ORIGINAL ARTICLE

A C G publications

Org. Commun. 6:4 (2013) 134-138

organic communications

Concise synthesis of a novel antifungal agent 4-methoxydecanoic acid

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(Received June 29, 2013; Revised September 13, 2013; Accepted December 19, 2013)

Abstract: 4-Methoxy decanoic acid is belongs to a fatty acid family and has a novel anti- fungal activity. The aliphatic molecule has been synthesized in seven steps with an overall yield 41%. The synthesis was started from a commercially available epichloro hydrin and all the reactions were very clean.

Keywords: Epichlorohydrin; Grignard reaction; methyliodide; oxidation; hydrolysis.

1. Introduction

Fungal opportunistic infections have increased in recent years, particularly in immuno compromised and debilitated patients. Currently used drugs for treatment of invasive fungal infections are limited to Amphotericin B and its novel formulations, including also a group of azoles and flucytosin.[1,2] Therefore a strong need exists for novel antifungals to treat these life threatening infections. 4-Methoxy decanoic acid (**1**) was found to be an inhibitor of the growth of bacteria such as *Bacillus subtilis, Fusarium oxysporum* and *Trichothecium roseum* at different concentrations.[3-6]

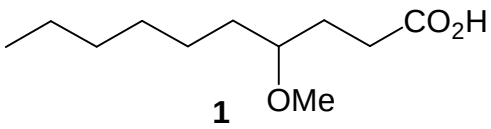

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Figure 1. 4-methoxy decanoic acid

Recently, synthesis of this molecule was reported by Carballeria[7] and Das.[8] In view of its biological importance and as part of our ongoing research program, in design and synthesis of biologically active compounds,[9-14] herein we report the total synthesis of 4-methoxydecanoic acid.

2. Results and Discussions

As shown in the scheme-1, the starting compound, 2-(benzyloxymethyl) oxirane (**2**) was obtained by treating the epichlorohydrin with a reported procedure.[15] The epoxide compound **2** was

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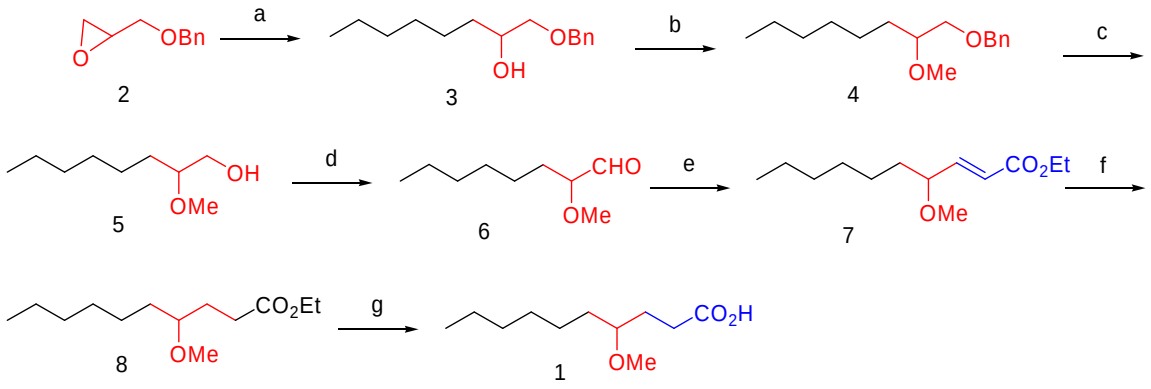
subjected to Grignard conditions for ring opening with 1-pentyl magnesium bromide using a catalytic amount of cupper (I) iodide in THF to afford the corresponding derivative, 1-(benzyloxy)-octa-2-ol (**3**) in very good yields.[16,17]



Reagents and reaction conditions: (a) 1-Bromopentane, Mg, CuI, THF, 4h, 83%. (b) CH_3I, NaH, THF, 2h, 87%. (c) Pd/C, MeOH, 8h, 92%. (d) IBX, DMSO, DCM, 10h, 86%. (e) $Ph_3P{=}CHCO_2Et$, DCM, 2h, 95%. (f) Pd/C, H_2, MeOH, rt, 5h, 90%. (g) LiOH, THF-H_2O, 0-rt, 85%.

Scheme 1. Synthetic route of 4-methoxy decanoic acid

Thus obtained hydroxy compound **3** was reacted with MeI in presence of NaH in THF to afford the corresponding product, [(2-methoxy octyloxy) methyl] benzene (**4**) in excellent yield. The compound **4** was treated for debenzylation in presence of Pd/C in MeOH under H_2 atmosphere to afford, 2-methoxy-octan-1-ol (**5**),[18] which on oxidation with iodoxybenzoic acid in DMSO-CH_2Cl_2 solvent mixture to yield, 2-methoxy octana1 (**6**) in very good yields.[19] The aldehyde compound **6** was allowed react with two carbon Wittig ylide in CH_2Cl_2 to afford, (*E*)-ethyl-4-methoxydec-2-enoate (**7**) in excellent yields.[20] Thus obtained olefin compound **7** was treated for hydrogenation in presence of Pd/C in MeOH to afford the double bond saturated product, ethyl-4-methoxydecanoate (**8**) and followed by ester hydrolysis with LiOH to obtain the target molecule, 4-methoxy decanoic acid (**1**) in very good yields. The synthesis was completed within seven steps with an overall yield 41 %. In general all the reactions were very clean and the isolation of products also very easy. All the products were characterized by their ^{1}H NMR, IR and mass spectroscopy analysis.

3. Conclusion

In conclusion, we have demonstrated a simple and efficient route for the synthesis of antifungal agent, 4-methoxy decanoic acid (**1**) in very good yields. All the reactions were very clean in terms of conversions and isolation of products. This synthetic pathway is very convenient for bulk preparation of the target molecule.

4. Experimental section

IR Spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophoto meter using KBr optics. ^{1}H NMR spectra were recorded on Bruker-300 MHz, spectro meter in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

4.1. 1-(Benzyloxy) Octan-2-ol (3): To a suspention of magnesium turnings (1.5 g, 61.0 mmol) in dry tetrahydrofuran (10 mL) was added 1-bromopentane (5.5 g, 36.6 mmol) dropwise while using reflux condenser with water circulation. After, 1 hour stirring at room temperature was added a catalytic amount of CuI at 0 ^{o}C and continued stirring for 30 minutes at same temperature. To this reaction

mixture was added drop-wise a solution of 2-(benzyloxymethyl) oxirane **(2)** (2 g, 12.2 mmol), which was dissolved in dry THF (10 mL) at 0 ^{o}C. The resulting reaction mixture was stirred at room temperature for a period of 2 hours. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to 0 ^{o}C and quenched with sat., ammonium chloride solution. Then, the solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (2x20 mL). The combined organic layers was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh), while eluting with ethyl acetate-hexane mixture (1:9) to give compound **3** as a light yellow liquid. 2.4 g (83%). IR (neat): υ 3444, 3031, 2927, 2858, 1457, 1367, 1207, 1104, 1026, 738, 698 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3H, *J* = 7.0 Hz), 1.22-1.50 (m, 10H), 2.18 (brs, 1H), 3.27 (t, 1H, *J* = 8.9 Hz), 3.45 (dd, 1H, *J* = 9.0 & 3.0 Hz), 3.70-3.80 (m, 1H), 4.53 (s, 2H), 7.22-7.36 (m, 5H).; EIMS *m/z* (%): 254 (m^{+18} 100) 236 (m^{+} 10), 210 (10), 163 (20), 157 (15), 102 (50), 96 (35), 85 (20), 79 (20), 59 (15).

4.2. [(2-Methoxyoctyloxy) methyl] Benzene (4): To a stirred solution of sodium hydride (0.62 g, 25.4 mmol) in dry THF (10 mL) was slowly added the compound, 1-(benzyloxy) octan-2-ol (**3**) (2 g, 8.5 mmol), which was dissolved in dry THF (10 mL) at 0 ^{o}C. After 30 minutes stirring at the same temperature was added methyl iodide (1.4 g, 10.2 mmol). The resulting reaction mixture was stirred for 1 hour at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with sat. ammonium chloride solution. Then the solvent was removed under reduced pressure and the mixture was extracted with ethyl acetate (2x20 mL). The combined ethyl acetate layers was washed with brine and dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh), while eluting with ethyl acetate-hexane mixture (1:9) to give compound **4** was as a light yellow liquid. 1.84 g (87%). IR (neat): υ 2925, 2855, 1458, 1369, 1270, 1216, 1107, 771, 698 cm.^{1}; ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3H, *J* = 7.0 Hz), 1.25-1.38 (m, 8H), 1.45-1.55 (m, 2H), 3.28 (q, 1H, *J* = 6.0 Hz), 3.40 (s, 3H), 3.44 (q, 1H, *J* = 6.0 Hz), 4.55 (s, 2H), 7.20-7.35 (m, 5H).; EIMS *m/z* (%): 273 (m^{+23} 100), 251 (m^{+1} 20), 159 (20), 143 (18), 127 (10), 115 (15), 111 (10), 102 (25), 92 (15), 91 (60), 88 (15), 73 (10).

4.3. 2-Methoxyoctan-1-ol (5): To a stirred mixture of [(2-methoxyoctyloxy) methyl] benzene (**4**) (1.5 g, 6 mmol) in methanol (10 mL) was added Pd/C (10%, 100 mg). The resulting reaction mixture was stirred at room temperature under hydrogen atmosphere for a period of 8 hours. After completion of the reaction as indicated by TLC, the reaction mixture was filtered on celite bed and the cake was washed with ethyl acetate (10 mL). The combined filtrates was directly adsobed on silica gel and eluted the column with ethyl acetate-hexane mixture (2:8) to give compound **5** as a colorless liquid, 0.88 g (92%). IR (neat): υ 3448, 2922, 2853, 1459, 1374, 1274, 1124, 1075, 770 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 0.89 (t, 3H, *J* = 7.0 Hz), 1.22-1.33 (m, 8H), 1.38-1.42 (m, 2H), 1.78 (brs, 1H), 3.18-3.24 (m, 1H), 3.38 (s, 3H), 3.45 (t, 1H, *J* = 7.0 Hz), 3.62 (d, 1H, *J* = 7.0 Hz).; EIMS *m/z* (%): 183 (m^{+23} 10), 157 (15), 149 (60), 129 (35), 115 (20), 111 (20), 91(70), 71 (50), 57 (45), 43 (100), 41 (40).

4.4. 2-Methoxyoctana1 (6): To a stirred solution of iodoxybenzoic acid (2.1 g, 7.5 mmol) in DMSO (1 mL) was added the compound, 2-methoxyoctan-1-ol (**5**) (0.8 g, 5 mmol), which was dissolved in methylenedichloride (8 mL). The resulting reaction mixture was stirred at room temperature for a period of 10 hours and the completion of the reaction was confirmed by TLC. Then the reaction mixture was extracted with diethyl ether (3x20 mL). The combined ether layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromategraphy using silica gel (60-120 mesh), while eluting with ethyl acetate-hexane mixture (1:9) to give aldehyde **6** as a pale yellow liquid, 0.68 g (86%). IR (neat): υ 2926, 2857, 1714, 1460, 1376, 1112, 725 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 0.89 (t, 3H, *J* = 7.0 Hz), 1.25-1.42 (m, 8H), 1.63 (q, 2H, *J* = 5.0 Hz), 3.40 (s, 3H), 3.42-3.44 (m, 1H), 9.60 (s, 1H).; EIMS *m/z* (%): 181 (m^{+23} 25), 129 (30), 113 (20), 97 (30), 91 (25), 83 (100), 57 (60), 43 (90).

4.5. (E)-Ethyl-4-methoxydec-2-enoate (7): To a stirred solution of 2-methoxyoctana1 (**6**) (0.6 g, 3.8 mmol) in methylenedichloride (15 mL) was added Wittig ylide (1.7 g, 4.9 mmol). The resulting

reaction mixture was stirred at room temperature for 2 hours. The complete conversion of the starting material was confirmed by TLC. Then, the reaction mixture was extracted with methylenedichloride (2x10 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh), while eluting with ethyl acetate-hexane mixture (1:9) to give ester **7** as yellow liquid, 0.82 g (95%). IR (neat): υ 2929, 2858, 1723, 1657, 1462, 1368, 1269, 1168, 1099, 1041, 983, 864, 722 $cm.^{-1}$; ^1H NMR ($CDCl_3$): δ 0.88 (t, 3H, *J* = 7.0 Hz), 1.25-1.38 (m, 11H), 1.50-1.65 (m, 2H), 3.30 (s, 3H), 3.65-3.75 (m, 1H), 4.24 (q, 2H, *J* = 6.0 Hz), 5.95 (d, 1H, *J* = 12.0 Hz), 6.75 (dd, 1H, *J* = 12.0 & 4.0 Hz).; EIMS *m/z* (%): 229 (m^{+1} 100), 197 (25), 183 (30), 170 (15), 149 (50).

4.6. Ethyl-4-methoxydecanoate (8): To a mixture of (*E*)-ethyl-4-methoxydec-2-enoate, (0.8 g) in methanol (10 mL) was added Pd/C (10%, 100 mg). The resulting reaction mixture was stirred at room temperature under hydrogen atmosphere for a period of 5 hours. After completion of the reaction as indicated by TLC, the reaction mixture was filtered on celite bed and the cake was washed with ethyl acetate (10 mL). The combined filtrates was directly adsorbed on silica gel and eluted the column with ethyl acetate-hexane mixture (5:95) to give ester **8**, 0.72 g (90%). IR (neat): υ 2928, 2857, 1738, 1461, 1373, 1250, 1170, 1098, 1034, 761 $cm.^{-1}$; ^1H NMR ($CDCl_3$): δ 0.88 (t, 3H, *J* = 6.0 Hz), 1.22-1.45 (m, 11H), 1.62-1.89 (m, 2H), 2.29-2.38 (m, 2H), 3.10-3.19 (m, 1H), 3.29 (s, 3H), 4.10 (q, 2H, *J* = 7.0 Hz).; EIMS *m/z* (%): 253 (m^{+23} 30), 231 (m^{+1} 100), 215 (10), 199 (50), 186 (10), 153 (10).

4.7. 4-Methoxydecanoic acid (1): To a mixture of ethyl-4-methoxydecanoate (0.7 g, 3 m mol) in THF-water [10 mL (2:1)] was added lithium hydroxide (0.11g, 4.5 mmol) at 0ºC. The resulting reaction mixture was stirred at room temperature for 6 hours. The complete conversion of the starting material was confirmed by TLC. Then, the solvent was removed under reduced pressure and the residue was acidified with 1N HCl and extracted with ethyl acetate (2x15 mL), washed with brine, dried (Na_2SO_4). The combined filtrates was adsobed on silica gel and eluted the column with ethyl acetate-hexane mixture (4:6) to give carboxylic acid **1** as a yellow color liquid, 0.52 g (85%). IR (neat): υ 3425, 2927, 2857, 1712, 1460, 1168, 1094, 1020, 761 $cm.^{-1}$; ^1H NMR ($CDCl_3$): δ 0.88 (t, 3H, *J* = 6.0 Hz), 1.22-1.45 (m, 10H), 1.62-1.89 (m, 2H), 2.42 (t, 2H, *J* = 7.0 Hz), 3.10-3.22 (m, 1H), 3.30 (s, 3H).; C^{13} NMR (75 MHz): δ 179.5, 80.0, 56.5, 33.2, 31.8, 30.0, 29.5, 28.3, 25.2, 22.6, 14.1.; EIMS *m/z* (%): 225 (m^{+23} 100), 203 (m^{+1} 10), 171 (25), 153 (30), 88 (18).

Acknowledgement

PN Thankful to CSIR-New Delhi for providing fellowship.

References

[1] Neely, N. N.; Ghannoum, M. A. The exciting future of antifungal therapy. *Eur. J. Clin. Microbiol. Infect. Dis.* **2000**, *19*, 897-914.

[2] Hossain, M. A.; Ghannoum, M. A. New investigational antifungal agents for treating invasive fungal infections. *Exp. Opin. Investig. Drugs*. **2000**, *9*, 1797-1813.

[3] Feron, G.; Dufosse, L.; Pierard, E.; Bonnarme, P.; Quere, J. L.; Spinnler, H. Production, Identification and toxicology of (gamma)- Decalactone and 4-hydroxy decanoic acid from *Sporidiobolus* spp. *Appl. Environ. Microbiol*. **1996**, *62*, 2826-2831.

[4] Greger, V.; Schieberle, P. Characterization of key aroma compounds in apricots (Prunus armeniaca) by application of the molecular sensory science concept. *J. Agric. Food. Chem*. **2007**, *55*, 5221-5228.

[5] Lozano, P. R.; Miracle, E. R.; Krause, A. J.; Drake, M.; Cadwallader, K. R. Effect of cold storage and packaging material on the major aroma components of sweet cream butter. *J. Agric. Food. Chem*. **2007**, *55*, 7840-7846.

[6] Sjogren, J.; Magnusson, J.; Broberg, A.; Schnurer, J.; Kenne, L. Antifungal 3-hydroxy fatty acids from Lactobacillus plantarum MiLAB 14. *Appl. Environ. Microbiol*. **2003**, *69*, 7554-7557.

[7] Carballeira, N. M.; Miranda, C.; Parang, K. The first total synthesis of (±) 4-methoxy decanoic acid: a novel antifungal fatty acid. *Tetrahedron Lett*. **2009**, *50*, 5699-5700.

[8] Das, B.; Shinde, D. B.; Kanth, B. S.; Kamle, A.; Kumar, C. G. Total synthesis of racemic and (*R*) and (*S*)-4-methoxyalkanoic acids and their antifungal activity. *Eur. J. Med. Chem*. **2011**, *46*, 3124-3129.
[9] Wadavrao, S. B.; Ghogare, R. S.; Narsaiah, A. V. Stereoselective synthesis of Oxylipin-3: [(6*R*,9*R*,10*R*,7*E*)-6,9,10-trihydroxyoctadec-7-enoic acid]. *Tetrahedron Lett*. **2012**, *53*, 3955-3958.
[10] Narsaiah, A. V.; Narsimha, P. Efficient synthesis of antihistamines Clocinizine and Chlorcyclizine. *Med. Chem. Res.* **2012**, *21*, 538-541.
[11] Narsaiah, A. V.; Nagaiah, B.; Karuna Devi, B. CNS-Agent precursor: a simple and efficient synthesis of an antipsychotic drug Fluanisone. *J. Heterocyclic Chem*. **2012**, *49*, 829-832.
[12] Narsaiah, A. V.; Kumar, J. K. A novel asymmetric synthesis of (*S*)-Esmolol using Hydrolytic Kinetic Resolution. *Synth. Commum.* **2011**, *41*, 1603-1608.
[13] Narsaiah, A. V.; Ghogare, R. S. An expedient stereoselective synthesis of the antifungal agent (6*S*)-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-5,6dihydro-2*H*-pyran-2-one. *Synthesis.* **2011**, 3271-3276.
[14] Narsaiah, A. V.; Kumar, J. K. A simple and efficient synthesis of Calcium channel blocker Flunarizine. *Int. J. Ind. Chem.* **2011**, *3*, 154-157.
[15] Jungk, S. J.; Moore, J. A.; Gandour, R. D. Efficient synthesis of C-pivot lariat ethers. 2-(alkoxymethyl)-1,4,7,10,13,16-hexaoxacyclooctadecanes.*J. Org. Chem*. **1983**, *48*, 1116-1120.
[16] Pandey, S. K.; Pandey, M.; Kumar, P. A concise synthesis of protected (2*S*,4*R*)-4-hydroxyornithine. *Tetrahedron Lett*. **2008**, *49*, 3297-3299.
[17] Bonini, C.; Chiummiento, L.; Pullez, M.; Solladie, G.; Colobert, F. Convergent highly stereoselective preparation of the C12-C24 fragment of macrolactin A. *J. Org. Chem*. **2004**, *69*, 5015-5022.
[18] Pattenden, G.; Gonzalez, M. A.; Little, P. B.; Millan, D. S.; Plowright, A. T.; Tornos, J. A.; Ye, T. Total synthesis of (+)-phorboxazole A: a potent cytostatic agent from the sponge phorbas sps. *Org. Biomol. Chem*. **2003**, *1*, 4173-4208.
[19] Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. Oxidation of alcohols with o-iodoxybenzoic acid in DMSO: a new insight into an old hypervalent iodine reagent. *J. Org. Chem*. **1995**, *60*, 7272-7276.
[20] Hoffman, R. W. Wittig and his accomplishments: still relevant beyond his 100th birthday. *Angew. Chem. Int. Ed*. **2001**, *40*, 1411-1416.