH_3CN, -20^{O}C, 20h; ii) triethyl phosphonoacetate, DBU, LiCl; iii) H_2, Pd/C, MeOH, 72%; b) CH_3I, NaH, DMF, 12h, 77%; c) NaOH, MeOH, 78%;

EXPERIMENTAL SECTION

Materials and Methods:

All solvents were purified and dried by standard procedures prior to use. IR spectra were recorded on a Shimadzu FTIR-8400 series instrument as a thin film and are expressed in cm-1. Optical rotations were obtained on Jasco P-1020 digital Polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury spectrometer on 300 and 75 MHz, respectively, using $CDCl_3$ as a solvent. Chemical shifts were reported in δ units (parts per million) with reference to TMS as an internal standard and coupling constants J are given in hertz. All HRESIMS were recorded on Bruker Impact HD ESI sourceat Shimadzu Analytical Centre, University of Pune.

Experiental Procedre:

(R)-Ethyl4-hydroxynonanoate (3). To a solution of nitroso benzene (1g, 9.3 mmol) and D-proline (158 mg, 15 mol %) in CH_3CN (20 mL) was added n-octanal (1.8 g, 11.2 mmol) slowly at -20^{O}C. The reaction mixture was stirredb 24 h further addition of LiCl (566 mg, 1.5 equiv.) and triethyl phosphonoacetate (3.13 g, 1.5 equiv.) contineously stirring for 5 min and DBU (1.4 g, 1 equiv.) was added. The reaction mixture was quenched with saturated NH_4Cl and extracted with ethylacetate (3 × 15 mL). Combined organic phases were concentrated, dried over anhydrous Na_2SO_4 offered crude aminoxy olefinic ester which was subjected to hydrogenation in dry metanol using Pd/C, in molecular hydrogen atmosphere to gave γ-hydroxy ethyl decanoate as a crude product. Then reaction mixture was filtred, evaporarted and purified by flash column chromatography (Petether: EtOAc = 85:15) afforded pure γ-hydroxy ethyl decanoate 3. Yield: 3 g, 79%; $[\alpha]_D^{25}$ +25.0 (c 1, $CHCl_3$); IR ($CHCl_3$) ν/cm^{-1} 3446, 2926, 2867, 2322, 2291, 1730, 1600, 1459, 1174, 1030; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.9 (t, 3H, J 7.1, CH_3), 1.25-1.34(m, 10H, CH_2), 1.4-1.45 (m, 3H, CH_2, CH), 1.65-1.70 (m, 1H, CH), 1.75-1.8. (m, 1H,CH), 1.9-1.95 (s(broad), 1H, OH), 2.45-2.5 (t, 2H, J 7.1, CH2), 3.55-3.62 (m, 1H,CH), 4.05-4.15(q, 2H, J 7.3, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.17, 22.55, 25.15, 28.53, 29.41, 30.07, 31.76, 33. 24, 56.46, 60.18, 79.89, 173.81; HRMS calcd. for $C_{12}H_{24}NaO_3$, [M+Na]: 239.1623, found: 239.1619;

(R)-Ethyl 4-methoxynonanoate (4). (17.85 g, 85.7 mmol) **3** in DMF (400 mL) was deprotonated with NaH (60%, 6.0 g, 214 mmol) at 0^{o}C.The mixture was stirred at room temperature for 1 h, cooled to 0^{O}C and treated dropwise with methyl iodide (21.3 mL, 343 mmol) in DMF (50 mL). The mixture was stirred overnight, quenched with water. The product was extracted with ether and the ether phase was dried over $MgSO_4$ and purified by column chromatography (hexanes/ ethyl acetate 10:1) to give the methyl ether (18.72 g, 98%) as a colorless oil. $[\alpha]_D^{25}$ +6.1 (c 2.0, $CHCl_3$) 2929, 2859, 1728, 1460, 1177, 1034; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85(t, J 7.0, 3H, CH_3), 1.2-1.4(m, 13H, CH_2 and CH_3), 1.68-1.73(m, 1H, CH), 1.75-1.85(m, 1H, CH), 2.30-2.4(q, J 6.4, 2H, CH_2), 3.15-3.20(m, 1H, CH), 3.27(s, 3H, OCH_3), 4.1-4.15(q, J 6.4, 2H, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 14.01, 14.17, 22.55, 25.15, 28.53, 29.41, 30.07, 31.76, 33.24, 56.46, 60.18, 173.81; HRMS calcd. for $C_{13}H_{26}NaO_3$, [M+Na]: 253.1779, found: 253.1773

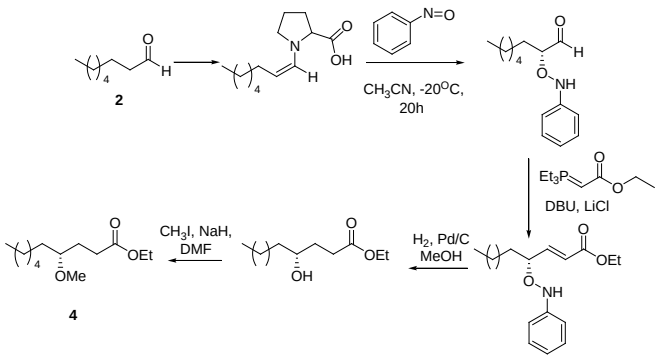
(R)-4-methoxynonanoic acid (1). To a stirred solution of 4 (400mg, 0.53 mmol) in dry DMF (2 mL), PDC (800 mg, 2.12 mmol) was added at room temperature. The reaction was stirred for 24 h. Then 10 mL water was added and the reaction mixture was extracted with ether (2 X 10 mL). aques layer was neutralised with acid and then again extracted with ether (2 X 10 mL).The combined organic layers were concentrated under reduced pressure and the residue was purified by column chromatography (10% ethyl acetate/hexane) to afford (R)-1 (280 mg, 63%) as a yellow liquid. $[\alpha]_D^{25}$ + 12.1 (c 1.0, $CHCl_3$);IR ($CHCl_3$) ν/cm^{-1} 3450, 2450, 2926, 1711, 1461, 1282; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J 7.0, 3H, CH_3), 1.36-1.21 (m, 10H, CH_2), 1.7-1.78(m, 1H, CH), 1.8-1.85(m, 1H, CH), 2.41 (t, J 7.0, 2H, CH_2),3.21 (m, 1H, CH), 3.34 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.03, 22.56, 25.12, 28.19, 29.41, 30.01, 31.76, 33.16, 56.48, 80.0, 179.57; HRMS calcd. for $C_{11}H_{22}NaO_3$, [M+Na]: 225.1466, found: 225.1464

RESULTS AND DISCUSSION

The synthesis of (R)-4-methoxydecanoic acid was started with D-proline catalyzed asymmetric α-aminoxylation of n-octanal **2**, which was carried out using nitrosobenzene as the electrophilic component followed by in situ Horner-Wadsworth-Emmons olefination with DBU as base that furnished anilinoxy olefinic ester.[7] Simultaneous reduction of both the C=C bond and the anilinoxy group in ester was achieved with 10% Pd/C, H_2 (1 atm.) to produce optically pure γ-hydroxy ester **3**.[8] The formation of product was confirmed by analytical data i.e. in 1H NMR it gives signal at 3.6 ppm for hydroxy substituted proton. In IR it shown characteristic absorption peak for carbonyl functionality of ester at 1730 cm^{-1}. HRMS data (239.1619) also matched with calculated data (239.1623), hence confirm the formation of product. Optical purity is measured by optical rotation value. The protection of free hydroxy functionality of

compound **3** was carried out using methyl iodide and sodium hydride strategy to afforded γ-methoxy ester **4** in 77% yield.[9] Methoxy peak at 3.27 ppm in ^{1}H NMR indicate product formation. Final hydrolysis of ester functionality was acheived by applying base catalysed ester hydrolysis to get final (R)-4-methoxydecanoic acid having rotation value $[\alpha]_D^{25}$ +12.1 (c1.0, $CHCl_3$), which was matched with liturature value $[\alpha]_D^{25}$ +11.5 (c1.0, $CHCl_3$).[5]

The high stereoselectivity in the proline-catalyzed reactions is possibly due to its formation of organized transition states with many hydrogen bonding frameworks. Proline is not the only molecule to promote catalysis, but it still seems to be one of the best in the diversity of transformations. Proline is known to catalyze aldol, Diels-Alder, Michael addition and α-functionalization among many other organic transformations. Particularly proline-catalyzed α-aminooxylation and α-amination of carbonyl compounds are emerged as powerful transformations because chiral building blocks can be synthesized in effective manner starting from easily available



materials.

Scheme 2: Mechanistic Pathway

Sequential alpha aminoxylation followed by in situ Horner-Wadsworth-Emmons olefination with DBU as base that furnished anilinoxy olefinic ester. Which on reduction of both the C=C bond and the anilinoxy group in ester to produce optically pure γ-hydroxy ester **3**.

CONCLUSION

In conclusion, we have successfully applied D-proline catalyzed α-hydroxylation strategy and Horner-Wadsworth-Emmons olefination for the synthesis of antifungal (R)-4-methoxydecanoic acid **1**. The synthesis is achieved in only four steps with good overall yield and optical purity.

ACKNOWLEDGMENTS

DNB,MNL,SCP,MDN is thankful to CSIR, New Delhi for senior research fellowship and department of chemistry Savitribai Phule Pune University for infrastructure.

SUPPLEMENTARY MATERIAL

Spectral analysis are provided as supplimentary file.

REFERENCES AND NOTES

1. H. A. Gallis, R. H. Drew W. W. Pickard Amphotericin B: 30 years of clinical experience. *Ref. Infect. Dis*. **1990**, 12, 308.
2. Y. Feron, L. Dufosse, E. Pierard, J.-L. Le Quere, H.-E. Spinnler, production, identification, and toxicity of (gamma)-decalactone and 4-hydroxydecanoic acid from sporidiobolus spp *Appl. Environ. Microbiol*. **1996**, 62, 2826; J. Sjogren, J. Magnusson, A. Broberg, J. Schnurer, L. Kenne. Antifungal 3-hydroxy fatty acids from lactobacillus plantarum milab 14. *Appl. Environ. Microbiol*. **2003**, 69, 7554.
3. H. J. Cardellina II, D. Dalietos, F.-J. Marner, J. S. Mynderse, R. E. Moore. (−)-trans-7(S)-Methoxytetradec-4-enoic acid and related amides from the marine cyanophyte Lyngbya majuscule. *Phytochemistry* **1978**, 17, 2091.
4. C.N.M. Carballeira, K.P. Miranda. Branched chain mono-glycerol ethers from a taiwanese marine sponge of the genus Aaptos. *Tetrahedron Lett.* **2009**, 50, 5699.
5. B. Das, D. B. Shinde, B. S. Kanth, A. Kamle, C. G. Kumar. Total synthesis of racemic and (R) and (S)-4-methoxyalkanoic acids and their antifungal activity. *Eur. J. of Med. Che*m. **2011**, 46, 3124.
6. a) N. M. Carballeira, C. Miranda, K. Parang. The first total synthesis of (±)-4-methoxydecanoic acid: a novel antifungal fatty acid. *Tetrahedron Lett.* **2009**, 50, 5699, b) M. N. Lokhande, M. U. Chopade, D. N. Bhanare, M. D. Nikalje. Asymmetric synthesis of propranolol, naftopidil and (R)-monobutyrin using a glycerol desymmetrization strategy. *J. Bra Chem. Soc.* **2013**, 24, 406.
7. a) G. Zhong, Y. Yu. Enantioselective synthesis of allylic alcohols by the sequential aminoxylation−olefination reactions of aldehydes under ambient conditions. *Org. Lett.* **2004**, 6, 1637. b) I. K. Mangion, D. W. C. MacMillan. Total synthesis of brasoside and littoralisone. *J. Am. Chem. Soc.* **2005**, 127, 3696. c) Y. Hayashi, J. Yamaguchi, T. Sumiya, K. Hibino, M. Shoji. Direct proline-catalyzed asymmetric alpha-aminoxylation of aldehydes and ketones . *J. Org. Chem.* **2004**, 69, 5966. d) G. Zhong, Angew. A facile and rapid route to highly enantiopure 1,2-diols by novel catalytic asymmetric α-aminoxylation of aldehydes. *Chem. Int. Ed.* **2003**, 42, 4247. e) P. Merino, T. Tejero, Organocatalyzed asymmetric alpha-aminoxylation of aldehydes and ketones an efficient access to enantiomerically pure alpha-hydroxycarbonyl compounds, diols, and even amino alcohols. *Angew. Chem. Int. Ed.* **2004**, 43, 2995. f) H.M. Guo, H.Y Niu, M.X. Xue, Q.X. Guo, L.F. Cun, A.Q. Mi, Y.Z. Jiang, J.J. Wang, L-Proline in an ionic liquid as an efficient and reusable catalyst for direct asymmetric α-aminoxylation of aldehydes and ketones. *Green Chem*. **2006**, 8, 682.
8. S. P. Kotkar, G. S. Suryavanshi, A. Sudalai, A short synthesis of (+)-harzialactone A and (R)-(+)-4-hexanolide via proline-catalyzed sequential α-aminooxylation and Horner–Wadsworth–Emmons olefination of aldehydes. *Tetrahedron: Asymmetry*. **2007**, 18, 1795.
9. J. Mulzer, U. Kaselow, K.D. Graske, H. Kuhne, A. Sieg, H. J. Martin. Bicyclobenzodiazepinones from 3-oxo-1,2-diazetidinium hydroxide, inner salts. *Tetrahedron* **2004**, 60, 9599.