SYNTHESIS OF A NEW TYPE OF ANTIOXIDANT POSSESSING INHIBITORY ACTIVITY AGAINST HMG-CoA REDUCTASE

Masakatsu Matsumoto*

Department of Materials Science, Kanagawa University

Tsuchiya, Hiratsuka, Kanagawa 259-12, Japan

Nobuko Watanabe, Eiko Mori, Misao Aoyama, Jun Kusunoki,

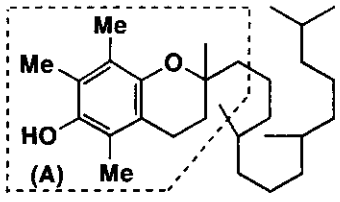
and Tetsuaki Yamaura

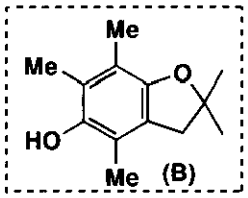
Central Research Laboratories, Fujirebio

Komiya, Hachioji, Tokyo 192, Japan

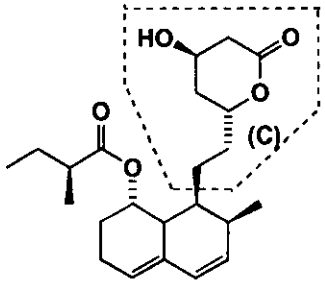
Abstract------The 6-hydroxychromans (**4**) and (**6**), and 5-hydroxy-2,3-dihydrobenzo[*b*]furans (**5**) and (**7**) bearing a 4-hydroxypyran-2-one moiety were synthesized. All the compounds exhibited potent activity against lipid peroxidation. The chroman (**4**) possessed inhibitory activity against HMG-CoA reductase in addition to the antioxidant character.

It has been well known that lipid peroxidation as well as high level of plasma cholesterol become the risk factors causing arteriosclerosis.[1] Tocopherol (**1**) has been reported to inhibit effectively the lipid peroxidation, though it improves scarcely the level of cholesterol in plasma.[2] On the other hand, HMG-CoA reductase inhibitors are now well established to lower plasma cholesterol in man.[3] These facts prompted us to design and synthesize a new type of antioxidant possessing together inhibitory activity against HMG-CoA reductase.[4]



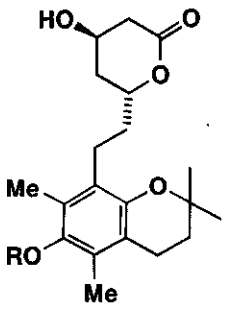


1

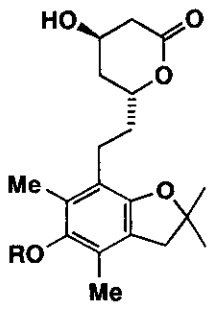


2

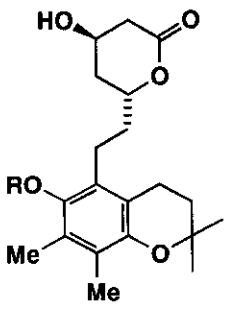
In tocopherol (**1**), 6-hydroxychroman (**A**) as a substructure acts to trap the radical species formed in the oxidation of lipid so that it lowers the serum lipid peroxides.[5] 5-Hydroxy-2,3-dihydrobenzo[*b*]furan (**B**) has also been reported to inhibit effectively peroxidation.[5] HMG-CoA reductase inhibitors represented by compactin (**2**) comprise, in general, of C-7 dihydroxycarboxylic acid or its lactone substructure (**C**), which is essential to exhibit the activity, and a large lipophilic group attached at the ω-position of the C-7 block.[6] These facts gave us the idea to hybridize substructures (**A**) or (**B**) with the lactone unit (**C**).



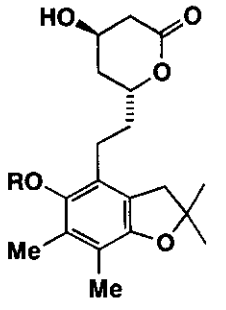
4: R = H
8: R =benzyl



5: R = H
9: R = benzyl



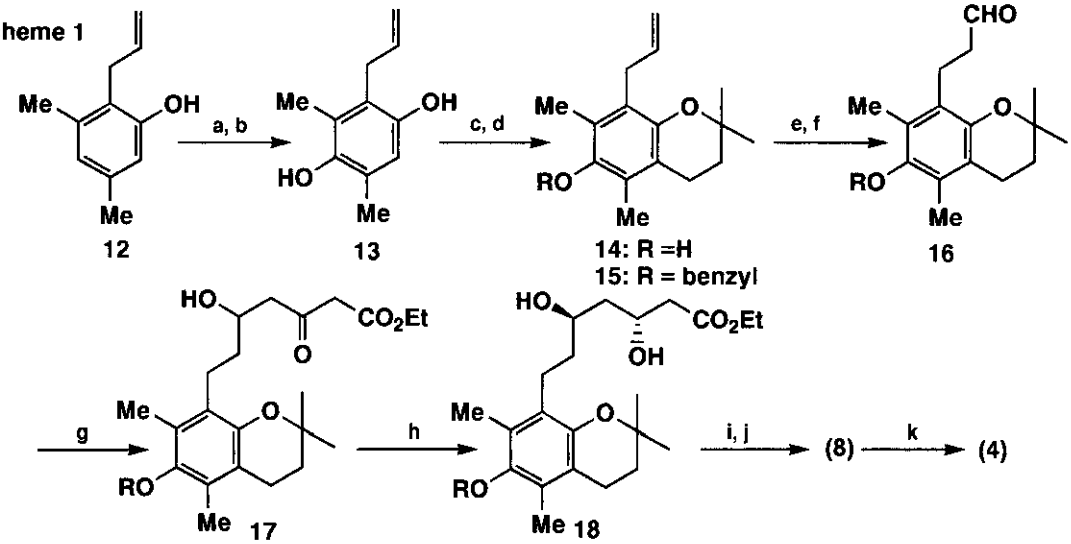
6: R = H
10: R = benzyl



7: R = H
11: R = benzyl

We undertook to synthesize phenolic lactones (**4** - **7**) and examine their activities together with those of benzyl ethers (**8** - **11**). The lactone (**4**) as a representative was synthesized as shown in **Scheme 1**. A hydroquinone (**13**) was prepared from a tri-substituted phenol (**12**) by the Co(II)salen-catalyzed aerobic oxidation (room temperature, ethanol) and successive reduction of the resulted quinone with $NaBH_4$ (60% from **12**). Treatment

Scheme 1

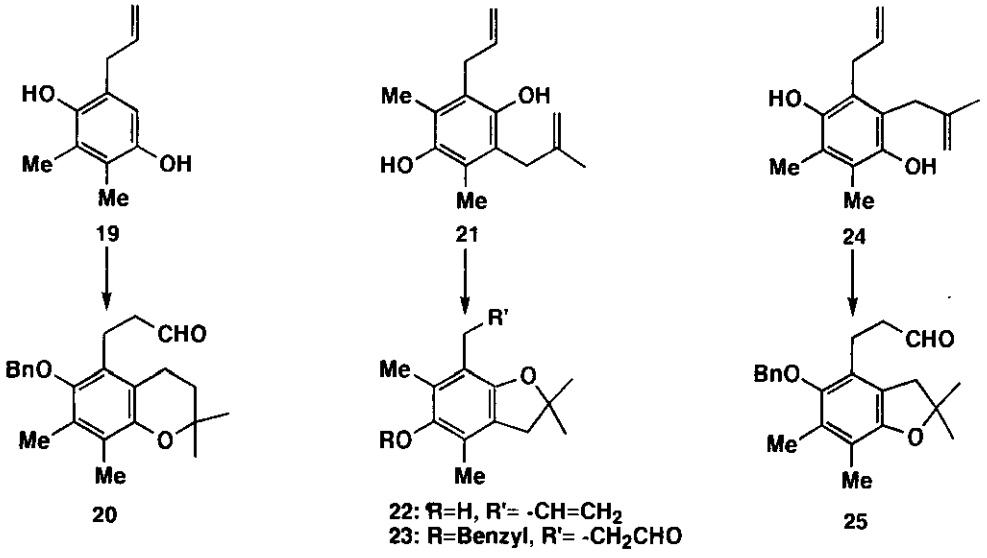


a) O_2/ Co(II)salen/EtOH; b) $NaBH_4$; c) $BF_3.Et_2O$/ prenol; d) NaH/ BnBr; e) 9-BBN; f)SO_3.Py / DMSO/ Et_3N
g) $^-CH_2COCH^-CO_2Et$; h) $NaBH_4$/ Et_3B/*t*-BuCOOH; i) NaOH, j) Δ/toluene; k) H_2/5%Pd-C

of the hydroquinone (**13**) with 3-methyl-2-buten-1-ol (prenol) in the presence of BF_3·OEt_2 in CH_2Cl_2 (at 0 °C)[7] afforded a chroman (**14**), whose hydroxyl group was then protected with benzyl to yield an ether (**15**) (88% from **13**). The hydroboration of the ether (**15**) with 9-BBN followed by usual work-up afforded a propanol which was further oxidized with SO_3-pyridine complex[8] to give a propanal (**16**) (67% from **15**). The C-4 homologation of the aldehyde (**16**) was attained by the reaction with dianion of ethyl acetoacetate to yield a keto alcohol (**17**), which was stereospecifically reduced into a dihydroxy ester (**18**) by means of Narasaka's method using $NaBH_4$/Et_3B/*t*-$BuCO_2H$.[9] The ester (**18**) was then subjected to hydrolysis with NaOH in MeOH to give a free acid, which was successively cyclized by heating in toluene to afford the lactone (**8**) (57% from **18**). The hydrogenolysis of **8** by H_2 (1 atm)/5% Pd-C in MeOH (at room temperature) produced the desired phenolic lactone (**4**).[10]

By using 2-allyl-5,6-dimethylhydroquinone (**19**) in place of the hydroquinone (**13**), the lactones (**6**) and (**10**) were similarly synthesized through a propanal (**20**). The lactone (**5**), (**9**), (**7**), and (**11**) were also synthesized from 3-substituted propanals (**23**) and (**25**). As in the case of **16**, the propanal (**23**) was synthesized from an allylic compound (**22**) obtained by the BF_3-catalyzed cyclization of a tetra-substituted hydroquinone (**21**). The propanal (**25**) was similarly prepared by the use of a hydroquinone (**24**).

The inhibitory activity of the synthesized hybrids (**4** - **7**) against lipid peroxidation was evaluated by measuring thiobarbituric acid reactive substance in rat brain microsomal fractions.[11] All four hybrids exhibited the inhibitory activity as potent as that of α-tocopherol (**1**) (IC_{50} (10^{-7} M) = **4**: 5.9, **5**: 1.5, **6**: 5.0, **7**: 2.1, and **1**: 5.6). On the other hand, the benzyl ethers (**8** - **11**) inhibited scarcely lipid peroxidation, as anticipated.



The HMG-CoA reductase inhibitory activity was measured by using the method reported by Kuroda and Endo.[12] Among the lactones synthesized here, the benzofuran (**11**) was the most potent and possessed about a half activity as that of compactin (**2**). The chromans (**4**) and (**8**) exhibited IC_{50} at 10^{-7}M [relative potency (**2** = 100): **4** = 30, **8** = 40] , while the lactones (**5** - **7**, **9**) were far less active (IC_{50} > 10^{-6}M) than compactin. These results clarified that the hybrid such as **4** composed of substructures (A) and (C) exhibits potent inhibitory activities against lipid peroxidation as well as HMG-CoA reductase.

REFERENCES AND NOTES

1. a) W. Heinecke, L. Baker, H. Rosen, and A. Chait, *J. Clin. Invest.*, 1986, **77**, 757. b) D. W. Morel, P. E. DiCorleto, and G. M. Chisolm, *Arteriosclerosis*, 1984, **4**, 357. c) A. Endo, *J. Med. Chem.*, 1985, **28**, 401. See also refs therein.
2. J. -P. Battioni, M. Fontecave, M. Jaouen, and D. Mansuy, *Biochem. Biophys. Res. Comm.*, 1991, **174**, 1103. See also refs therein.
3. a) S. M. Grundy, *N. Eng. J. Med.*, 1988, **319**, 24. b) R. A. Parker, R. W. Clark, S. -Y. Sit, T. L. Lanier, R. A. Grosso, and J. J. K. Wright, *Lip. Res.*, 1990, **31**, 1271.
4. A hybrid of the structural elements of probucol and HMG-CoA reductase inhibitors has been reported to possess moderate inhibitory activities against HMG-CoA reductase and microsomal lipid peroxidation; H. Jendralla, E. Granzer, B. V. Kerekjarto, R. Krause, U. Schacht, E. Baader, W. Bartmann, G. Beck, A. Bergmann, K. Kesseler, G. Wess, L. -J. Chen, S. Granata, J. Herchen, H. Klein, H. Schussler, and K. Wagner, *J. Med. Chem.*, 1991, **34**, 2962.
5. E. Niki, *J. Syn. Org. Chem. Japan*, 1989, **47**, 903.
6. B. D. Roth, D. R. Sliskovic, and B. K.Triverdi, *Annu. Rep. Med. Chem.* 1989, **24**, 147.
7. BF_3 etherate was the most effective to attain the expected cyclization among acid catalysts such as formic acid and $ZnCl_2$. See also, S. Wawzonek, 'Chromans: Heterocyclic Compounds,' ed. by R. C. Elderfield, Wiley, N. Y., 1951, pp. 393-418.
8. T. T. Tidwell, *Synthesis*, 1990, 857.
9. K. Narasaka and F. -C. Pai, *Tetrahedron*, 1984, **40**, 2233.
10. The chroman (**4**): colorless granules (from hexane-ethyl acetate), mp 136.0-137.0 °C. ^{1}HNmr(300MHz, $CDCl_3$) δ1.28 (s, 6H), 1.70-1.95 (m, 4H), 1.78 (t, J=6.9 Hz, 2H), 1.96-2.08 (m, 1H), 2.12 (s, 3H), 2.20 (s, 3H), 2.62 (t, J=6.9 Hz, 2H), 2.59-2.69 (m, 1H), 2.70-2.84 (m, 3H), 4.22 (s, 1H), 4.37-4.46(m, 1H), 4.67-4.80 (m, 1H) ppm; ir(KBr) 3380, 2980, 2930, 1708 cm^{-1}; mass(m/z, %) 348 (M^+, 100), 330 (10), 293 (25), 219 (15).
11. J. Robak and B. Sobanska, *Biochem. Pharmacol.*, 1976, **25**, 2233.
12. A. Endo, Y. Tsujita, M. Kuroda, and K. Tanzawa, *Biochem. Biophys. Acta*, 1979, **575**, 266.

Received, 24th August, 1994