

SYNTHESIS OF A NEW FLAVONOID-ANTIOXIDANT

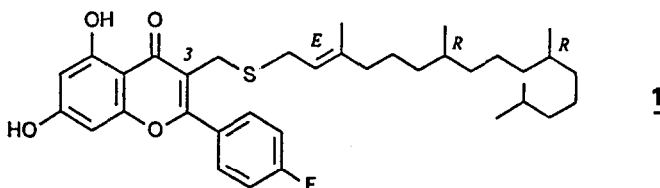
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Abstract: A new, highly lipophilic inhibitor 1 of LDL-oxidation has been synthesized from 3-bromomethyl-flavonoid 7 and isomerically pure 2(E)-phytyl mercaptan 8.

The generation of free radicals in biological systems has received increasing attention during the last years ^{1,2}). Oxidation of low density lipoproteins (LDL) by free radicals is considered to be an important event in atherogenesis ³). Antioxidants can inhibit LDL-oxidation and prevent development of arteriosclerosis at least in animal models ⁴).

We wish to report the synthesis of a new, potent lipophilic flavonoid-antioxidant 1. The preferential incorporation of such compounds with long chain hydrocarbons that contain one or more double bonds, into LDL has been published recently ⁵).



Compound 1 was prepared through alkylation of 2(E)-phytyl mercaptan 8 with 3-bromomethyl-flavonoid 7 (triethylamine, 25°C, 4h), subsequent removal of the acetate protecting groups (CH₃OH, K₂CO₃, 25°C, 4h under argon, workup with 2M HCl) and chromatography on silica, cyclohexane/ethyl acetate = 5:1 in 70 % yield, mp. 110°C ⁶) (scheme 1).

2(E)-Phytyl mercaptan 8 was obtained from 2(E)-phytol 7) by the method of Folkers ⁸⁾. Flavonoid 7 has been synthesized from phloroglucine dimethyl-ether 2 in five steps. Reaction of 2 with propionitrile ⁹⁾ (neat, 0.25 equiv. $ZnCl_2$, saturation with hydrochloric acid, 50°C, 10 h) provided propiophenone 3 in 67 % yield ¹⁰⁾, mp. 113°C. Conversion of 3 into flavonoid 4 was achieved by O-acetylation with 4-fluoro-benzoyl chloride (1.3 equiv., K_2CO_3 , acetone, reflux, 6 h) and subsequent Robinson synthesis ¹¹⁾, which brings about rearrangement and cyclisation in a single experimental step (1. DMSO, 1 equiv. NaH, 25°C, 2. aqueous oxalic acid, 0°C) in an overall yield of 75 %, mp. 228°C.

Demethylation of 4 (57 % hydroiodic acid, 100°C, 4 h) after aqueous workup gave 5 in 98 % yield, mp. 282°C. Acetylation of 5 with 10 equiv. acetylanhydride in the presence of 5 equiv. pyridine at 100°C for 3 h, provided after extraction with ethylacetate/water 5,7-bisacetoxy-flavonoid 6 in 90 % yield, mp. 147°C. Selective bromination of 6 ¹²⁾ (1 equiv. N-bromo-succinimide, CCl_4 , reflux, 4 h) was catalyzed with 4 equiv. N,N-azobis-isobutyronitrile (AIBN) and gave 7 in 95 % yield, mp. 165°C.

On inhibition of LDL-oxidation ¹³⁾ in vitro, 1 was 15 times more potent than vitamin E. (IC_{50} (mol/l): 3.3×10^{-7} 1, 4.8×10^{-6} (vitamin E)). Results from animal studies will be reported separately.

Acknowledgements: We wish to thank S. Jäger and K. Hohm for skillful technical assistance, Dr. Fehlhaber, Dr. Kogler, M. Weber and R. Saric for analytical support. Dr. Granzer and Dr. Schacht for biological data.

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 6. 1 : ^1H NMR (CDCl_3) δ in ppm: 0.85 (dd,6H), 0.88 (dd, $J=7\text{Hz}$,6H), 1.0-1.4 (m,16H), 1.52 (p, $J=7,5\text{Hz}$,3H), 1.62 (s,3H), 1.95 (t, $J=8\text{Hz}$,2H), 3.35 (d, $J=8\text{Hz}$,2H), 3.58 (s,2H), 5.25 (t, $J=8\text{Hz}$,1H), 5.70 (broad s,OH), 6.32 (dd, $J=16\text{Hz}$,2H), 7.21 (t, $J=8\text{Hz}$,2H), 7.8-7.9 (m,2H), 12.8 (s,OH)
1 : HPLC: RP 18 (Lichrospher 60, E. Merck), acetonitrile/ H_2O = 9:1 + 0.1 % ammonium acetate, retention time: Z-Isomer = 6.72 min. 3 %, E-isomer = 7.25 min, 97 %.
 7. Commercial phytol from Aldrich (E/Z-mixture 67:33) was purified by chromatography on silica, cyclohexane/ethyl acetate = 20:1. Purity (98 %) has been proven by GLC (column DB-5, J + W, Rancho Cordova, CA 95670, 1.0 bar helium, 220°C).
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 10. Minor amounts (10 %) of the corresponding 4-acyl-isomer were removed by crystallisation from ethanol.
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 12. Under the same reaction conditions, bromination of 5,7-bismethoxy-flavonoid 4 failed to give the corresponding 3-bromomethyl-flavonoid.
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(Received in Germany 25 September 1990)