BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 49 (9), 2649—2650 (1976)

Syntheses of 4-(4-Hydroxy-2,6-dimethylphenyl)-1,2-butanediol and 4-(4-Hydroxy-2,6-dimethylphenyl)-2-butanol.

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(Received May 4, 1976)

Synopsis. 4-(4-Hydroxy-2,6-dimethylphenyl)-1,2-butanediol (**3**) and 4-(4-hydroxy-2,6-dimethylphenyl)-2-butanol (**4**) as precursors for a theaspirone synthesis have been synthesized starting from 3,5-dimethylphenyl methyl ether.

One of the synthetic approach toward theaspirone[1] (**1**) has been focused on how to prepare efficiently the key intermediate, 3,5,5-trimethyl-4-(3-hydroxybutyl)-4-hydroxy-2-cyclohexenone which undergoes acid promoted cyclization leading to **1**. A promising approach would be an electrochemical cyclization of the phenol derivatives **3** and **4** leading to cyclohexadienones **2**, since 3-(4-hydroxyphenyl)propanoic acid,[2] hydroquinone bis(2-hydroxyethyl) ether,[3] and 2,4,6-tri-*t*-butylphenol[4] have been known to suffer anodic oxidation affording 1-oxa-spiro[4,5]deca-6,9-diene-2,8-dione, 8-(2-hydroxyethoxy)-8-methoxy-1,4-dioxaspiro[4,5]deca-6,9-diene, and 2,4,6-tri-*t*-butyl-4-methoxy-2,5-cyclohexadienone, respectively.

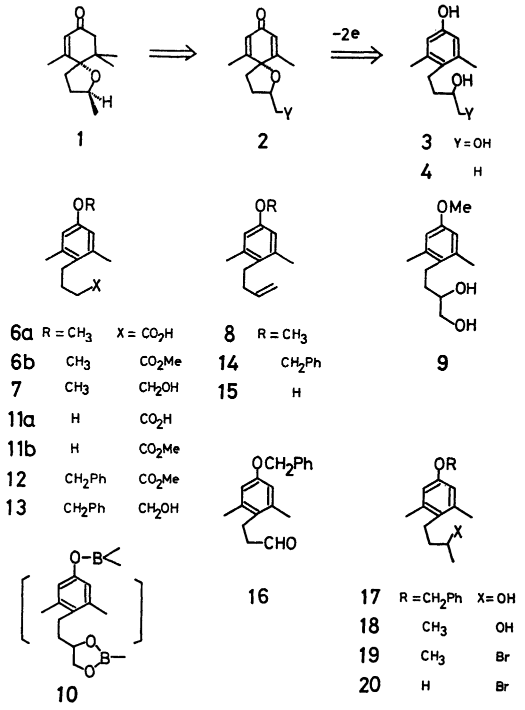
Thus, our attention has been paid to the syntheses of 4-(4-hydroxy-2,6-dimethylphenyl)-1,2-butanediol (**3**) and 4-(4-hydroxy-2,6-dimethylphenyl)-2-butanol (**4**) as starting compounds for the electrolytic cyclization.

The Clemmensen reduction of 3-(2,6-dimethyl-4-methoxybenzoyl)propanoic acid (**5**) and subsequent methylation with diazomethane afforded **6b** in 90% yield. The alcohol **7** obtained by the reduction of **6b** with lithium aluminum hydride was converted into the corresponding xanthate in quantitative yield. The thermal decomposition of the xanthate[5] took place instantaneously at the temperature range between 300—360 °C affording the olefin **8** in 73% yield. Oxidation of **8** with potassium permanganate at −45—−40 °C gave the diol **9** in 57% yield along with 19% of the starting material.

Treatment of **9** with boron tribromide[6] in anhydrous dichloromethane at −70 °C furnished the triol **3** in 69% yield without suffering bromination of aliphatic hydroxy groups on C_1 and C_2. The inertness of the vicinal hydroxyl groups toward the bromination reagent would be due to the formation of the stable chelated complex as illustrated in **10**.[7] In fact, the action of boron tribromide to the alcohol **18** induced the formation of the bromides **19** and **20** preferentially. In order to affect the efficient formation of the phenolic alcohol **4**, lithium metal reduction of the benzyl ether **17** in liquid ammonia was performed.

The cleavage of the methoxyl group of **6a** with boron tribromide followed by methylation with diazomethane provided the phenol ester **11b**. Benzylation of **11b** in DMF was accomplished in 84% yield. The subsequent reduction of **12** to **13** with lithium aluminum hydride and the transformation of **13** to the corresponding xanthate were performed similarly in 88% yield from **12**. The thermolysis of the xanthate took place at 350 °C affording the desired olefin **14** and the phenolic olefin **15** in 40% and 18%, respectively. The higher temperature on the thermolysis and the prolonged heating of the products facilitated the cleavage of the benzyl group.

Ozonolysis of **14** followed by reduction of the ozonide yielded the aldehyde **16** in 74%. Grignard reaction of **16** with methyl magnesium iodide afforded the alcohol **17** in 86%. Finally, reductive scission of the benzyl group of **17** with lithium in liquid ammonia provided the diol **4** in 76%.



Experimental

The NMR and IR spectra were determined with Hitachi R-24 and Hitachi WPI-S2, respectively.

3-(2,6-Dimethyl-4-methoxybenzoyl)propanoic Acid (5). Friedel-Crafts reaction of 1 g of 3,5-dimethylanisole and 0.82 g of succinic anhydride with 2.2 g of aluminum chloride in 6 ml of nitrobenzene and 0.5 ml of CS_2 at −10—−5 °C for 9 h gave 1.58 g (85%) of **5** as colorless crystals, mp 102—102.5 °C: IR (Nujol) 3300—2350 (CO_2H), 1713 (CO_2H), 1696 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 9.35 (br. s, 1H, CO_2H), 6.59 (br. s, 1H, ArH), 6.53 (br. s, 1H, ArH), 3.75 (s, 3H, CH_3O), 3.29—2.53 (m, 4H, CH_2), 2.29 (s, 3H, CH_3), 2.16 (s, 3H, CH_3). Found: C, 66.33; H, 6.99%. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83%.

4-(2,6-Dimethyl-4-methoxyphenyl)butanoic Acid (6a). Clemmensen reduction of 3.88 g of **5** gave 3.66 g (90%) of **6** as colorless crystals, mp 96.5—97 °C (benzene–hexane): IR (Nujol) 3350—2350, 1699 (CO_2H) cm^{-1}; NMR ($CDCl_3$) δ

10.05 (br. s, 1H, CO_2H), 6.58 (br. s, 1H, ArH), 6.53 (br. s, 1H, ArH), 3.75 (s, 3H, CH_3O), 2.87—2.11 (m, 4H, CH_2Ar, CH_2CO), 2.27 (br. s, 6H, CH_3) 2.11—1.61 (m, 2H, CH_2). Found: C, 70.14; H, 7.93%. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16%.

4-(2,6-Dimethyl-4-methoxyphenyl)-1-butanol (7). Reduction of the methyl ester **6b** was performed with $LiAlH_4$ in ether affording **7** as a colorless oil in 98% yield: IR (neat) 3350 (OH) cm^{-1}; NMR ($CDCl_3$) δ 6.58 (br. s, 1H, ArH), 6.54 (br. s, 1H, ArH), 3.76 (s, 3H, CH_3O), 3.65 (t, J=6.0 Hz, 2H, CH_2O), 2.63 (t, J=7.2 Hz, 2H, CH_2Ar), 2.26 (br. s, 6H, CH_3), 1.75 (br. s, 1H, OH), 1.81—1.16 (m, 4H, CH_2). Found: C, 74.76; H, 9.97%. Calcd for $C_{13}H_{20}O_2$; C, 74.96: H, 9.68%.

4-(2,6-Dimethyl-4-methoxyphenyl)-1-butene (8). The xanthate of **7** was prepared in 98% yield as described previously.[5] The decomposition of 3.496 g of the xanthate took place at 360 °C to form a fumy vapor which was collected in a receiver to give 2.2 g of a yellow oil, whose chromatography over alumina (hexane–CH_2Cl_2 20:1) gave 1.624 g (73%) of **8** as a colorless oil; IR (neat) 1640 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 6.58 (br. s, 1H, ArH), 6.54 (br. s, 1H, ArH), 6.30—4.82 (m, 3H, CH_2=CH), 3.77 (s, 3H, CH_3O), 2.93—2.53 (m, 2H, CH_2Ar), 2.53—1.93 (m, 2H, CH_2), 2.28 (br. s, 6H, CH_3). Found: C, 81.87; H, 9.82%. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53%.

4-(2,6-Dimethyl-4-methoxyphenyl)-1,2-butanediol (9). Into a stirred solution of 0.2 g of **8** in 3 ml of EtOH was added dropwise aq $KMnO_4$ (0.16 g of $KMnO_4$, 0.12 g of $MgSO_4$, 4 ml of H_2O) at −45—−40 °C in 20 min. After stirring at the temperature for additional 2 h and warming to room temperature, the mixture was decantated and the precipitate was rinced with hot water. The combined organic layer was concentrated and extracted with AcOEt to yield 0.135 g of **9** as a colorless oil after chromatographed over silica gel (AcOEt–CH_2Cl_2 1:1): IR (neat) 3367 (OH) cm^{-1}; NMR (CCl_4) δ 6.41 (br. s, 1H, ArH), 6.35 (br. s, 1H, ArH), 4.02 (br. s, 2H, OH), 3.69 (s, 3H, CH_3O), 3.80—3.20 (m, 3H, CH_2O, CHO), 2.64 (t, J=7.8 Hz, 2H, CH_2Ar), 2.18 (br, s, 6H, CH_3) 1.84—1.01 (m, 2H, CH_2). Found: C, 69.34; H, 9.13%. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99%.

4-(2,6-Dimethyl-4-hydroxyphenyl)-1,2-butanediol (3). Into a stirred solution of 96 mg of **9** in 2 ml of dry CH_2Cl_2, was added dropwise cautiously 429 mg of BBr_3 at −70 °C under nitrogen. After stirring at −70 °C for 1 h and then at 0 °C for 30 min, the mixture was quenched with 2 ml of saturated $NaHCO_3$ followed by saturated Na_2CO_3. The organic layer was extracted with AcOEt, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed over silica gel (AcOEt–CH_2Cl_2 1:1) to yield 62 mg (69%) of **3** as a white solid, mp 107—108 °C (benzene); IR (Nujol) 3345 (OH) cm^{-1}; NMR ($CDCl_3$) δ 8.18—7.18 (br. s, 1H, OH), 6.62 (br. s, 2H, ArH), 4.91—2.96 (m, 5H, OH, OH, CH_2O, CHO), 2.96—2.54, (m, 2H, CH_2Ar), 2.24 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 1.94—1.28 (m, 2H, CH_2). Found: C, 68.54; H, 8.91%. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63%.

4-(2,6-Dimethyl-4-hydroxyphenyl)butanoic Acid (11a). In a similar manner, reaction of 0.5 g of **6a** with 0.43 ml of BBr_3 gave 0.45 g (97%) of **11a** as colorless crystals, mp 127.5—128.5 °C (benzene–AcOEt); IR (Nujol) 3504 (OH), 3400—2400, 1688 (CO_2H) cm^{-1}; NMR ($CDCl_3$) δ 7.66 (br. s, 2H, OH, CO_2H), 6.53 (br. s, 1H, ArH), 6.45 (br. s, 1H, ArH), 2.95—2.23 (m, 4H, CH_2Ar, CH_2CO), 2.25 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.23—1.62 (m, 2H, CH_2). Found: C, 68.94; H, 7.94%. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%.

Methyl 4-(2,6-dimethyl-4-benzyloxyphenyl)butanoate (12). *O*-Benzylation of **11b** gave **12** as a colorless oil: IR (neat) 1735 (CO_2Me) cm^{-1}; NMR ($CDCl_3$) δ 7.34 (br. s, 5H, Ph), 6.57 (br. s, 2H, ArH), 4.97 (br. s, 2H, CH_2O), 3.55 (s, 3H, CH_3O), 2.89—2.14 (m, 4H, CH_2Ar, CH_2CO), 2.25 (br. s, 6H, CH_3), 2.14—1.59 (m, 2H, CH_2). Found: C, 76.77; H, 8.03%. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74%.

4-(2,6-Dimethyl-4-benzyloxyphenyl)butanol (13). Reduction of **12** with $LiAlH_4$ in ether was performed in an usual manner affording **13** as a colorless oil; IR (neat) 3320 (OH) cm^{-1}; NMR ($CDCl_3$) δ 7.24 (br. s, 5H, Ph), 6.51 (br. s, 2H, ArH), 4.83 (s, 2H, CH_2O), 3.46 (t, J=6.0 Hz, 2H, CH_2O), 2.92 (br. s, 1H, OH), 2.64 (t, J=6.6 Hz, 2H, CH_2), 2.19 (s, 6H, CH_3), 1.71—1.28 (m, 4H, CH_2). Found: C, 80.09; H, 8.79%. Calcd for $C_{19}H_{24}O_2$: C, 80.24: H, 8.51%.

4-(2,6-Dimethyl-4-benzyloxyphenyl)-1-butene (14) and 3,5-Dimethyl-4-(3-butenyl)phenol (15). The thermolysis of the xanthate of **13** was performed similarly as described[5] affording **14** (40%) and **15** (18%) as colorless oils: **14** IR (neat) 1636 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 7.30 (br. s, 5H, Ph), 6.54 (br. s, 2H, ArH), 6.32—4.74 (m, 3H, CH_2=CH), 4.95 (s, 2H, CH_2O), 2.98—2.53 (m, 2H, CH_2Ar), 2.53—1.90 (m, 2H, CH_2), 2.24 (s, 6H, CH_3). Found: C, 85.60; H, 8.61%. Calcd for $C_{19}H_{22}O$: C, 85.67; H, 8.32%. **15** IR (neat) 3400 (OH), 1636 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 6.54 (br. s, 1H, ArH), 6.40 (br. s, 1H, ArH), 6.24—4.75 (m, 3H, CH_2=CH), 4.63 (br. s, 1H, OH), 2.96—2.45 (m, 2H, CH_2Ar), 2.45—1.94 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.21 (s, 3H, CH_3). Found: C, 82.01; H, 9.34%. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15%.

3-(2,6-Dimethyl-4-benzyloxyphenyl)propanal (16). Ozonolysis of **14** was carried out as usually to give **16** (74%) as a colorless oil: IR (neat) 1721 (CHO) cm^{-1}; NMR ($CDCl_3$) δ 9.66 (t, J=1.8 Hz, 1H, CHO), 7.31 (br. s, 5H, Ph), 6.56 (br. s, 2H, ArH), 4.99 (s, 2H, CH_2O), 3.18—2.79 (m, 2H, CH_2Ar), 2.79—2.15 (m, 2H, CH_2), 2.27 (s, 6H, CH_3). Found: C, 80.41; H, 7.80%. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51%.

4-(2,6-Dimethyl-4-benzyloxyphenyl)-2-butanol (17). The alcohol **17** was prepared in 86% yield by Grignard reaction of **16** with MeMgI: IR (neat) 3360 (OH) cm^{-1}; NMR ($CDCl_3$) δ 7.31 (br. s, 5H, Ph), 6.57 (br. s, 2H, ArH), 4.94 (s, 2H, CH_2O), 3.65 (m, 1H, CH), 2.96—2.40 (m, 2H, CH_2Ar), 2.45 (br. s, 1H, OH), 2.26 (s, 6H, CH_3), 2.02—1.30 (m, 2H, CH_2), 1.09 (d, J=6.0 Hz, 3H, CH_3). Found: C, 80.00; H, 8.67%. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51%.

4-(2,6-Dimethyl-4-hydroxyphenyl)-2-butanol (4). Treatment of 62 mg of **17** with 13 mg of Li metal in 0.2 ml of dry THF and 5 ml of liquid ammonia at −50 °C for 4 h and an usual work-up provided 32 mg (76%) of **4** as a colorless oil: IR (neat) 3300 (OH) cm^{-1}; NMR (CCl_4) δ 8.24—4.54 (br. m, 2H, OH), 6.42 (br. s, 2H, ArH), 3.66 (m, 1H, CH), 3.08—2.34 (m, 2H, CH_2Ar), 2.19 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 1.94—1.34 (m, 2H, CH_2), 1.15 (d, J=6.6 Hz, 3H, CH_3) Found: C, 73.90; H, 9.42%. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34%.

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