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

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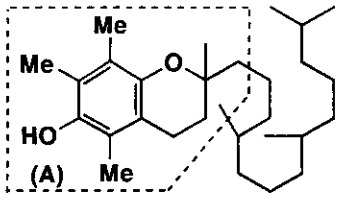
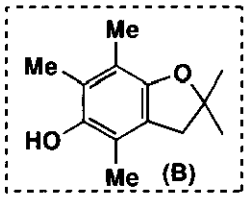
**Abstract**------The 6-hydroxychromans (**4**) and (**6**), and 5-hydroxy-2,3-dihydrobenzo[*b*]furans (**5**) and (**7**) bearing a 4-hydroxypyran-2-one moiety were synthesized. All the compounds exhibited potent activity against lipid peroxidation. The chroman (**4**) possessed inhibitory activity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

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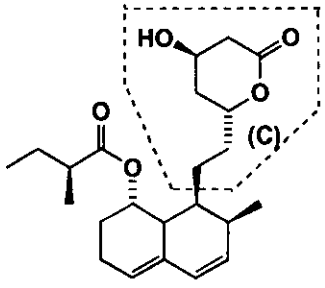


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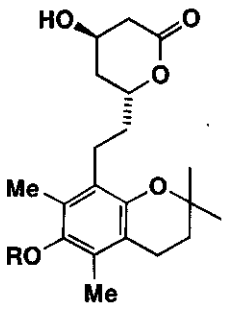
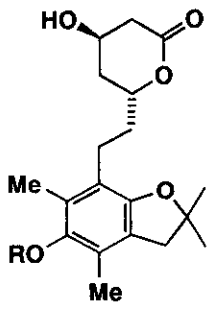
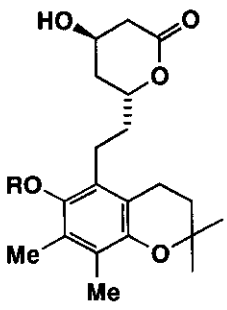
In tocopherol (**1**), 6-hydroxychroman (**A**) as a substructure acts to trap the radical species formed in the oxidation of lipid so that it lowers the serum lipid peroxides.[5] 5-Hydroxy-2,3-dihydrobenzo[*b*]furan (**B**) has also been reported to inhibit effectively peroxidation.[5] HMG-CoA reductase 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**).



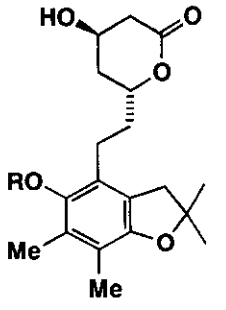
**4**: R = H
**8**: R =benzyl



**5**: R = H
**9**: R = benzyl



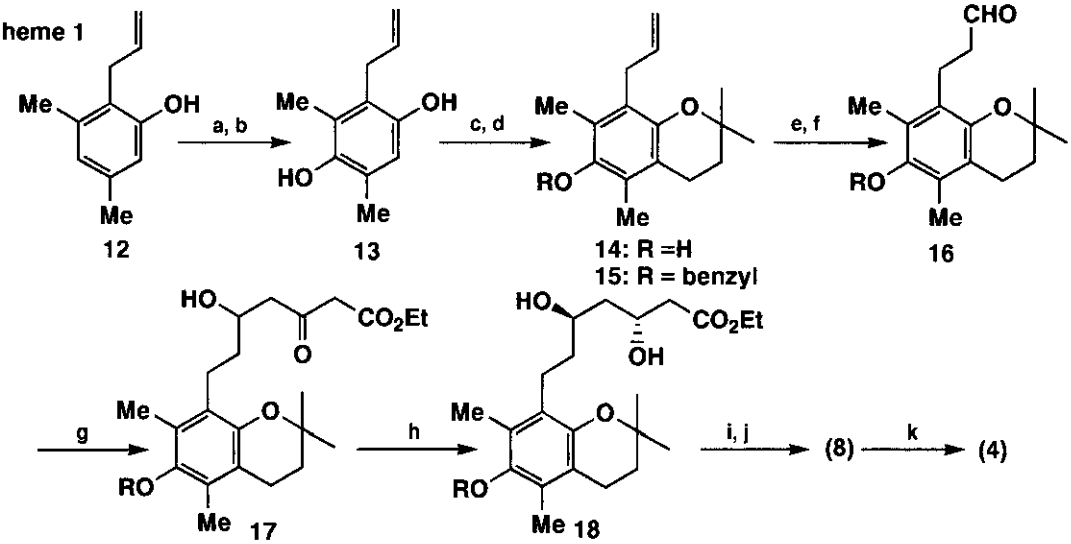
**6**: R = H
**10**: R = benzyl



**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**

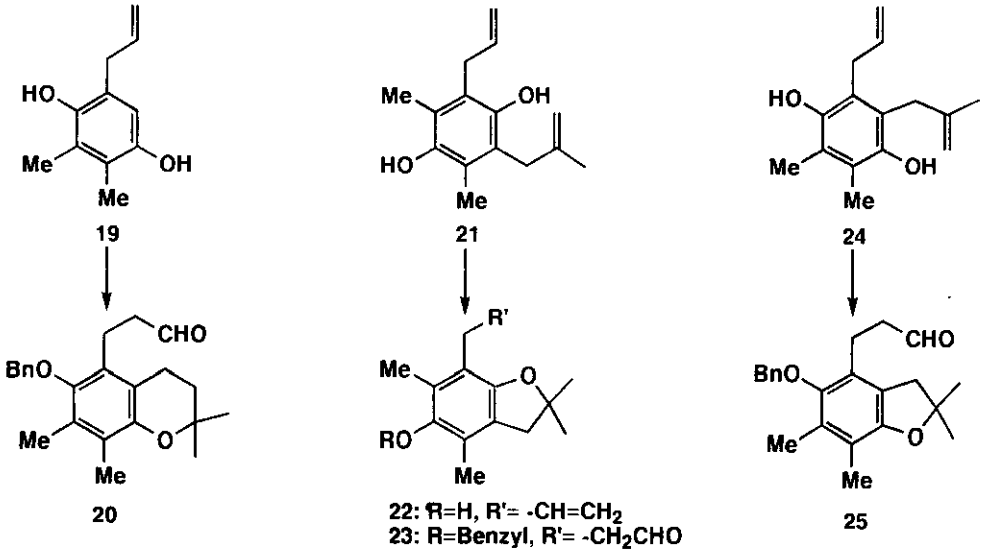


a) $O_2$/ Co(II)salen/EtOH; b) $NaBH_4$; c) $BF_3.Et_2O$/ prenol; d) NaH/ BnBr; e) 9-BBN; f)$SO_3$.Py / DMSO/ $Et_3N$
g) $^-CH_2COCH^-CO_2Et$; h) $NaBH_4$/ $Et_3B$/*t*-BuCOOH; i) NaOH, j) Δ/toluene; k) $H_2$/5%Pd-C

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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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).
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