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Short Synthesis of *tert*-Butyl-Hydroxylated 3,5-Di-*tert*-butyl-4-hydroxybenzaldehyde: Synthesis of *tert*-Butyl-Hydroxylated S-2474

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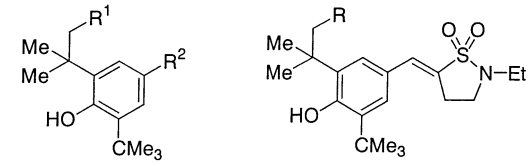
Abstract: We have developed a very short synthesis of *tert*-butyl-hydroxylated di-*tert*-butyl-4-hydroxybenzaldehyde in which the HBr-DMSO system is used as an effective oxidant (overall yield of 45% for the entire four-step process from 2-*tert*-butyl-*p*-cresol). We also accomplished the synthesis of a major metabolite of the antiarthritic drug candidate S-2474.

The enzymatic hydroxylation (oxidation) of a *tert*-butyl group in the food antioxidant BHT (butylated hydroxytoluene, **1** in Figure 1) to produce the *tert*-butyl-hydroxylated metabolite **2** occurs in hepatic and pulmonary microsomes of rats and mice and has been found to be an important step in both BHT bioactivation and the resulting toxicity in these species.[1] A similar hydroxylation reaction has also been found to be a metabolic pathway in in vitro rat or human microsomes for our di-*tert*-butylphenol derivative, (*E*)-(5)-(3,5-di-*tert*-butyl-4-hydroxybenzylidene)-2-ethyl-1,2-isothiazolidine-1,1-dioxide (S-2474; **4**), which has been identified as a new type of antiarthritic drug candidate having both NSAID (nonsteroidal antiinflammatory drug) and cytokine modulating properties.[2] Among several synthetic methods[3] of



1: R^1 = H, R^2 = Me; BHT
2: R^1 = OH, R^2 = Me
3a: R^1 = H, R^2 = CHO
3b: R^1 = OH, R^2 = CHO

4: R = H; S-2474
5: R = OH

FIGURE 1.

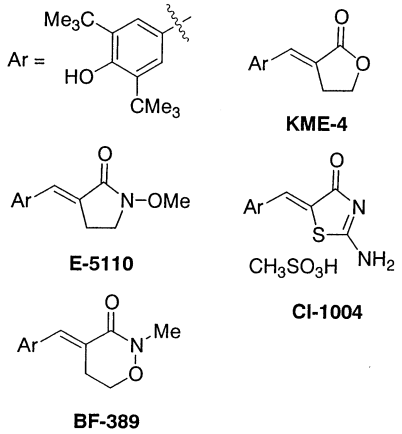


FIGURE 2.

the *tert*-butyl-hydroxylated di-*tert*-butylphenols involving direct microbial oxidation,[3b] only one example is clear and feasible.[3a] However, while this method[3a] is suitable for the preparation of the unsubstituted derivative at the 4-position of phenol (R^1 = OH, R^2 = H in Figure 1), it cannot be applied for the preparation of aldehyde **3b**, a key intermediate for the synthesis of a major metabolite of S-2474, without any modifications or multistep functional group transformations. Since not only our compound but also several known antiinflammatory drug candidates, such as KME-4,[4] E-5110,[5] BF-389,[6] and CI-1004[7] (Figure 2), having the common structure of a 3,5-di-*tert*-butyl-4-hydroxybenzylidene moiety are prepared from 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (**3a**), predicted metabolites can be easily prepared from the common key intermediate, *tert*-butyl-hydroxylated 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (**3b**). A widely ap-

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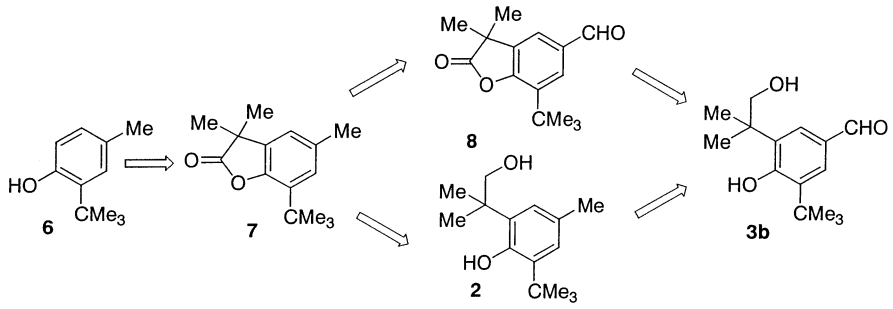
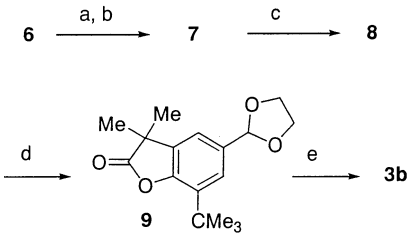
SCHEME 1

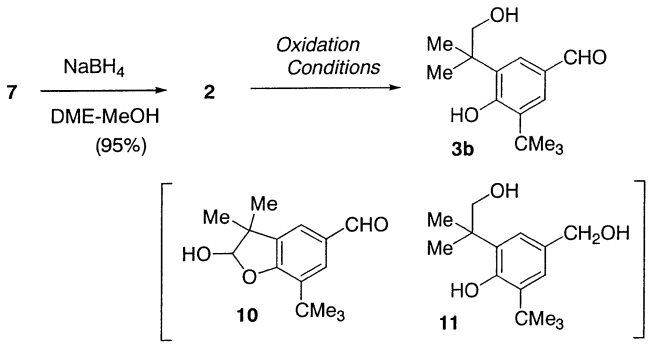


SCHEME 2[a]



[a] Reagents: (a) glyoxal, conc HCl, AcOH (79%); (b) MeI, *t*-BuOK (84%); (c) (1) NBS, AlBN; (2) KOAc, AcOH then aq HCl (87%); (d) ethylene glycol, PPTS (88%); (e) $LiAlH_4$ then H_3O^+ (86%).

SCHEME 3



plicable and efficient synthetic method for **3b** is reported here and was used to synthesize a major metabolite of S-2474.

Two approaches were considered initially to convert 2-*tert*-butyl-*p*-cresol (**6**) into **3b** through the benzofuranone derivative **7** as described in Scheme 1. The first approach via compound **8** proceeded via oxidation of the benzylic methyl group of **7**, followed by reduction of the lactone moiety. The second pathway is reduction of **7** to phenol **2**, followed by selective oxidation of the benzylic methyl group.

The details of the first approach are as follows. A commercially available 2-*tert*-butyl-*p*-cresol (**6**) was converted to 7-*tert*-butyl-5-methyl-*3H*-benzofuran-2-one with glyoxal in acetic acid,[8,9] and then directly converted to **7** by geminal dimethylation with MeI and *t*-BuOK in 66% yield in 2 steps. Oxidation of **7** to the lactone-aldehyde **8** could be achieved via geminal dibromination and hydrolysis in 87% yield. The formyl group of **8** was protected with ethylene acetal to give **9** in 88% yield. Reduction of **9** with $LiAlH_4$ and subsequent acidic workup provided the desired key-intermediate **3b** in 86% yield, with an overall yield of 44% for the entire six-step process summarized in Scheme 2.

This route was shown to be effective, but a shorter synthesis would be even better. Next, we attempted direct oxidation of phenol **2** to aldehyde **3b**. Some methods of oxidation of 2,6-di-*tert*-butyl-*p*-cresol (**1**) to 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (**3a**) were reported.[10] In general, symmetrically hindered cresols are oxidized by bromine in aqueous acetic acid or *tert*-butyl alcohol in good yield.[10h] Recently, Baik and co-workers have reported that NBS promotion of DMSO oxidation is very effective for this class of cresols and the oxidation could remarkably proceed smoothly even with a catalytic amount of NBS.[10i]

TABLE 1. Oxidation of 2 in DMSO under Various Conditions

entry	reagents (mol %)	temp (°C)	time (h)	yields (%) of **3b**, **10**, and **11**
1	NBS (120)	120	1	59 (**10**)
2	NBS (20)	120	1	41 (**3b**), 31 (**10**)
3	47% HBr (50)	100	1	60 (**3b**), 10 (**11**)
4	47% HBr (50)	100	4	67 (**3b**)
5	47% HBr (120)	100	2	65 (**3b**)
6	47% HBr (240)	100	1	72 (**3b**)

Phenol **2** was obtained from **7** by $NaBH_4$ reduction in DME-MeOH in almost quantitative yield (Scheme 3). We first tried the oxidation of phenol **2** to aldehyde **3b** under the conditions (Br_2/aq AcOH or aq *t*-BuOH) that gave complex mixtures containing only a trace amount of **3b**. The other conditions (1.2 equiv of NBS in DMSO at 120 °C for 1 h) gave an exclusively over-oxidation product, the lactol **10** (59% yield, entry 1 in Table 1). Oxidation with NBS (0.2 equiv in DMSO at 120 °C for 1 h) gave **3b**

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(9) Using 4-bromo-2-*tert*-butylphenol or 2-*tert*-butylphenol as starting materials, this synthetic method of 2(*3H*)-benzofuranones could not proceed cleanly, and only trace amounts of benzofuranone derivatives (6% and 5% yield, respectively) were obtained. We thus decided that the benzaldehyde derivative **3b** would be led by oxidation of a benzylic methyl group.

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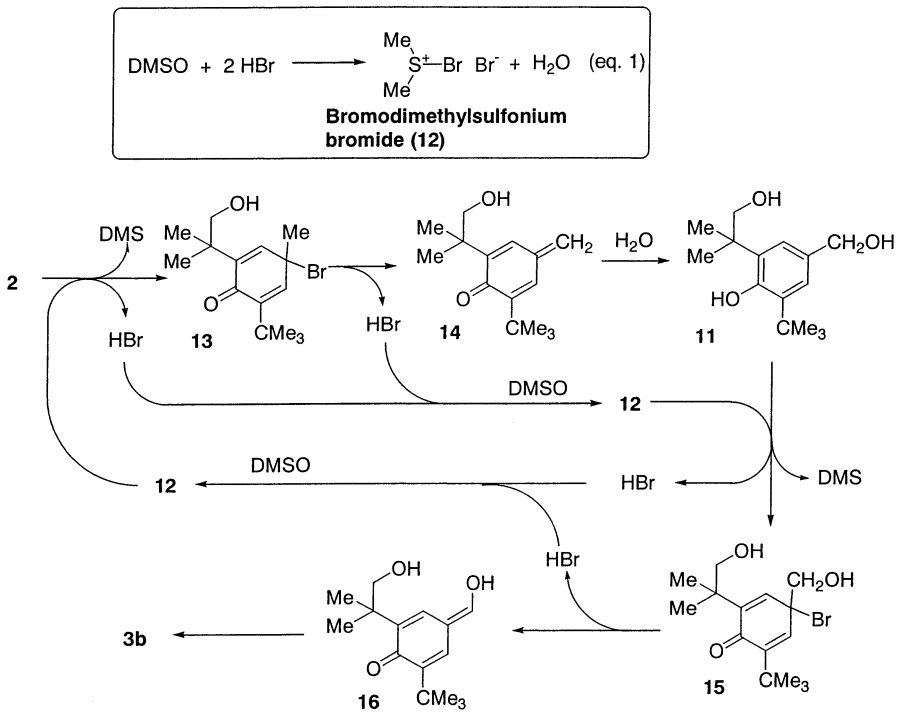
SCHEME 4



in 41% and the lactol **10** in 31% yield, respectively (entry 2 in Table 1). In the NBS-DMSO oxidation, production of the lactol **10** could not be avoided and it tended to increase as the reaction time became longer. According to Baik's report,[10i] "the reaction mechanism (**1** → **3a**) could involve a phenoxy radical or a hypobromite, in either case *p*-benzoquinone methide (QM) derivative and hydrogen bromide were formed, and bromodimethylsulfonium bromide (**12**)[11] would be generated in situ from HBr and DMSO (eq 1 in Scheme 4)." Moreover, this reaction (**1** → **3a**) also proceeded with a catalytic amount of NBS, and we thought it to be more reasonable that **12** is the only active species, because the first step of formation of the QM derivative via either phenoxy radical or hypobromite is not a catalytic cycle. On the other hand, **12** is a useful synthetic reagent,[12−14] especially for electrophilic aromatic bromination.[15] We attempted to investigate whether this reaction occurred with HBr-DMSO as an oxidant. As expected, HBr-DMSO was revealed to be a very effective reagent for oxidation of phenol **2**, giving **3b** in moderate to good yield (entries 3, 4, 5, and 6 in Table 1). Under the conditions of 0.5 equiv of concentrated HBr (47% aqueous) and DMSO at 100 °C, a reaction time over 3 h was needed for a complete reaction because an intermediate benzyl alcohol **11** remained under shorter reaction time (entry 3). Using a larger amount of HBr shortened the reaction time but did not have any effect on the yield of **3b** (entries 4, 5, and 6). From these experiments, the oxidation of phenol **2** to aldehyde **3b** by HBr-DMSO gave much better results, especially in over-oxidation, and was revealed to be more reproducible than NBS-DMSO oxidation. HBr-DMSO oxidation has some advantages in handling, safety, and cost compared to NBS-DMSO oxidation.

The reaction mechanism initiated by an ionic bromination on the 4-position of the phenol **2** and the HBr catalytic cycle are summarized in Scheme 4.[10h] We have accomplished the synthesis of the widely applicable key intermediate **3b** from 2-*tert*-butyl-*p*-cresol (**6**) with an overall yield of 45% for the entire four-step process.

As mentioned above, we also tried to obtain an authentic sample of the *tert*-butyl-hydroxylated S-2474 derivative **5** to be prepared from **3b**. Aldehyde **3b** was converted to THP ether **17** almost quantitatively by selective protection of the primary alcohol. Ether **17** was treated with *N*-ethyl-γ-sultam (**18**) in the presence of LDA to provide an aldol-type adduct **19** as diastereoisomeric mixtures. A crude adduct **19** was treated with MsCl and triethylamine following deprotection of the THP ether to afford *tert*-butyl-hydroxylated S-2474 (**5**) in 86% yield in three steps (Scheme 5).

In summary, we have demonstrated two approaches and developed an efficient and widely applicable synthesis of *tert*-butyl-hydroxylated 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (**3b**) from 2-*tert*-butyl-*p*-cresol (**6**). The key compound **3b** could be obtained from **2** in one step by HBr-DMSO oxidation, which is the first example, to our knowledge, of HBr-DMSO being used as an oxidant of hindered *p*-cresol to the corresponding *p*-hydroxybenzaldehyde. Using this convenient method, we have accomplished the synthesis of the major metabolite, *tert*-butyl-hydroxylated S-2474 (**5**). This new preparative sequence should be very important in metabolic studies of this class of compounds and should be adaptable in

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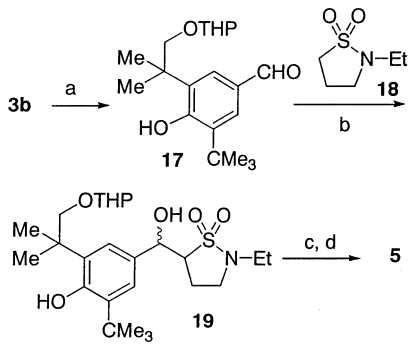
SCHEME 5[a]



[a] Reagents: (a) dihydropyran, PPTS (97%); (b) LDA; (c) MsCl, Et_3N; (d) *p*-TsOH, MeOH (86% for 3 steps).

the future to the preparation of important derivatives possessing this functionality.

Experimental Section

Melting points are uncorrected. ^1H NMR spectra were determined at 200 or 300 MHz. ^{13}C NMR spectra were determined at 75.5 MHz. Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere with guaranteed grade solvents that had been dried over type 4A or 3A molecular sieves. Drying of organic extracts over anhydrous sodium sulfate is simply indicated by the word "dried". Column chromatography using Merck Silica gel 60 (70−230 or 230−400 mesh) is referred to as "chromatography on silica gel".

7-*tert*-Butyl-3,3,5-trimethyl-3*H*-benzofuran-2-one (7). A mixture of 2-*tert*-butyl-*p*-cresol (**6**) (82 g, 0.50 mol), 40 wt % glyoxal (87 g, 0.60 mol), concentrated HCl (5.5 mL), and AcOH (375 mL) was heated at reflux for 3 h.[8] The reaction mixture was cooled to room temperature and a precipitate was collected and washed with water and MeOH. Yield 80.6 g (79%). The precipitate was used for the next reaction without further purification. The above benzofuran-2-one intermediate (80 g, 0.39 mol) and MeI (69 mL, 1.11 mol) were dissolved with THF (1000 mL) and *t*-BuOK (110 g, 0.98 mol) was added in small portions with ice-cooling. The reaction was stirred for 1 h at 5 °C. The reaction mixture was poured into 0.1 N HCl and a product was extracted with AcOEt. The organic layer was washed with 5% $NaHCO_3$ followed by brine and dried. Removal of the solvent gave a crystalline residue that was crystallized from MeOH−H_2O (1:4) to give the title compound (76.4 g, 84%) as yellow solids. Mp 77−79 °C. ^1H NMR ($CDCl_3$): δ 1.39 (s, 9H), 1.48 (s, 6H), 2.35 (s, 3H), 6.86 (d, J = 1.2 Hz, 1H), 7.01 (d, J = 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 21.36, 25.38, 29.55, 34.08, 42.22, 120.41, 125.97, 133.29, 133.65, 133.79, 147.68, 181.18. IR (KBr): 2970, 1799, 1458, 1273, 1059, 1028 cm^{-1}. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.31; H, 8.61.

2-*tert*-Butyl-6-(2-hydroxy-1,1-dimethylethyl)-4-methylphenol (2). To a mixture of the lactone **7** (35 g, 0.151 mol), $NaBH_4$ (20 g, 0.528 mol), and DME (200 mL) was added slowly MeOH (105 mL) at 65−75 °C over 1 h. The reaction was stirred for an additional 0.5 h at 70 °C and then allowed to cool to 23 °C and quenched with AcOEt and water. The organic layer was separated and an aqueous layer was back-washed with AcOEt. The combined organic layer was washed with dil. HCl and brine, dried, and evaporated. A crude solid was obtained, which was crystallized from *n*-hexane to afford the pure title compound as colorless crystals (33.6 g, 95%). Mp 114−116°C. ^1H NMR ($CDCl_3$): δ 1.41 (s, 9H), 1.43 (s, 6H), 2.27 (s, 3H), 2.47 (br s, 1H), 3.79 (s, 2H), 6.93 (d, J = 1.8 Hz, 1H), 7.01 (d, J = 1.8 Hz, 1H), 8.92 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 21.13, 25.48, 29.92, 34.87, 39.60, 74.32, 125.53, 126.11, 127.20, 132.70, 137.83, 152.69. IR (Nujol): 3521, 3407, 3230, 2855, 1462, 1425, 1378, 1234, 1211 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.11; H, 10.09.

3-*tert*-Butyl-4-hydroxy-5-(2-hydroxy-1,1-dimethylethyl)-benzaldehyde (3b). (a) A Stoichiometric Reaction. Phenol **2** (236 mg, 1.00 mmol) was dissolved with DMSO (4.7 mL) and 47% HBr (0.28 mL, 2.4 mmol) was added at 23 °C. The reaction was heated at 100 °C for 1 h. After being cooled to 23 °C, the reaction was quenched with water. A product was extracted with *n*-hexane−AcOEt (1:1) and the organic layer was washed with water twice, followed by brine, dried, and evaporated. The crude residue was subjected to column chromatography on silica gel (*n*-hexane:AcOEt 85:15) to afford the title compound as a pale pink solid (181 mg, 72%). Mp 119−121 °C. ^1H NMR ($CDCl_3$): δ 1.44 (s, 9H), 1.47 (s, 6H), 3.02 (br s, 1H), 3.85 (br s, 2H), 7.69 (d, J = 2.1 Hz, 1H), 7.73 (d, J = 2.1 Hz, 1H), 9.81 (s, 1H), 10.42 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 24.81, 29.24, 34.62, 39.67, 71.56, 126.80, 127.15, 127.86, 134.56, 137.74, 161.76, 191.51. IR (KBr): 3249, 2960, 1658, 1595, 1581, 1387, 1296, 1271, 1207 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.91; H, 8.95. **(b) A Catalytic Reaction.** Phenol **2** (4.73 g, 20.0 mmol) was dissolved with DMSO (95 mL) and 47% HBr (1.16 mL, 10 mmol) was added at 23 °C. The reaction was heated at 100 °C for 4 h. The title compound was obtained in a similar manner as described above. Yield 3.35 g (67%). The data for byproducts **10** and **11** are described in the Supporting Information.

3-*tert*-Butyl-5-[1,1-dimethyl-2-(tetrahydropyran-2-yloxy)-ethyl]-4-hydroxybenzaldehyde (17). A mixture of **3b** (1.09 g, 4.35 mmol), dihydropyran (1.6 mL, 17.4 mmol), PPTS (100 mg, 0.44 mmol), and CH_2Cl_2 (10 mL) was stirred for 40 min at room temperature. To the reaction were added sat. $NaHCO_3$ and AcOEt. The organic layer was separated and washed with brine, dried, and evaporated. The residue was purified by chromatography on silica gel (*n*-hexane:AcOEt 4:1) to give the title compound (1.40 g, 97%) as a colorless oil. ^1H NMR ($CDCl_3$): δ 1.44 (s, 9H), 1.49 (s, 3H), 1.52 (s, 3H), 1.52−1.90 (m, 6H), 3.47 (d, J = 9.0 Hz, 1H), 3.51−3.72 (m, 2H), 3.92 (d, J = 9.0 Hz, 1H), 7.70 (d, J = 2.1 Hz, 1H), 7.74 (d, J = 2.1 Hz, 1H), 9.83 (s, 1H), 10.09 (s, 1H). IR ($CHCl_3$): 3195, 2952, 1680, 1585, 1429, 1385, 1277, 1263, 1225, 1215, 1203, 1190, 1122, 1036 cm^{-1}. Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.64; H, 9.12.

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Supporting Information Available: Experimental procedures for the synthesis of **8**, **9**, **3b**, and **5**, and data for **8**, **9**, **5**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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