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The first total synthesis of (±)-4-methoxydecanoic acid: a novel antifungal fatty acid

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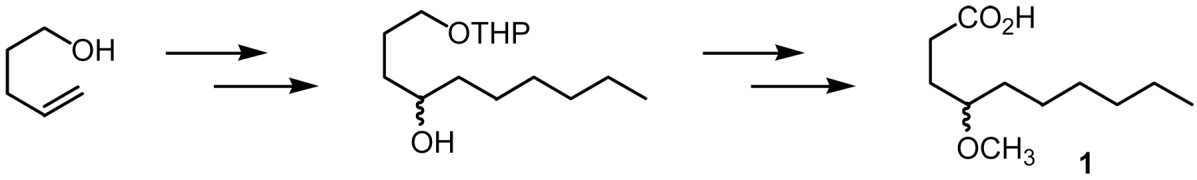
Abstract

The hitherto unknown (±)-4-methoxydecanoic acid was synthesized in six steps and in 25% overall yield starting from commercially available 4-penten-1-ol. The title compound demonstrated seventeen fold higher antifungal activity (MIC = 1.5 mM) against *Candida albicans* ATCC 60193 and *Cryptococcus. neoformans* ATCC 66031 when compared to unsubstituted *n*-decanoic acid. Our results demonstrate that Mid-chain methoxylation appears to be a viable strategy for increasing the fungitoxicity of fatty acids.



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Keywords

Antifungal; *Candida albicans*; Decanoic acid; Methoxylated Fatty Acids; Synthesis

The (±)-4-hydroxydecanoic acid is an elusive fatty acid to isolate from either a natural or synthetic source because of its tendency to easily cyclize to the well known γ-decalactone.[1] In fact, the spectral data for 4-hydroxydecanoic acid was first reported in 1996 by G. Feron and collaborators, attesting to the difficulty of isolating the pure hydroxylated fatty acid from the γ-decalactone.1 The γ-decalactone is an important compound for the aroma and food industries since the compound imparts a peach-apricot flavor to foods2–3 and is also responsible for the fruity flower odor of gardenia perfumes.[1] The γ-decalactone has also been used in <5 ppm concentrations in a selected number of cigarette brands.[4]

There are just a few scattered reports on the toxicity of (±)-4-hydroxydecanoic acid but it has been reported that the presence of a hydroxyl group in the acyl chain greatly decreases toxicity.

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However, the γ-decalactone has been reported to have higher antibacterial activity than (±)-4-hydroxydecanoic acid since it inhibits the growth of some bacteria such as *Bacillus subtilis* and some fungi such as *Fusarium oxysporum* and *Trichothecium roseum* at concentrations between 0.1 and 0.7 mM.[1] It should also be noted here that the 3-(*R*)-hydroxydecanoic acid has been isolated from *Lactobacillus plantarum* and displayed considerable antifungal activity (MIC = 10–100 μg/mL) against different molds and yeasts.[5]

We have previously shown that α-methoxylation increases the antifungal activity of fatty acids,[6–7] but nothing is known as to the effect of mid-chain methoxylation on the antifungal activity of these compounds. We envisioned that a compound such as the (±)-4-methoxydecanoic acid (**1**) could be a good starting template to study such an effect. In addition, we were expecting this methoxylated fatty acid to be more fungitoxic than the corresponding compounds, unsubstituted *n*-decanoic acid (capric acid) or isolated (±)-4-hydroxydecanoic acid. The choice of a 10-carbon chain length for this study is justified by the fact that capric acid kills *Candida albicans* at 10 mM by the postulated mechanism of the fungal plasma membrane disintegration while other saturated fatty acids are not effective.[8]

Furthermore, unlike (±)-4-hydroxydecanoic acid, (±)-4-methoxydecanoic acid (**1**) cannot be cyclized to the corresponding γ-lactone thus allowing the facile study of its fungitoxicity. This investigation was also designed to determine whether mid-chain methoxylation is a viable substitution to α-methoxylation for enhancing the antifungal activity of fatty acids such as capric acid. Previous studies by our group with the (±)-2-methoxydecanoic acid has shown that the 2-OMe-10:0 acid is only 1.5 fold more fungitoxic than capric acid (10:0) against *C. albicans* (ATCC 14053). However, against *C. neoformans* (ATCC 66031) the 2-OMe-10:0 acid was not more antifungal than capric acid.[6]

Our six-step synthesis started with the protection of the primary alcohol of commercially available 4-penten-1-ol (**2**) with dihydropyran (DHP) and catalytic amounts of *p*-toluenesulfonic acid (PTSA) in $CHCl_3$ at rt for 5h to afford the 1-[(tetrahydropyran-2-yl) oxy]-2-pentene in an 88% yield (Scheme 1). The double bond was effectively epoxidized in the presence of magnesium monoperoxyphthalate (MMPP) in EtOH as solvent for 48 h, to yield the 4,5-epoxy-1-[(tetrahydropyran-2-yl)oxy]pentane (**3**) in 89% yield after purification of the crude product using silica gel column chromatography (60–200 mesh) and eluting with hexane/diethyl ether (8:2). MMPP turned out to be more efficient than the classical *m*-chloroperoxybenzoic acid (*m*-CPBA) in epoxidizing these alkenes, since the latter reagent only afforded moderate to low yields even after long reaction times. The THP protected epoxide **3** was then opened with 1-pentylmagnesium bromide assisted by catalytic amounts of copper (I) chloride in THF at a reaction temperature range of −78°C to −30°C, which afforded the desired 4-hydroxy-1-[(tetrahydropyran-2-yl)oxy]decane (**4**) in an 81% yield after silica gel (60–200 mesh) column chromatographic purification. The free hydroxyl group in **4** was then readily methylated with methyl iodide in the presence of sodium hydride in THF, which afforded the 4-methoxy-1-[(tetrahydropyran-2-yl)oxy]decane (**5**) in an 88% yield. Deprotection of the primary alcohol was effectively accomplished with PTSA in $CHCl_3$ at 45° C for 2h, which afforded the (±)-4-methoxydecan-1-ol in a 73% yield (Scheme 1). Final oxidation to the acid was accomplished by reaction of the alcohol with pyridinium dichromate (PDC) in DMF for 24h, which resulted in a 63% yield of **1**.[9] The overall yield for this six step synthesis was 25%.

The most significant absorption in the NMR spectrum of **1** was observed for the carbons and hydrogens bearing the methoxy functionality. For example, the methoxy protons resonated at δ 3.32 ppm and the methoxy carbon was observed at δ 56.5 ppm, while the methine hydrogen ($CHOCH_3$) resonated at δ 3.20 ppm and the methine carbon ($CHOCH_3$) at δ 79.9 ppm. These ^1H NMR and ^{13}C NMR displacements seem to be characteristic for saturated mid-chain

methoxylated fatty acids and useful as a future reference for other similar analogs. It is also interesting to mention that in the 70 eV electron impact (EI) mass spectrum of **1** the typical McLafferty rearrangement of fatty acids at *m/z* = 60 was greatly reduced (1% relative abundance) by the presence of the methoxy functionality at C-4. In the mass spectrum of **1** the α fragmentation at both sides of the methoxylated carbon predominated, but the fragments containing the carboxyl end (at *m/z* =117 corresponding to $C_5H_90_3^+$ and at *m/z* = 85 corresponding to $C_4H_50_2^+$) were the most abundant.

The antifungal activity of **1** was determined against a fluconazole-resistant strain of *Candida albicans* (ATCC 60193) and against *Cryptococcus neoformans* (ATCC 66031) following our previously published protocol (Table 1).[6–7] *n*-Decanoic acid was also tested as a control. As can be seen from the data in Table 1 the (±)-4-methoxydecanoic acid (**1**) was approximately seventeen fold more antifungal against both fungal strains (MIC = 1,457 μM) when compared to *n*-decanoic acid (MIC = 25,478 μM). Therefore, the antifungal results clearly show that C-4 methoxylation increased the antifungal activity of the parent *n*-decanoic acid. In fact, for *n*-decanoic acid C-4 methoxy substitution seems to be more effective than C-2 methoxy substitution in increasing the antifungal activity of *n*-decanoic acid.[6]

As to the reasons for the better antifungal activity of **1** over that of *n*-decanoic acid we can only speculate at this stage and more mechanistic studies are required. The addition of the C-4 methoxy functionality possibly makes the fatty acid more soluble than unsubstituted *n*-decanoic acid thus facilitating its interaction with the target sites. In addition, based on the previously published antifungal mechanism of decanoic acid[8] we can also speculate that acid **1** seems to be able to more efficiently disrupt the fungal membranes due to the mid-chain methoxy substitution. Moreover, the title compound **1** may also inhibit fatty acid biosynthesis within the fungi interacting with some key enzymes. In summary, our results clearly demonstrate that mid-chain methoxylated fatty acids are valuable compounds that can be optimized for developing more potent antifungal agents and thus merit further scrutiny in the search for better antifungal analogs.

Acknowledgments

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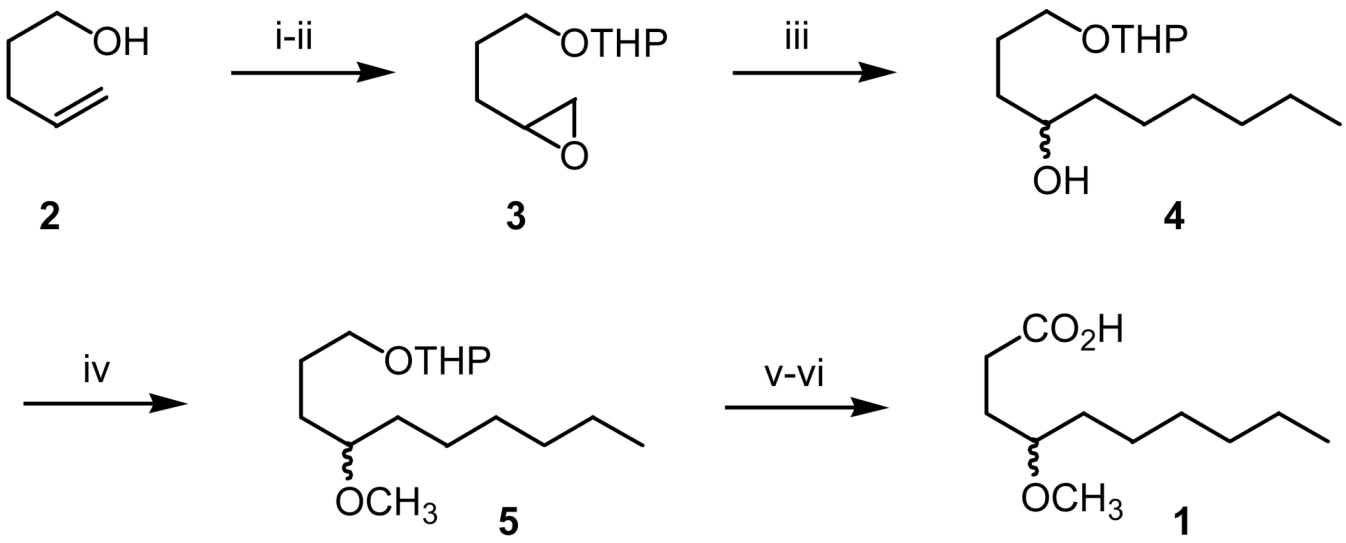
References and notes

1. Feron Y, Dufosse L, Pierard E, Bonnarme P, Le Quere J-L, Spinnler H-E. Appl. Environ. Microbiol 1996;62:2826. [PubMed: 16535376]
2. Greger V, Schieberle P. J. Agric. Food Chem 2007;55:5221. [PubMed: 17530862]
3. Lozano PR, Miracle ER, Krause AJ, Drake M, Cadwallader KR. J. Agric. Food Chem 2007;55:7840. [PubMed: 17705437]
4. Carmines EL. Food Chem. Toxicol 2002;40:77. [PubMed: 11731038]
5. Sjögren J, Magnusson J, Broberg A, Schnürer J, Kenne L. Appl. Environ. Microbiol 2003;69:7554. [PubMed: 14660414]
6. Carballeira NM, Ortiz D, Parang K, Sardari S. Arch. Pharm. Pharm. Med. Chem 2004;337:152.
7. Carballeira NM, O'Neill R, Parang K. Chem. Phys. Lipids 2007;150:82. [PubMed: 17662704]
8. Bergsson G, Arnfinnsson J, Steingrímsson Ó, Thormar H. Antimicrob. Agents Chemother 2001;45:3209. [PubMed: 11600381]
9. *Spectral data for the (±)-4-methoxydecanoic acid* (**1**): transparent oil; IR (neat): ν_{max} 3500-2500, 2928, 1712, 1462, 1377, 1282, 1096, 936 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.32 (s, 3H, -OCH_3), 3.20 (m, 1H, H-4), 2.43 (t, *J* = 7.5 Hz, 2H, H-2), 1.97-1.67 (m, 2H, H-3), 1.52 (m, 2H, H-5), 1.27(m, 8H,

-CH_2-), 0.87 (t, J = 6.7 Hz, 3H, -CH_3); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 179.6, 79.9, 56.5, 33.1, 31.8, 29.9, 29.4, 28.2, 25.1, 22.6, 14.0; GC-MS (70 eV) *m/z* (rel. intensity) 201(M^+-1, 0.1), 187(2), 170(1), 169(2), 129(18), 116(54), 97(16), 85(100), 71(14), 60(1), 57(7), 55(24); HRMS (APCI): calcd for $C_{11}H_{23}O_3$ $(M+H)^+$ 203.1642, found: 203.1639.



Scheme 1.

i) DHP/PTSA,$CHCl_3$, rt, 5h, 88%; *ii*) MMPP/EtOH, 48h, 89%; *iii*) $CH_3(CH_2)_3CH_2MgBr$, Cu (I) / THF, −78°C to −30°C, 81%; *iv*) NaH/CH_3I, THF, 0°C to rt, 2h, 88%; *v*) PTSA, $CHCl_3$, 45°C, 2h, 73%; *vi*) PDC/DMF, 24h, 63%.

Table 1

Antifungal activity (MIC values, μM) against *Candida albicans* (SDB) and *Cryptococcus neoformans* (SDB) at 35–37°C after 24–48h[a].

Compound	*C. albicans* ATCC 60193	*C. neoformans* ATCC 66031
(±)-4-methoxydecanoic acid (**1**)	1457	1457
Decanoic acid	25478	25478
Fluconazole	>500	<0.9
Amphotericin B	<0.3	<0.3
DMSO	>5000	>5000

[a]The results are the average of three separate experiments. The upper limit of the standard error of the mean (SEM) was ± 10%.