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A New Approach Towards (±)-4-Ipomeanol and Its 2-Furyl Regioisomer

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Dedicated to Prof. Dr. Dr. h.c. F. Eiden, München, on the occasion of his 80^{th} birthday

The cytotoxic furan derivative (±)-4-ipomeanol (**1**) and its regioisomer (**8**) were prepared in a new and efficient way starting from commercially available furan derivatives. In both cases the key step was a regioselective solvolysis of the terminal double bond with trifluoroacetic anhydride and boron trifluoride. The resulting compounds were tested in an agar diffusion assay against several bacteria and fungi, but did not show significant activity.

Key Words: (±)-4-ipomeanol, solvolysis, antimicrobial activity

Introduction

(±)-4-Ipomeanol (**1**) is a well known cytotoxic metabolite of microbially infected sweet potatoes, *Ipomoea batata*, which was first isolated in 1972 by Boyd and coworkers.[1] (±)-4-Ipomeanol (**1**) is a stress metabolite in response to microbial infection with an LD_{50} of 20–70 mg/kg.[2] It behaves as a relative specific lung toxic agent. The mechanism of action is restricted to the lung Clara cells, which leads to a bioactivation of the compound by cytochrome P450 monooxygenase to a highly reactive alkylating furan epoxide.[13] Because of the specific lung toxicity (±)-4-ipomeanol (**1**) is being tested as a new drug for the treatment of lung carcinoma. On the other hand, (±)-4-ipomeanol (**1**) is metabolized by liver cells too, and so it was recently tested in phase II studies in patients with hepatocellular carcinoma,[3–5] but the results were not encouraging. The first total synthesis of **1** was published in 1972 by Harris et al.[6] In this approach (±)-4-ipomeanol was built up in 5 steps starting from diethyl 3,4-furandicarboxylate.

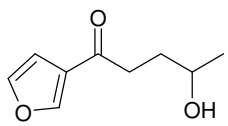

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Figure. Structure of (±)-ipomeanol (**1**).

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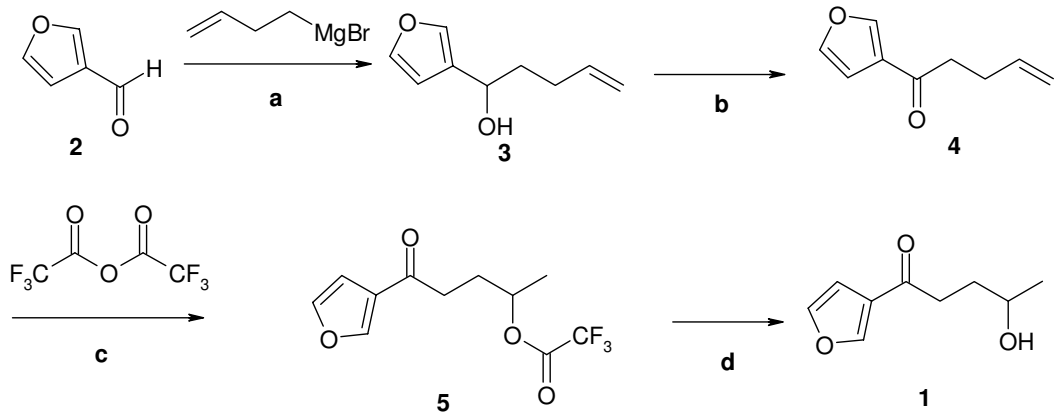
Results and Discussion

In continuation of our research on the total synthesis of cytotoxic and antimicrobial furan and tetrahydrofuran compounds[7] we developed a new approach for (±)-4-ipomeanol (**1**). **1** was built up in 4 steps starting from commercially available furan-3-carbaldehyde (**2**). **2** was reacted in a Grignard reaction with but-3-enylmagnesium bromide to give the racemic alcohol **3**.[8] Alcohol **3** was oxidized under Dess-Martin conditions to the corresponding alkenyl ketone **4**.[9] The regioselective solvolysis of the terminal C/C-double bond of **4** was carried out with a mixture of trifluoroacetic anhydride (containing a small amount of trifluoro acetic acid) and $BF_3 \times Et_2O$ as Lewis acid to give the (±)-4-ipomeanol ester **5**.[10] Under these conditions only the 4-substituted product was isolated. The ester **5** was hydrolyzed with KOH in methanol to give the racemic target compound **1**.

In a similar way the 2-furyl regioisomer of (±)-4-ipomeanol (**1**) was prepared in 2 steps starting from furan (**6**). **6** was reacted with pent-4-enoic acid, trifluoroacetic anhydride and $BF_3 \times Et_2O$ over 4 h in a Friedl-Crafts acylation and concomitant solvolysis of the double bond to give the ester **7**, which was subsequently hydrolyzed with KOH in methanol to give racemic **8**. If the reaction mixture was stirred for only 1 h, the alkenone **9** was isolated as the main product. The progress of the reaction was controlled by GLC-MS.

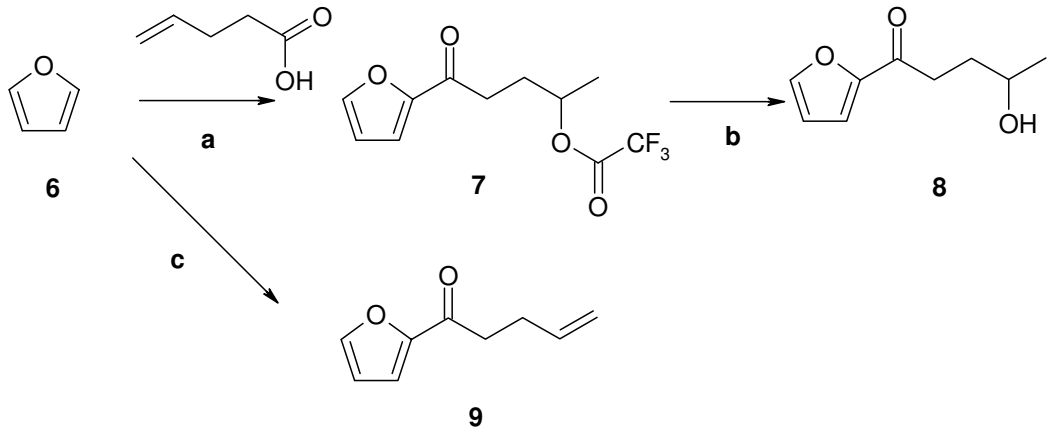
The target compounds and their precursors were tested in an agar diffusion assay against the Gram-negative bacteria *Escherichia coli* and *Pseudomonas antimicrobia*, the Gram-positive bacterium *Staphylococcus hominis* and the fungi *Yarrowia lipolytica* and *Hypopichia burtonii*. The zones of inhibition were compared with those of the common antibiotic tetracycline and antifungal clotrimazole. The new compounds did not show significant activity in this screening.



Scheme 1. a: THF, RT; b: Dess-Martin periodinane, CH_2Cl_2, 1 h; c: $BF_3 \times Et_2O$, H_2O, RT, 4 h; d: KOH, methanol.

Experimental

IR-Spectra: Perkin-Elmer FT-IR Paragon 1000; MS: Hewlett Packard MS-Engine, electron ionization (EI) 70 eV, chemical ionization (CI) with CH_4 (300 eV); NMR (400 MHz): Jeol GSX 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz); GLC-MS: Shimadzu GC 17 A; flash column chromatography (FCC): silica gel 60 (230 – 400 mesh, E. Merck, Darmstadt, Germany).



Scheme 2. a: $BF_3\times Et_2O$, $(F_3C\text{-}CO)_2O$, 4 h, RT, b: KOH, methanol, reflux c: $BF_3\times Et_2O$, $(F_3C\text{-}CO)_2O$, 1 h, RT.

(±)-1-(Furan-3-yl)pent-4-en-1-ol (3). 500 mg (5.2 mmol) of furan-3-carbaldehyde (**2**) was dissolved in 20 mL dry THF and a solution of 7 mmol of but-3-enylmagnesium bromide in 5 mL of dry THF was added dropwise. The mixture was stirred for 12 h, diluted with a saturated aqueous NH_4Cl solution and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The residue was purified with FCC (n-hexane/ethyl acetate 10:3) to give 630 mg (80%) of **3** as a pale yellow oil. MS (EI): m/z (%) = 152 (M^+, 1.0), 97 (100). Calcd.: C: 71.03 H: 7.95 Found: C: 70.79 H: 8.13. The ^{1}H-NMR data were in full accordance to the literature[11].

1-(Furan-3-yl)pent-4-en-1-one (4). 600 mg (3.9 mmol) of **3** was dissolved in 20 mL of dry CH_2Cl_2 and 2.0 g of periodinane (Dess-Martin reagent) was added. The mixture was stirred for 1 h, diluted with 20 ml aqueous 10% $Na_2S_2O_3$ solution and 20 mL of aqueous 10% Na_2CO_3solution and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The residue was purified with FCC (n-hexane/ethyl acetate 5:1) to give 520 mg (89%) of **4** as a colorless oil. The ^{1}H-NMR data were in full accordance with the literature[11]. ^{13}C-NMR ($CDCl_3$) δ (ppm) = 28.2 (CH_2), 39.6 (CH_2), 108.6 (aromat. CH), 115.4 (=CH_2), 127.8 (quart. C), 137.2 (aromat. CH), 144.3 (aromat. CH), 147.4 (-CH=), 194.2 (CO). MS (EI): m/z (%) = 150 (M^+, 0.56), 95 (100). Calcd.: C: 71.98 H: 6.71 Found: C: 71.35 H: 6.85. IR (KBr): ν[cm^{-1}] = 3133, 2925, 1680, 1641, 1563, 1510, 1157, 913, 873, 743.

(±)-(4-Furan-3-yl-1-methyl-4-oxo-butyl) trifluoro-acetate (**5**). 500 mg (3.3 mmol) of **4** was dissolved in 15 mL of trifluoroacetic anhydride, 1 ml of water and 3 mL of $BF_3\times Et_2O$. The mixture was stirred for 3 h, quenched with 30 mL of a 10% aqueous of Na_2CO_3 solution and extracted with diethyl ether (3 × 30 mL). The aqueous layer was extracted with diethyl ether (2 × 30 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated and the residue was purified with FCC (n-hexane/ethyl acetate 10:1) to give 290 mg (34%) of **5** as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.41 (d, J = 5.9 Hz, 3 H, CH_3), 2.11 (m, 2 H, CH_2), 2.86 (m, 2 H, CH_2), 5.19 (m, 1 H, CH), 6.77 (dd, J = 0.9 Hz, J = 1.8 Hz, 1 H, aromat. CH), 7.47 (d, J = 1.5 Hz, 1 H, aromat. CH), 8.06 (d, J = 0.8 Hz, 1 H, aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 19.6 (CH_3), 29.5 (CH_2), 35.5 (CH_2), 75.8 (CH), 108.5 (aromat. CH), 127.3 (quart. C), 144.7 (aromat. CH), 147.6 (aromat. CH), 194.3 (CO). MS (EI): m/z (%) = 264 (M^+, 0.14), 150 (0.71), 110 (40), 95 (100).

(±)-4-Ipomeanol (**1**). 190 mg (0.7 mmol) of **5** was dissolved in 25 mL 5% methanolic KOH and heated under reflux for 1 h. The solvent was evaporated, the residue dissolved in 5% aqueous HCl and

extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated to give 100 mg (85%) of **1** as a pale yellow oil. The ^{1}H-NMR spectroscopic data were in full accordance with literature [6]. ^{13}C-NMR ($CDCl_3$) δ (ppm) = 23.1 (CH_3), 32.5 (CH_2), 36.8 (CH_2), 68.3 (CH), 108.6 (aromat. CH), 127.4 (quart. C), 144.5 (aromat. CH), 147.9 (aromat. CH), 195.4 (CO). MS (EI): m/z (%) = 168 (M^+, 3), 110 (30), 95 (100).

(±)-(4-Furan-2-yl-1-methyl-4-oxo-butyl) trifluoro-acetate (**7**). 680 mg (10 mmol) of furan and 1.0 g (10 mmol) of pent-4-enoic acid were dissolved in 15 mL of trifluoroacetic anhydride and 3 mL of BF_3 × Et_2O. The mixture was stirred for 4 h, quenched with 30 ml of a 10 % solution of Na_2CO_3 and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The residue was purified with FCC (n-hexane/ethyl acetate 10:1) to give 570 mg (22%) of **7** as a pale brown oil. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.42 (d, J= 6.2 Hz, 3 H, CH_3), 2.13 (m, 2 H, CH_2), 2.95 (t, J = 7.6 Hz, 2 H, CH_2), 5.19 (m, 1 H, CH), 6.57 (dd, J = 1.7 Hz, J = 3.6 Hz, 1 H, aromat. CH), 7.26 (dd, J = 0.7 Hz, J= 3.6 Hz, 1 H, aromat. CH), 7.62 (dd, J = 0.7 Hz, J = 1.7 Hz, 1 H, aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 19.6 (CH_3), 29.5 (CH_2), 33.6 (CH_2), 75.7 (CH), 112.6 (aromat. CH), 114.6 (d, J = 286.7 Hz, CF_3), 118.1 (aromat. CH), 147.1 (aromat. CH), 152.24 (quart. C), 157.2 (d, J = 42.3 Hz, CO), 188.8 (CO). MS (EI): m/z (%) = 264 (M^+, 0.14), 151 (0.43), 110 (69), 95 (100).

1-(Furan-2-yl)pent-4-en-1-one (9). **9** was prepared under the same conditions as described for **7**. If the reaction time was only 1 h, 750 mg (49%) of **9** was isolated as a pale yellow oil. The ^{1}H-NMR spectroscopic data were in full accordance with the literature[12]. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 2.48 (dt, J = 6.5 Hz, J = 7.9 Hz, 2 H, 3-H), 2.91 (t, J = 7.9 Hz, 2-H), 5.01 (dd, J = 10.1 Hz, J = 1.7 Hz, 5-H), 5.08 (dd, J =17.2 Hz, J = 1.7 Hz, 1 H, 5-H), 5.88 (ddt, J = 6.5 Hz, J = 17.2 Hz, J = 10.1 Hz, 1 H, 4-H), 6.54 (dd, J = 1.7 Hz, J = 3.5 Hz, 1 H, 4'-H), 7.19 (d, J = 3.5 Hz, 1 H, aromat. CH), 7.58 (d, J = 1.7 Hz, 1 H, aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 28.1 (CH_2), 37.6 (CH_2), 112.2 (aromat. CH), 115.4 (=CH_2), 116.9 (aromat. CH), 137.0 (aromat. CH), 146.3 (=CH-) 152.8 (quart. C), 188.7 (CO). MS (EI): m/z (%) = 150 (M^+, 0.9), 95 (100).

(±)-1-(Furan-2-yl)-4-hydroxypentan-1-one (**8**). 150 mg (0.56 mmol) of **7** was dissolved in 25 ml 5% methanolic KOH and heated under reflux for 1 h. The solvent was evaporated, the residue dissolved in 5% HCl and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated to give 80 mg (85%) of **8** as a pale yellow oil. The ^{1}H-NMR spectroscopic data were in full accordance with the literature.[11] ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.24 (d, J = 6.2 Hz, 3 H, CH_3), 1.84 (m, 2 H, CH_2), 2.99 (t, J = 7.3 Hz, 2 H, CH_2), 3.88 (m, 1 H, CH), 6.54 (dd, J = 1.7 Hz, J = 3.6 Hz, 1 H, aromat. CH), 7.22 (d, J = 3.6 Hz, 1 H, aromat. CH), 7.59 (d, J = 1.7 Hz, 1 H, aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 23.7 (CH_3), 32.9 (CH_2), 34.8 (CH_2), 67.5 (CH), 112.2 (aromat. CH), 117.2 (aromat. CH), 146.4 (aromat. CH), 152.6 (quart. C), 189.8 (CO). MS (CI): m/z (%) = 169 (M^++1, 12), 151 (100).

References

1. M.R. Boyd, and B.J. Wilson, **J. Agric. Food. Chem. 20**, 428–430 (1972).
2. L.T. Burka, L. Kuhnert, B.J. Wilson, and T.M. Harris, **J. Am. Chem. Soc. 99**, 2302-2305 (1977).
3. M.C. Christian, R.E. Wittes, B. Leyland-Jones, T.L. Mc Lemore, A.C. Smith, C.K. Grieshaber, B.A. Chabner, and M.R. Boyd, **J. Nat. Cancer Inst. 81**, 1133–1143 (1989).
4. S.M. Smiley-Jewell, and C.G. Plopper, **Toxicol. Appl. Pharm. 192**, 69–77 (2003).
5. S. Lakhanpal, R.C. Donehower, and E.K. Rowinsky, **Invest. New Drug. 19**, 69 – 76 (2001).
6. R. Boyd, B.J. Wilson, and T.M. Harris, **Nat. New Biol. 236**, 158–159 (1972).
7. J. Krauss, D. Unterreitmeier, and D. Antlsperger, **Arch. Pharm. Pharm. Med. Chem. 336**, 381–384 (2003).
8. J. Krauss, and D. Unterreitmeier, **Arch. Pharm. Pharm. Med. Chem. 335**, 94–98 (2002).
9. D.B. Dess, and J.C. Martin, **J. Org. Chem. 48,** 4155-4156 (1983).
10. P.E. Peterson, **J. Am. Chem. Soc. 82**, 5834–5837 (1960).
11. W.H. Liu, and H.J. Wu, **J. Chin. Chem. Soc. 35,** 241–246 (1988).
12. K. Fischer, and S. Huenig, **J. Org. Chem. 52**, 564–569 (1987).
13. B.R. Baer, A.E. Rettie, and K.R. Henne, **Chem. Res. Toxicol. 18**, 855-864 (2005).