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# A new strategy for the synthesis of 4,6-di-*tert*-butyl-2,2-dipentyl-2,3-dihydro-5-benzofuranol (BO-653), a potent antiatherogenic antioxidant

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ABSTRACT

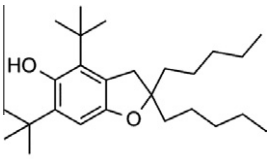
An efficient alternative route to 4,6-di-*tert*-butyl-2,2-dipentyl-2,3-dihydro-5-benzofuranol (BO-653), a potent antiatherogenic antioxidant, has been developed by the application of the base-promoted dienone-phenol rearrangement reaction. A decisive effect of $MgBr_2$ in the reaction of Grignard reagents is also described.



4,6-Di-*tert*-butyl-2,2-dipentyl-2,3-dihydro-5-benzofuranol (BO-653) **1** is found to be the most promising candidate as an antiatherogenic antioxidant among a series of 4,6-di-*tert*-butyl-2,3-dihydro-5-benzofuran derivatives which were designed and synthesized in Chugai Pharmaceutical (Fig. 1).[1] It has been reported that this compound **1** shows radical scavenging activities against lipid peroxidation and the inhibitory action on LDL oxidation.[1b,c] The mobility of the LDL incubated with 1 μM of this compound **1** in the case of $CuSO_4$ oxidation is similar to that of native LDL. However, the synthesis of **1** we previously established required nine steps of reactions to attain 10% overall yield which is far less than satisfactory for its practical production (Scheme 1).[1a]

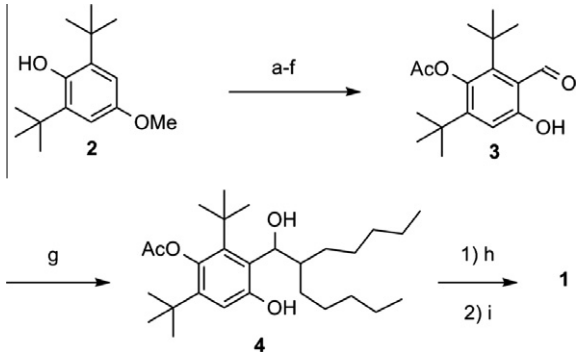
As outlined in Scheme 1, although the synthesis allowed using an inexpensive readily accessible starting material **2** already carrying the requisite two *tert*-butyl substituents, it required rather tedious and extra steps including protection–deprotection steps for the installation of the 2,2-gem-substituted dihydrobenzofuran moiety of the target molecule. Namely, it necessitates a sequence of six steps of reactions to introduce the 3-formyl group to give **3** which further requires three steps including the acidic conditions often inducing rearrangement and removal of the tertiary butyl group to reach the final product **1** in 10% overall yield from the starting material **2** (Scheme 1).

We, therefore, turned our attention to the way of more efficient and shorter construction of the dihydrofuran moiety on the aromatic ring carrying the requisite functionalities without employing strong acidic conditions. To this end, a base-induced dienone-phenol type rearrangement reported by Nishinaga et al. in 1976 seemed to be the most promising. As appeared it was reported that the hydroxy-dienone (quinol) **6**, generated from the phenol **5** by oxidation ($O_2$, KOH), brought about the selective 1,2-shift of an alkyl group to furnish excellently the phenol (hydroquinone) **7** upon exposure to potassium *tert*-buthoxide in DMF. We thought that this without employing acidic conditions indicates a facile acquisition of our target molecule provided an appropriately functionalized hydroxyl-dienone precursor could be prepared (Scheme 2).[2]




**BO-653 (1)**

**Figure 1.** The structure of BO-653.




**Scheme 1.** Reagents: (a) $H_2SO_4$, $Ac_2O$; (b) TMSI, $CH_2Cl_2$; (c) $HOCH_2NHCOCH_2Cl$, $H_2SO_4$, $Ac_2O$; (d) *c*-HCl, EtOH; (e) hexamethylenetetramine, AcOH, $H_2O$; (f) HCl (aq); (g) $(Pen)_2CHMgBr$; (h) $BF_3OEt_2$, $CH_2Cl_2$; (i) $LiAlH_4$, THF.

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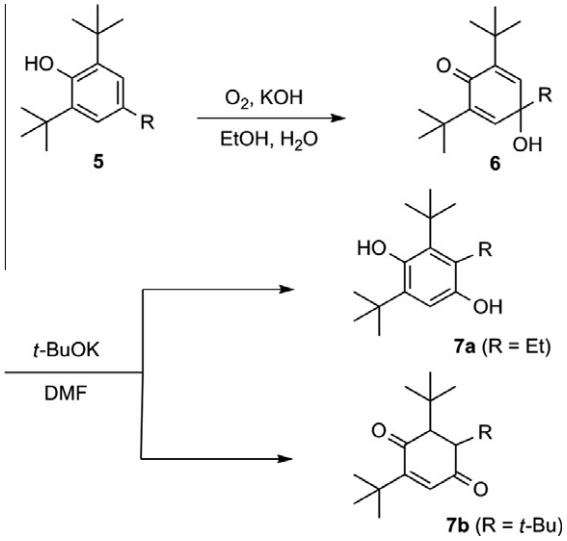
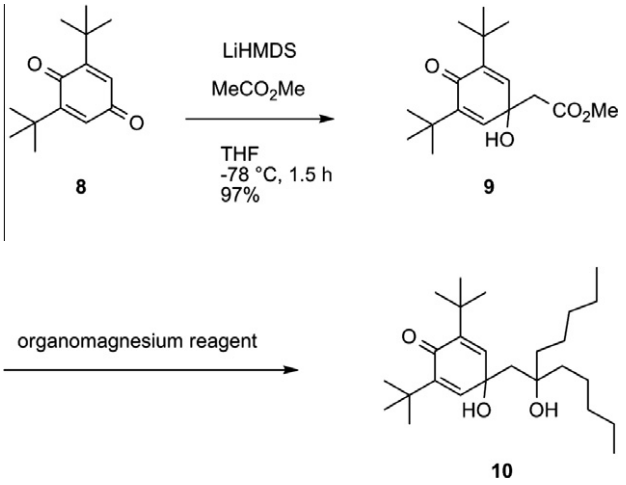



**Scheme 2.** Base-induced dienone-phenol type rearrangement.




**Scheme 3.** Synthesis of bis-tertiary alcohol **10**.

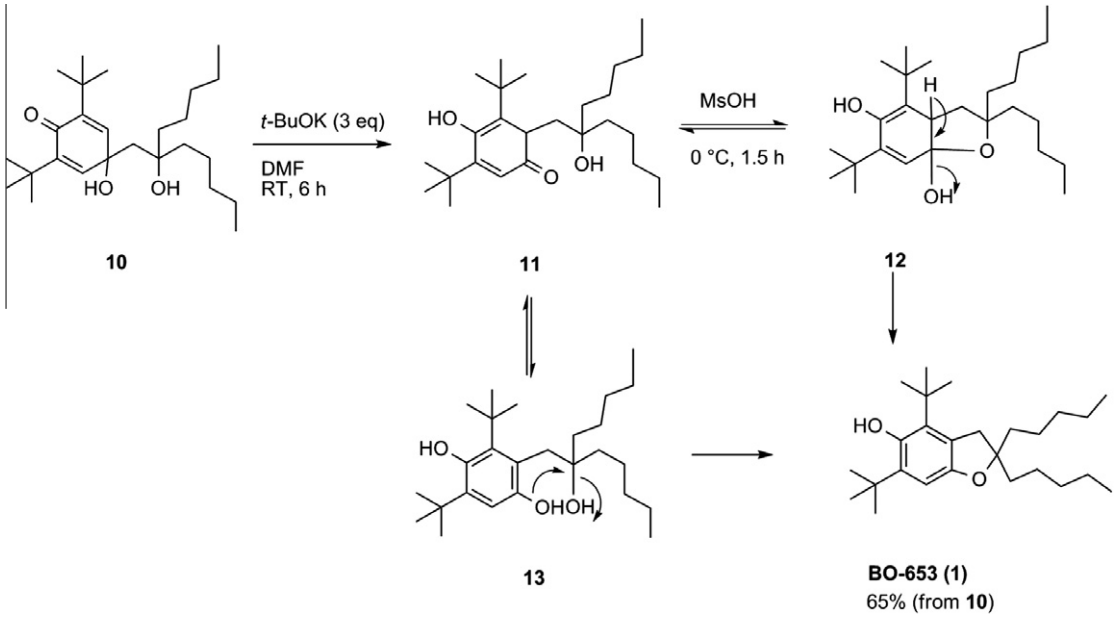
**Table 1**
Additions of Grignard reagents to dienone-ester **9**[a]

| Entry | Reagent | Temp. (°C) | Yield[b] (%) | Conversion[c] (%) |
|---|---|---|---|---|
| 1 | $Bu_2Mg$ | −25 | Trace | 55 |
| 2 | PenMgBr | −78 to rt | 35 | 86 |
| 3 | PenMgBr | −25 | 46 | 78 |
| 4 | PenMgBr–$MgBr_2$ | −20 | 81 | 99 |
| 5 | PenMgBr–$MgBr_2$ | −50 | 88 | 97 |
| 6 | PenMgBr–$MgBr_2$ | 0 | 62 | 99 |

[a] All reactions were carried out with 3 equiv of reagents in $Et_2O$ for 18 h.
[b] Determined by crude NMR spectra with anthracene as an internal standard.
[c] Conversion: ratio of target material to starting material.

To visualize our intention of developing a new synthesis of BO-653 **1** by application of 'the dienone-phenol rearrangement' reaction, the benzoquinone **8**, bearing two *tert*-butyl groups and available in bulk, was chosen for the starting material. Thus, **8** was treated with the lithium enolate generated in situ by treating methyl acetate with lithium hexamethyldisilazide (LiHMDS) in THF at −78 °C to yield regioselectively the dienone-ester **9** in an excellent yield producing neither regioisomer nor double-addition product.[3] The gem-pentyl group was installed at this stage to yield the bis-tertiary alcohol **10** (Scheme 3).

At first, the ester **9** was treated with 3 equiv of pentylmagnesium bromide in ether. The expected reaction occurred both at −78 and −25 °C to give the desired dienone **10** both in moderate yields, both accompanied by a complex mixture of unidentified by-products, and the starting material **9** (entries 2 and 3). Under these conditions, the dienone carbonyl group of **9** was found to be intact presumably due to the interference of the adjacent two tertiary butyl groups.[4] Since it is known that a Grignard reagent is in a Schlenk equilibrium between diorganomagnesium and $MgBr_2$,[5] we next examined the reaction in the presence of the same equivalent of $MgBr_2$ to the Grignard reagent as the additive so as to shift the equilibrium to the Grignard reagent side. In precedence to the addition experiment, we treated the ester **9** with dibutylmagnesium at −25 °C in ether in order to confirm the effect of the additive.[6] Virtually, no desired reaction occurred to give a trace of the target product after consumption of half of the starting material (entry 1). In contrast, when $MgBr_2$ was present, the desired reaction readily occurred to give the tertiary alcohol **10**, in yields of 81% at −20 °C and 88% at −50 °C, respectively, without the genera-




**Scheme 4.** Formation of BO-653 (**1**) by a base-promoted dienone-phenol rearrangement reaction followed by an acid-treatment.

tion of a substantial amount of the by-product mixture (entries 4 and 5).[7] However, the yield of **10** was diminished considerably when the reaction was carried out at 0 °C (Table 1, entry 6).[8,9]

Having established the reaction conditions suitable for the generation of the desired dienone intermediate **10**, its rearrangement to the penultimate hydroquinone **13** was then examined under basic conditions. Upon exposure of **10** to 3 equiv of potassium *tert*-butoxide in DMF at room temperature, the expected 'dienone-phenol rearrangement' did really occur to furnish the hydroquinone **13**,[10] which was immediately treated with methanesulfonic acid to yield the target molecule, BO-653 **1**, directly, in 65% yield, with neither initiation of rearrangement nor removal of tertiary butyl moiety.[11] Although the exact mechanism for the generation of the hydrofuran moiety of **1** from the hydroquinone intermediate **13** is not clear, it is presumed to take place only under acidic conditions through either a substitution pathway (via **13**) or an addition–elimination pathway (via **13**–**11**–**12**)[10a] as **1** was not detected under the basic conditions initiating the rearrangement. Overall yield of **1** from the starting benzoquinone **8** was 53% in four steps without including any sequence of the protection–deprotection steps (Scheme 4).

In conclusion, we have established an alternative procedure capable of producing 4,6-di-*tert*-butyl-2,2-dipentyl-2,3-dihydro-5-benzofuranol (BO-653) **1**, a potent antiathrogenic antioxidant, in 53% overall yield starting from a readily accessible starting material **8** through a sequence of four steps of reactions by the application of the base-promoted dienone-phenol rearrangement reaction in the key step.

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M.M. thanks Dr. Kunio Ogasawara, Professor Emeritus, Tohoku University, for helpful suggestions for this study and preparation of the manuscript. Thanks are also due to Dr. Masahiro Kato, Deputy Department Manager of API Process Development Department, Mr. Toshiro Kozono, Department Manager of API Process Development Department, and Dr. Hidetoshi Ushio, General Manager of Pharmaceutical Technology Division of Chugai Pharmaceutical Co., Ltd, for their support of this work.

## References and notes

1. (a) Tamura, K.; Kato, Y.; Ishikawa, A.; Kato, Y.; Himori, M.; Yoshida, M.; Takashima, Y.; Suzuki, T.; Kawabe, Y.; Cynshi, O.; Kodama, T.; Niki, E.; Shimizu, M. *J. Med. Chem.* **2003**, *46*, 3083; (b) Noguchi, N.; Iwaki, Y.; Takahashi, M.; Komuro, E.; Kato, Y.; Tamura, K.; Cynshi, O.; Kodama, T.; Niki, E. *Arch. Biochem. Biophys.* **1997**, *342*, 236; (c) Noguchi, N.; Okimoto, Y.; Tsuchiya, J.; Cynshi, O.; Kodama, T.; Niki, E. *Arch. Biochem. Biophys.* **1997**, *347*, 141.
2. (a) Nishinaga, A.; Itahara, T.; Matsuura, T.; Berger, S.; Henes, G.; Rieker, A. *Chem. Ber.* **1976**, *109*, 1530; rearrangement of quinol catalysed by bases or acids has reported, see: (b) Abe, Y. *Bull. Chem. Soc. Jpn.* **1943**, *18*, 93; (c) Although this type of rearrangement in the present paper should be called 'quinol-hydroquinone rearrangement', we use the term 'dienone-phenol rearrangement' as a well-known expression.
3. Compound **9**: $^1$H NMR ($CDCl_3$) $\delta$ 1.22 (18H, s), 2.63 (2H,s), 3.58 (1H, s), 3.72 (3H, s), 6.61 (2H, s).
4. Precedents of the reactions between benzoquinones and nucleophiles. For ester enolates, see: (a) Fischer, A.; Henderson, G. N. *Tetrahedron Lett.* **1983**, *24*, 131. and references cited therein; For alkyllithiums and alkylmagnesium bromides, see: (b) Liotta, D.; Saindane, M.; Barnum, C. *J. Org. Chem.* **1981**, *46*, 3369. and references cited therein.
5. (a) Schlenk, W.; Schlenk, W., Jr. *Chem. Ber.* **1929**, *62*, 920; (b) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, 1995; (c)*Grignard Reagents New Developments*; Richey, H. G., Jr., Ed.; Wiley: New York, 2000.
6. $Bu_2Mg$ in place of $Pen_2Mg$ was used for the preliminary examination because of commercial availability.
7. General procedure is as follows: Under an argon atmosphere, to a suspension of Mg (10.71 mmol) in $Et_2O$ (10 mL) under vigorous stirring was added dropwise 1,2-dibromoethane (10.71 mmol) keeping a gentle reflux and the stirring was continued at rt for 1.5 h. To the resulting suspension was added a solution of PenMgBr in $Et_2O$ (4.31 mL, 8.62 mmol) at rt. The resulting clear solution was added dropwise to a solution of the ester **9** in $Et_2O$ (2.85 mmol) at the temperature described in Table 1, and the stirring was continued for 18 h at the same temperature described. After the addition of aqueous $NH_4Cl$, the mixture was extracted with $Et_2O$. The organic extract was washed with saturated aqueous NaCl, and dried over $MgSO_4$. Compound **10**: $^1$H NMR ($CDCl_3$) $\delta$ 0.89 (6H, t, $J$ = 6.8 Hz), 1.10–1.60 (16H, m), 1.23 (18H, s), 1.79 (2H, s), 4.34 (1H, s), 6.75 (2H, s). The conversions were estimated through the ratio of the integration of an olefinic proton in starting material **9** [$\delta$ 6.61 (2H, s)] and an olefinic proton in target material **10** [$\delta$ 6.75 (2H, s)]. The yields were determined with anthracene as an internal standard.
8. Representative examples regarding the use of $MgBr_2$, see: (a) Swain, C. G.; Boyles, H. B. *J. Am. Chem. Soc.* **1951**, *73*, 870; (b) Wotiz, J. H.; Hollingsworth, C. A.; Dessy, R. E. *J. Org. Chem.* **1956**, *21*, 1063; (c) Holm, T. *Acta Chem. Scand.* **1967**, *21*, 2753; (d) Ashby, E. C.; Chao, L.-C.; Neumann, H. M. *J. Am. Chem. Soc.* **1973**, *95*, 4896; (e) Yamazaki, S.; Yamabe, S. *J. Org. Chem.* **2002**, *67*, 9346. and references cited therein; for $MgCl_2$: e.g. (f) Sobota, P.; Duda, B. *J. Organomet. Chem.* **1987**, *332*, 239; Concentration and solvents used have also influence on Schlenk equilibrium, see: (g) Smith, M. B.; Becker, W. E. *Tetrahedron* **1966**, *22*, 3027.
9. $MgBr_2$ in $Et_2O$ was a suspension, however, it became a clear solution as PenMgBr was added indicating that a mixed aggregation of PenMgBr–$MgBr_2$ would take place in $Et_2O$.
10. The structure of compound **13** was deduced from a $^1$H NMR analysis of its crude product: $^1$H NMR ($CDCl_3$) $\delta$ 0.87 (6H, t, $J$ = 6.5 Hz), 1.2–1.5 (16H, m), 1.42 (s, 9H), 1.57 (s, 9H), 3.3(2H, s), 4.8(OH, 1H, s), 6.82 (1H, s).
11. Related cyclization of hydroquinone or its keto tautomer, see: (a) Cohen, N.; Lopresti, R. J.; Neukom, C. *J. Org. Chem.* **1981**, *46*, 2445; (b) The reaction could proceed under aqueous acidic conditions (e.g., a solution of citric acid) to give the desired product though capriciously perhaps due to bi-phase reactions.