Turk J Chem
30 (2006) , 451 – 454.


# Short and Effective Synthesis of a Thiophene Analogue of (±)-4-Ipomeanol and Its Biological Evaluation

**Jürgen KRAUSS*, Doris UNTERREITMEIER, Franz BRACHER**
*Department of Pharmacy. Ludwig-Maximilians-University, Butenandtstr. 5-13, 81377 Munich-GERMANY*
*e-mail: hjkra@cup.uni-muenchen.de*

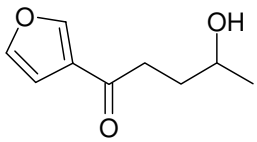
Received 06.01.2006

The thiophene analogue of (±)-4-ipomeanol (**1**) was prepared in 2 steps starting from 3-iodothiophene and pent-4-yn-2-ol. The key steps were a Sonogashira reaction, followed by HgO catalysed hydratisation of the triple bond. The resulting thiophene was tested in the MTT assay for its cytotoxic activity against HL 60 cells.

**Key Words:** Sonogashira reaction, 4-ipomeanol, cytotoxic activity, MTT assay.

## Introduction

(±)-4-Ipomeanol (**1**) is a natural cytotoxin, first isolated from *Fusarium solani* infected sweet potatoes, *Ipomoea batata*, in 1972 by Boyd and coworkers.[1,2] 4-Ipomeanol (**1**) is a stress metabolite in response to microbial infection, with an $LD_{50}$ of 20-70 mg/kg.[2] The mechanism of action is closed to the lung Clara cells, which leads to a bioactivation of the compound by cytochrome P-450 monooxygenase to a highly reactive alkylating furan epoxide as recently published by Baer et al.[3] Because of its 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 metabolised by liver cells as well, and so it was recently tested in a phase II clinical trial on patients with hepatocellular carcinoma,[4−7] but the results were not encouraging.




**1**

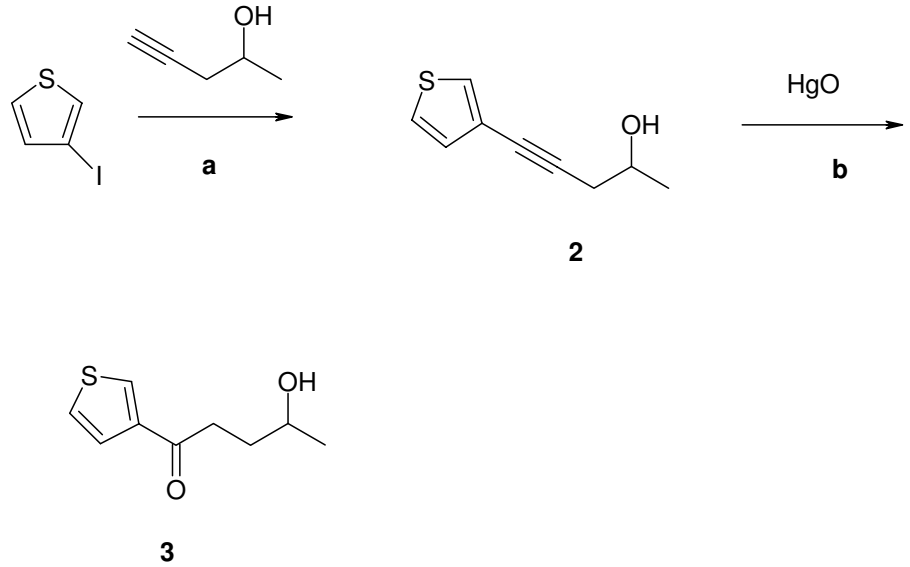
**Figure 1.** (±)-4-Ipomeanol (**1**).

In continuation of our work on 4-ipomeanol derivatives we developed the first synthesis of a thiophene analogue. The described synthesis can also be used for the synthesis of (±)-ipomeanol (**1**).

*Corresponding author

# Chemistry

The target compound **3** was synthesised by a Sonogahira reaction of the commercially available 3-iodothiophen and pent-4-yn-2-ol under catalysis of $PdCl_2(PPh_3)_2$ and CuI in ethyldimethylamine (EDMA) to give the alkyne **2** in almost quantitative yield.[8] The triple bond of **2** was regioselective hydrated under HgO catalysis to give the aromatic ketone **3**.[9]




**Scheme.** a: CuI, EDMA, $PdCl_2(PPh_3)_2$. b: HgO, methanol, $H_2SO_4$.

Compound **3** was tested in the MTT assay for its cytotoxic activity against HL 60 cells using the method described by Mosman[10]. The compound showed only weak cytotoxic activity.

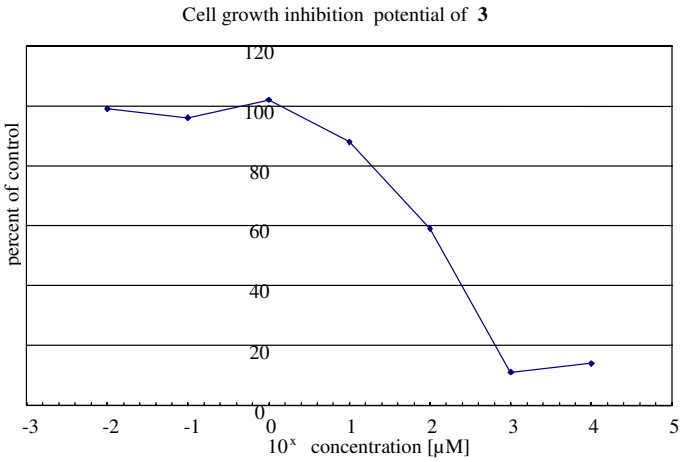



**Figure 2.** MTT-assay of thioipomeanol (**3**).

# Discussion

As diagrammed in Figure 2, the thiophene analogue showed only weak cytotoxic activity against HL 60 cells ($IC_{50} = 10^2$ $\mu$M). Work is in progress to test the cytotoxicity after cytochrome P450 activation as described

for (±)-4-ipomeanol (**1**). The described synthesis might also be used for the synthesis of (±)-ipomeanol (**1**), when starting from 3-iodofuran. The synthesis allowed us to build up enantiomeric pure products by starting from enantiomeric pure pent-4-yn-2-ol.

# Experimental

IR-spectra: Perkin-Elmer FT-IR Paragon 1000; MS: Hewlett Packard MS-Engine, electron ionisation (EI) 70 eV, chemical ionisation (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).

### (±)-5-Thiophen-3-ylpent-4-yn-2-ol (2).

First 950 mg (4.5 mmol) of 3-iodothiophen and 800 mg (9.5 mmol) of (±)-pent-4-yn-2-ol were dissolved in 30 mL of EDMA; then 190 mg (1.0 mmol) of CuI and 150 mg (0.2 mmol) of $PdCl_2(PPh_3)_2$ were added and the mixture was stirred for 12 h at room temperature under $N_2$atmosphere. The solvent was evaporated and the residue was dissolved in 50 mL of 5% aqueous $Na_2S_2O_3$ solution, extracted with diethyl ether (3 × 50 mL) and the combined organic layers were dried over $Na_2SO_4$. The organic solvent was evaporated and the residue purified by FCC (n-hexane / ethyl acetate 10:1) to give 710 mg (95%) of **2** as a brown oil.

$^1$H-NMR ($CDCl_3$) $\delta$ (ppm) = 1.32 (d, $J$= 6.2 Hz, 3 H, $CH_3$), 2.01 (s, 1 H, OH), 2.53 (dd, $J$ = 6.8 Hz, $J$ = 16.7 Hz, 1 H, $CH_2$), 2.61 (dd, $J$ = 6.8 Hz, $J$ = 16.7 Hz, 1 H, $CH_2$), 4.04 (m, 1 H, CH), 7.09 (dd, $J$ = 1.1 Hz, $J$ = 5.0 Hz, 1 H, aromat. CH), 7.25 (dd, $J$ = 3.2 Hz, $J$ = 5.0 Hz, 1 H, aromat. CH), 7.39 (dd, $J$ = 3.2 Hz, $J$ = 1.1 Hz, 1 H, aromat. CH). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm) = 22.41 ($CH_3$), 30.01 ($CH_2$), 66.52 (CH), 78.07 (quart. C), 85.68 (quart. C), 122.27 (quart. C), 125.20 (aromat. CH), 128.25 (aromat. CH), 129.95 (aromat. CH). MS (CI): m/z (%) = 333 (2 x $M^+$+1, 100), 167 ($M^+$+1, 20). IR (KBr): $\nu$ [$cm^{-1}$] = 3390, 3106, 2970, 2926, 2905, 1114, 1084. $C_9H_{10}OS$ (166.24) Calcd: C: 65.03 H: 6.06 S: 19.29. Found: C: 64.54. H: 6.06. S: 18.41.

### (±)-4-Hydroxy-1-thiophen-3-yl-pentan-1-one (3).

First 250 mg (1.5 mmol) of **3** was dissolved in 20 mL of methanol, and 10 mL of 5% $H_2SO_4$ and 800 mg (3.7 mmol) of yellow HgO were added. The solution was stirred for 12 h at room temperature. The methanol was evaporated and residue was quenched with 20 mL of saturated $Na_2CO_3$ solution and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over $Na_2SO_4$ and the residue was purified by FCC (n-hexane/ethyl acetate 5:1) to give 70 mg (25%) of **3** as a colourless oil. $^1$H-NMR ($CDCl_3$) $\delta$ (ppm) = 1.25 (d, $J$ = 6.2 Hz, 3 H, $CH_3$), 1.82 (m, 1 H, $CH_2$), 1.94 (m, 1 H, $CH_2$), 3.06 (t, $J$ = 6.9 Hz, 2 H, $CH_2$), 3.89 (m, 1 H, CH), 7.32 (ddd, $J$ = 0.6 Hz, $J$ = 2.9 Hz, $J$ = 5.1 Hz, 1 H, aromat. CH), 7.56 (ddd, $J$ = 5.1 Hz, $J$ = 1.2 Hz, $J$= 0.7 Hz, 1 H, aromat. CH), 8.10 (dd, $J$ = 1.2 Hz, $J$ = 2.9 Hz, 1 H, aromat. CH). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm) = 23.85 ($CH_3$), 33.04 ($CH_2$), 36.20 ($CH_2$), 67.51 (CH), 126.37 (aromat. CH), 126.96 (aromat. CH), 132.10 (aromat. CH), 142.17 (quart. C), 195.12 (CO). MS (CI): m/z (%) = 185 ($M^+$+1, 58), 167 (100), 111 (20). MS (EI): m/z (%) = 184 ($M^+$, 3), 167 (16), 126 (56), 111 (100). IR

(KBr): $\nu$ [$cm^{-1}$] = 3433, 3106, 2965, 2925, 1669, 1510, 1411, 913, 743. $C_9H_{12}O_2S$(184.26). HR-MS: Calcd.: 184.0558. Found: 184.0562.

## 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. B.R. Baer, A.E. Rettie and K.R. Henne, **Chem. Res. Toxicol. 18**, 855-864 (2005).
4. M.C. Christian, R.E. Wittes, B. Leyland-Jones, T.L. McLemore, A.C. Smith, C.K. Grieshaber, B.A. Chabner and M.R. Boyd, **J. Natl. Cancer Inst.**, **81**, 1133-1143 (1989).
5. S.M. Smiley-Jewell and C.G. Plopper, **Toxicol. Appl. Pharm. 192**, 69-77 (2003).
6. S. Lakhanpal, R.C. Donehower and E.K. Rowinsky, **Invest. New Drugs 19**, 69-76 (2001).
7. R. Boyd, B.J. Wilson and T.M. Harris, **Nature. New Biol. 236**, 158-159 (1972).
8. T. Sakamoto, F. Shiga, A. Yasuhara, D. Uchiyama, Y. Kondo and H. Yamanaka, **Synthesis**, **8**, 746-748 (1992).
9. G.F. Hennion and C.J. Pillar, **J. Am Chem. Soc**., **72**, 5317-5318 (1950).
10. T.J. Mosmann, **Immunol. Meth. 65**, 55-63 (1983).