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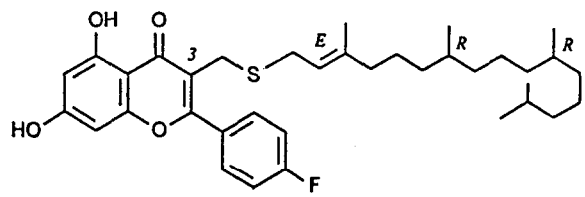
SYNTHESIS OF A NEW FLAVONOID-ANTIOXIDANT

G. Beck, A. Bergmann, K. Keßeler, G. Wess

Hoechst AG, Postfach 80 03 20, D-6230 Frankfurt/Main-80

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.

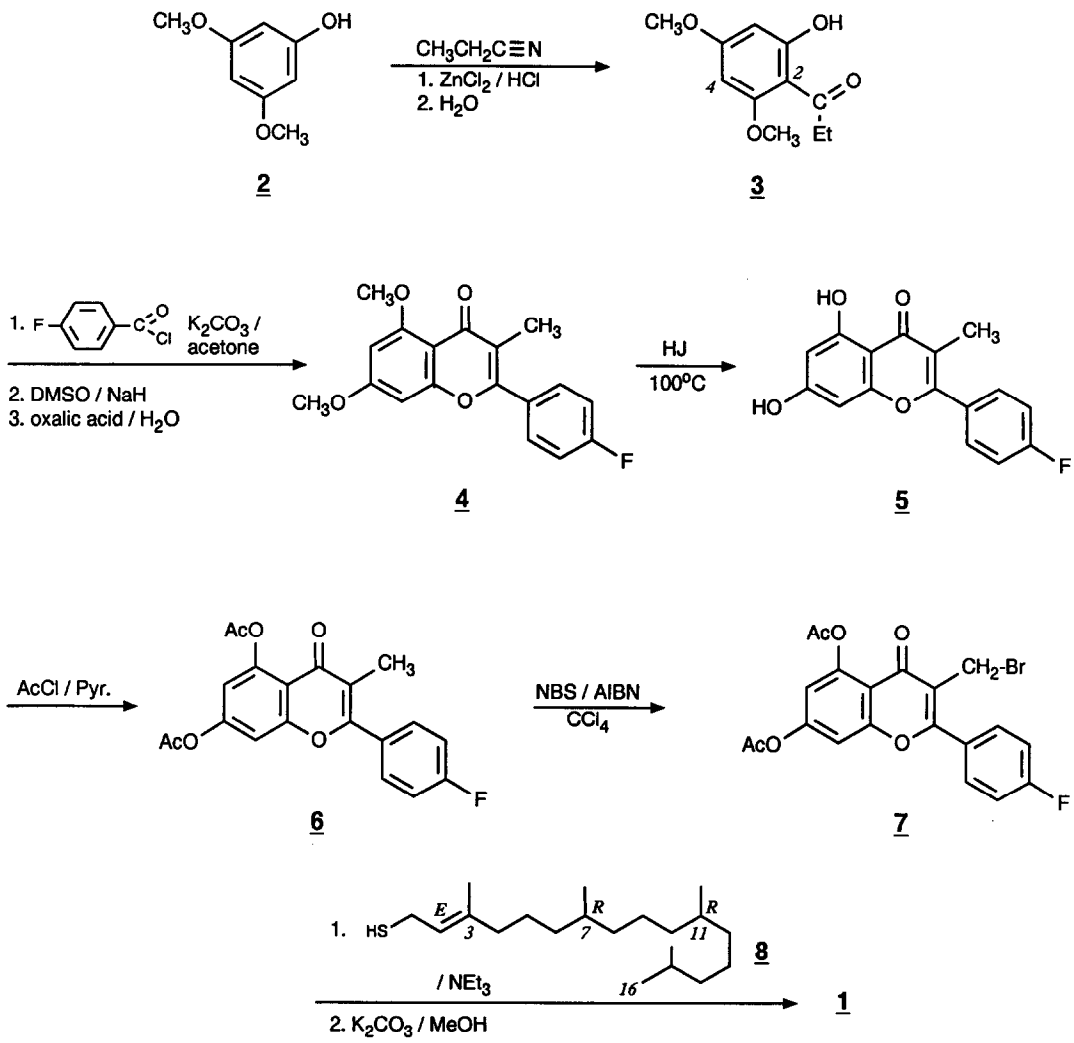
The generation of free radicals in biological systems has received increasing attention during the last years [1,2]. Oxidation of low density lipoproteins (LDL) by free radicals is considered to be an important event in atherogenesis [3]. Antioxidants can inhibit LDL-oxidation and prevent development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



1

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 (CH_3OH, K_2CO_3, 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).

Scheme 1


CH3O
OH
OCH3
2
CH3CH2C≡N
1. ZnCl2 / HCl
2. H2O
CH3O
OH
2
4
C
O
OCH3
Et
3
1. F
C
O
Cl
K2CO3 /
acetone
2. DMSO / NaH
3. oxalic acid / H2O
CH3O
O
CH3
CH3O
O
F
4
HJ
100°C
HO
O
CH3
HO
O
F
5
AcCl / Pyr.
AcO
O
CH3
AcO
O
F
6
NBS / AIBN
CCl4
AcO
O
CH2-Br
AcO
O
F
7
1. HS
E
3
R
7
R
11
16
8
/ NEt3
2. K2CO3 / MeOH
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 dimethylether 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. acetanhydride 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.

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6. 1 : ^{1}H NMR ($CDCl_3$) δ in ppm: 0.85 (dd,6H), 0.88 (dd,J=7Hz,6H), 1.0-1.4 (m,16H), 1.52 (p,J=7,5Hz,3H), 1.62 (s,3H), 1.95 (t,J=8Hz,2H), 3.35 (d, J=8Hz,2H), 3.58 (s,2H), 5.25 (t,J=8Hz,1H), 5.70 (broad s,OH), 6.32 (dd,J=16Hz,2H), 7.21 (t,J=8Hz,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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