Studies on Selective Preparation of Aromatic Compounds. 20. Selective Preparation of 2-Mono- and 2,2′-Disubstituted Biphenyl Using the *tert*-Butyl Group as a Positional Protective Group[1]

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The *tert*-butyl group is an important positional protective function in the selective preparation of aromatic compounds, since it can be introduced on aromatic rings by Friedel–Crafts *tert*-butylation and its removal can be easily carried out by transalkylation and dealkylation. Biphenyls 2-methyl- (**4a**), 2-bromo- (**4b**), 2-iodo- (**4d**), 2-nitro- (**4e**), 2-amino- (**4f**), 2,2′-dibromo- (**7a**), 2,2′-dichloro- (**7b**), 2,2′-dinitro- (**7d**), and 2,2′-diamino-4,4′-di-*tert*-butylbiphenyl (**7e**) were selectively prepared from 4,4′-di-*tert*-butylbiphenyl (**2**). The $AlCl_3$–CH_3NO_2 and $AlCl_3$ catalyzed transalkylation of 2-substituted and 2,2′-disubstituted 4,4′-di-*tert*-butylbiphenyls was carried out in benzene under various conditions in order to obtain the corresponding 2-substituted and 2,2′-disubstituted biphenyls. Thus, 2-methyl- (**12**), 2-bromo- (**15**), 2,2′-dibromo- (**26a**), and 2,2′-dichlorobiphenyl (**26b**) were obtained in good yields by this method. However, 2-iodobiphenyl (**18**) was obtained in very poor yield, since transiodonation was accompanied with transalkylation of the *tert*-butyl group of **4d**. Also it was found that the $AlCl_3$-catalyzed transalkylation of **4e** and **4f** afforded 2-nitro- (**21**) and 2-amino-4-*tert*-butylbiphenyl (**22**) in which only one of the *tert*-butyl groups of **4e** and **4f** was transalkylated, respectively. However, the *tert*-butyl groups of **7d** and **7e** were not transalkylated. Also 2,2′-dimethyl- (**27a**), 2,2′,3,3′-tetramethyl- (**27b**), and 2,2′,6,6′-tetramethylbiphenyl (**27c**) and *o*-quaterphenyl (**20**) were prepared through the iodonation of the corresponding *tert*-butylbenzenes, the Ullmann condensation, and the $AlCl_3$ catalyzed transalkylation. Thus, the *tert*-butyl group can serve as a positional protective group in the selective preparation of methylbiphenyls such as **12**, **27a**, **27b**, and **27c**, halobiphenyls such as **15**, **26a**, **26b**, and *o*-quaterphenyl (**20**), but not in the preparation of **18** and 2,2′-diamino- and 2,2′-dinitrobiphenyls.

It has been previously reported that the *tert*-butyl group could serve as a positional protective group for the preparation of some phenolic compounds,[2-8] diarylalkanes,[9] dibenzocycloheptadiene,[10] 4-hydroxyphenyl aryl ethers,[11] dimethyl[2.2]metacyclophane,[1] and 1,2-di- and 1,2,3-trisubstituted benzenes.[12]

We now wish to report on the selective preparation of 2-mono- and 2,2′-disubstituted biphenyls from biphenyl using the *tert*-butyl group as a positional protective group.

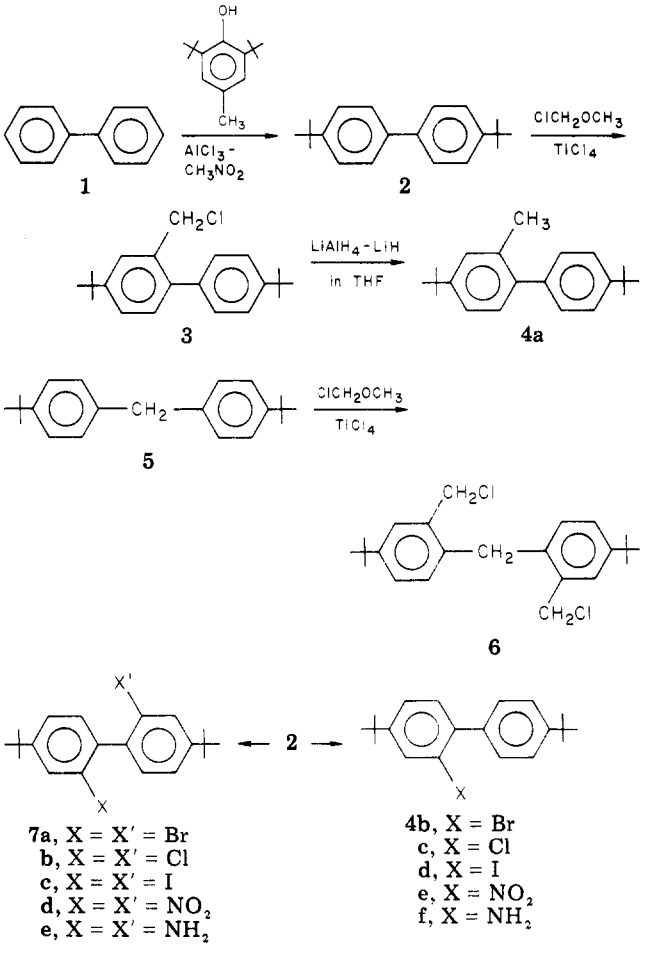
Results and Discussion

Preparation of Some *tert*-Butylbiphenyls. The $AlCl_3$–CH_3NO_2 catalyzed *tert*-butylation of biphenyl (**1**) with 2,6-di-*tert*-butyl-*p*-cresol afforded 4,4′-di-*tert*-butylbiphenyl (**2**) in 70% yield.[13] 2-Methyl-4,4′-di-*tert*-butylbiphenyl (**4a**) was prepared from **2** via **3**.

Although the chloromethylation of 4,4′-bis(*tert*-butylphenyl)methane (**5**)[9] afforded the corresponding 2,2′-bis(chloromethyl)-4,4′-di-*tert*-butylbiphenyl (**6**), the chloromethylation of **2** gave only **3** (Scheme I).

The bromination of **2** with 1 mol and 2 mol of bromine to 1 mol of **2** afforded 2-bromo- (**4b**) and 2,2′-dibromo-4,4′-di-*tert*-butylbiphenyl (**7a**) in 73 and 90% yields, respectively. Although the expected 2-chloro-4,4′-di-*tert*-butylbiphenyl (**4c**) was formed in the chlorination of **2** with chlorine together with 2,2′-dichloro-4,4′-di-*tert*-butylbi-

Scheme I



(1) Part 19: M. Tashiro and T. Yamato, *Synthesis*, 738 (1978).
(2) M. Tashiro, H. Watanabe, and O. Tsuge, *Org. Prep. Proced. Int.*, 6, 107 (1974).
(3) M. Tashiro, H. Watanabe, and O. Tsuge, *Org. Prep. Proced. Int.*, 6, 117 (1974).
(4) M. Tashiro, G. Fukata, S. Mataka, and K. Oe, *Org. Prep. Proced. Int.*, 7, 231 (1975).
(5) M. Tashiro, H. Watanabe, K. Oe, and O. Tsuge, *Org. Prep. Proced. Int.*, 7, 255 (1975).
(6) M. Tashiro and G. Fukata, *Org. Prep. Proced. Int.*, 8, 241 (1976).
(7) M. Tashiro, G. Fukata, T. Yamato, H. Watanabe, K. Oe, and O. Tsuge, *Org. Prep. Proced. Int.*, 8, 249 (1976).
(8) M. Tashiro and G. Fukata, *J. Org. Chem.*, 42, 1208 (1977).
(9) M. Tashiro, T. Yamato, and G. Fukata, *J. Org. Chem.*, 43, 1413 (1978).
(10) M. Tashiro and T. Yamato, *Synthesis*, 214 (1978).
(11) M. Tashiro, H. Yoshiya, and T. Yamato, *Synthesis*, 678 (1978).
(12) M. Tashiro and T. Yamato, *J. Chem. Soc., Perkin Trans. 1*, 176 (1979).
(13) M. Tashiro and T. Yamato, *Org. Prep. Proced. Int.*, 10, 143 (1978).

0022-3263/79/1944-3037$01.00/0

Table I. The Lewis Acid Catalyzed Transalkylation of *tert*-Butylbiphenyls in Benzene at 50 °C[a]

run	substrate	catalyst[b]	time, h	product (%)
1	4a	A	4	**12** (80)
2	4b	A	6	**14** (87)
3	4b	B	6	**15** (82)
4	14	B	6	**15** (86)
5	4d	A	6	**18** (1), **13** (51), **17** (20), **1** (28)
6	4d	B	6	**16** (45), **13** (42), **17** (3), **1** (10)
7	4e	A	6	no reaction
8	4e	B	6	**21** (70)
9	4f	A	6	**22** (80)
10	4f	B	6	no reaction
11	7a	B	0.5	**26a** (74)
12	7d	B	1	**26b** (77)
13	7c	B	3	no reaction
14	7d	B	3	no reaction
15	11a	A	4	**27a** (90)
16	11b	A	4	**27b** (92)
17	11c	A	4	**27c** (80)

[a] 10 mmol of *tert*-butylbiphenyl was dissolved in 60 mL of benzene unless otherwise indicated. [b] A, $AlCl_3$–CH_3NO_2; B, $AlCl_3$.

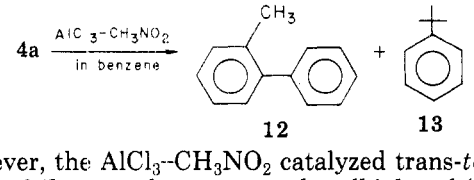
phenyl (**7b**), the isolation of **4c** from the reaction mixture was difficult.

The iodonation of **2** with HIO_4–I_2[14] afforded 2-iodo- (**4d**) but not 2,2′-diiodo-4,4′-di-*tert*-butylbiphenyl (**7c**).

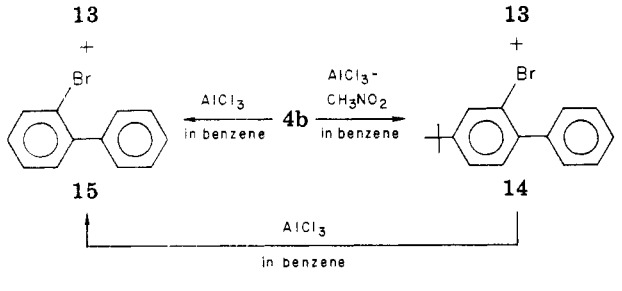
The nitration of **2** with fuming HNO_3 and a mixed acid (HNO_3/H_2SO_4) afforded 2-nitro- (**4e**) and 2,2′-dinitro-4,4′-di-*tert*-butylbiphenyl (**7d**) in almost quantitative yields, respectively. Both compounds **4e** and **7d** were easily reduced with Sn–HCl to give the corresponding amino compounds **4f** and **7e** in 98 and 90% yields, respectively.

Di- and tetramethyl-3,3′-*tert*-butylbiphenyls (**11**) were prepared from the corresponding *tert*-butylmethylbenzenes according to the following reactions (Scheme II).

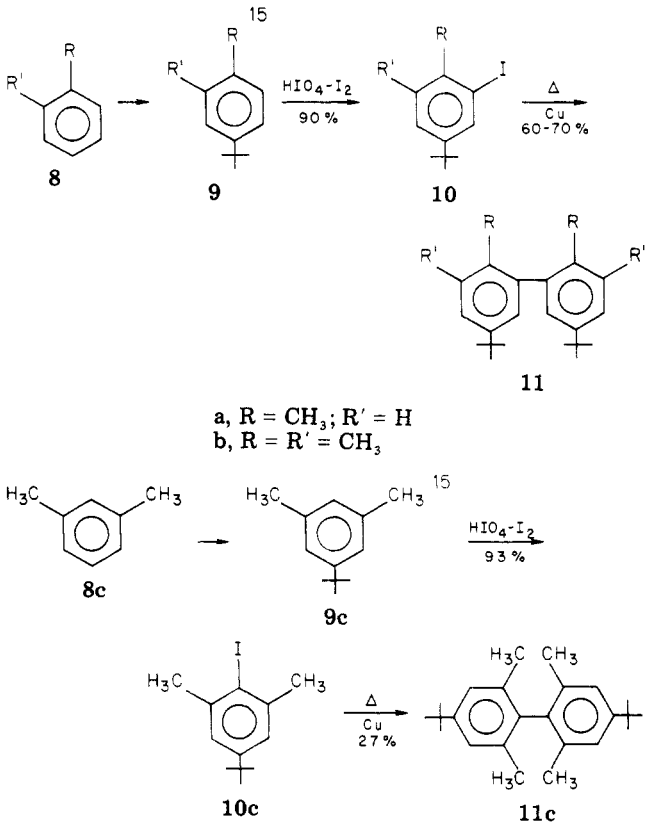
Transalkylation of *tert*-Butylbiphenyls. The Lewis acid catalyzed transalkylation of *tert*-butylbiphenyls such as **4**, **7**, and **11** was carried out under various conditions and the results are summarized in Table I. The *tert*-butyl group is transferred from **4a** to benzene to give biphenyl **12** together with *tert*-butylbenzene (**13**).



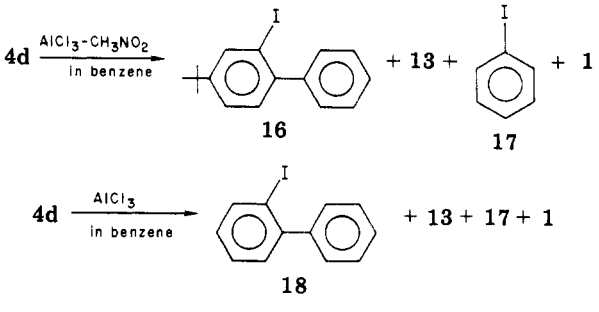
However, the $AlCl_3$–CH_3NO_2 catalyzed trans-*tert*-butylation of **4b** gave 2-bromo-4-*tert*-butylbiphenyl (**14**) but not the expected 2-bromobiphenyl (**15**), which was obtained from the $AlCl_3$ catalyzed trans-*tert*-butylation of **4b** or **14**.



Scheme II



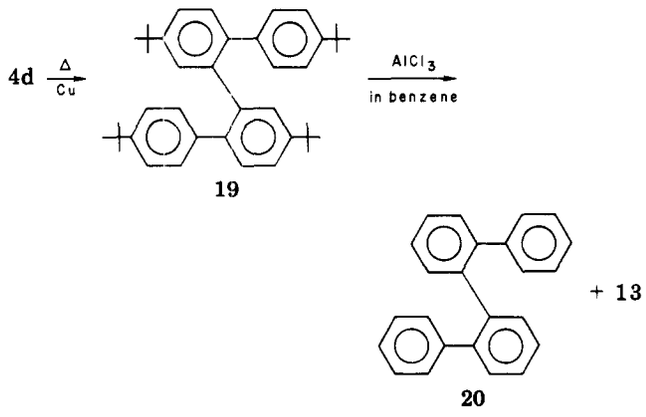
These results show clearly that **14** should be the intermediate in the $AlCl_3$ catalyzed trans-*tert*-butylation of **4b**. Although the $AlCl_3$–CH_3NO_2 catalyzed trans-*tert*-butylation of **4d** as well as **4b** afforded the corresponding 2-iodo-4-*tert*-butylbiphenyl (**16**), the transiodonated product **1** and iodobenzene (**17**) were also formed together with **16**.



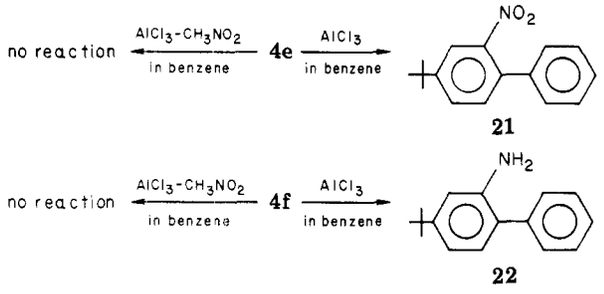
It was also found in the $AlCl_3$-catalyzed trans-*tert*-butylation of **4d** that the expected 2-iodobiphenyl (**18**), which is a good starting material for the preparation of *o*-quaterphenyl (**20**),[16] was obtained only in poor yield together with a large amount of the transiodonated products **1** and **17**. The results suggest that this method is not suitable for the preparation of iodobiphenyls such as **16** and **18**. However, **20** was prepared by the $AlCl_3$-catalyzed transbutylation of **19**, which was easily obtained by the Ullmann reaction of **4d**.

When **4e** or **4f** was treated with $AlCl_3$–CH_3NO_2 catalyst in benzene only starting compound **4e** or **4f** was recovered in quantitative yield. In contrast to $AlCl_3$–CH_3NO_2 catalyst, $AlCl_3$ catalyst afforded 2-nitro- (**21**) and 2-amino-

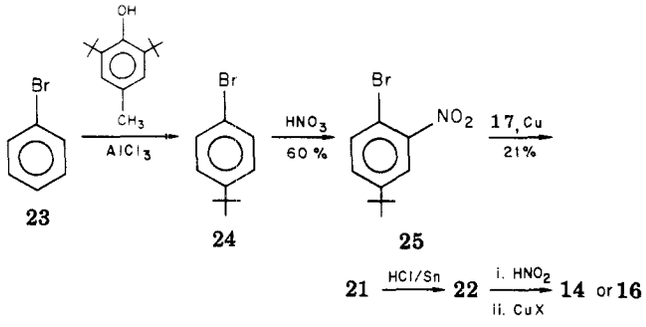
(14) H. Suzuki, K. Nakamura, and R. Goto, *Bull. Chem. Soc. Jpn.*, **39**, 128 (1968).
(15) M. Tashiro, G. Fukata, and T. Yamato, *Org. Prep. Proced. Int.*, **8**, 263 (1976).
(16) W. E. Bachmann and H. T. Clarke, *J. Am. Chem. Soc.*, **49**, 2094 (1927).
(17) M. Tashiro and T. Yamato, *Org. Prep. Proced. Int.*, **9**, 151 (1977).



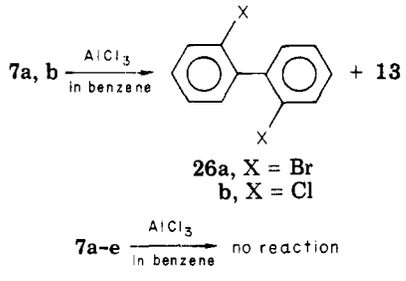
4-*tert*-butylbiphenyl (**22**) from **4e** and **4f** in 70 and 80% yield, respectively.



The structures of the selective trans-*tert*-butylated compounds such as **14**, **16**, **21**, and **22** were determined by their spectral data, elemental analyses, and comparison with authentic compounds, which were prepared by the following reactions.

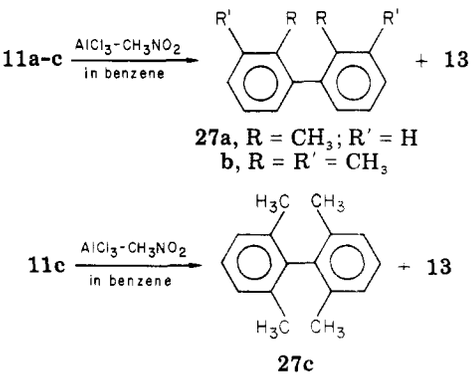


Although the $AlCl_3$–CH_3NO_2 catalyzed trans-*tert*-butylation of **7** did not give any product and the starting compound **7** was recovered in quantitative yield, the expected 2,2′-dibromo- (**26a**) and 2,2′-dichlorobiphenyl (**26b**) were obtained by the $AlCl_3$-catalyzed reaction.



In the cases of **7d** and **7e**, the trans-*tert*-butylation did not occur even under the influence of the $AlCl_3$ catalyst.

As is shown in Table I, the polymethylbiphenyls such as 2,2′-dimethyl- (**27a**), 2,2′,3,3′-tetramethyl- (**27b**), and 2,2′,6,6′-tetramethylbiphenyl (**27c**) were also easily prepared by the $AlCl_3$–CH_3NO_2 catalyzed transbutylation of the corresponding *tert*-butylmethylbiphenyls (**11**).



Although **11** cannot be directly prepared from **1**, it was selectively obtained from the corresponding alkylbenzenes as described above. As mentioned above, the method using the *tert*-butyl group as a positional protective group is useful for the preparation of polyalkylbiphenyls as well as halobiphenyls such as **15** and **26a–c** and monomethylbiphenyls such as **12**, but not for nitro- and amino-substituted biphenyls.

Experimental Section

All melting and boiling points are uncorrected. NMR spectra were determined at 60 MHz with a Hitachi R-20 NMR spectrometer with Me_4Si and internal references and IR spectra were measured as KBr pellets or liquid film on NaCl plates on a Nippon Bunko IR-S spectrometer.

Preparation of 2-(Chloromethyl)-4,4′-di-*tert*-butylbiphenyl (3). To a solution of 25.1 g (0.1 mol) of 4,4′-di-*tert*-butylbiphenyl[13] were added 16 g (0.2 mol) of chloromethyl methyl ether in 150 mL of CS_2 and 8 mL of $TiCl_4$ at 5 °C.

After the reaction mixture was stirred for 90 min, it was poured into large amount of ice–water. The organic layer was extracted with ether. The ether solution was dried over Na_2SO_4, evaporated in vacuo, and distilled under reduced pressure to give 24.6 g (82%) of **3** as a colorless liquid: bp 175–180 °C (3 mm); NMR (CCl_4) δ 1.34 [18 H, s, $-C(CH_3)_3$], 4.54 (2 H, s, CH_2Cl), and 7.20–7.50 (7 H, m, aromatic protons). Anal. Calcd for $C_{21}H_{27}Cl$: C, 80.10; H, 8.64. Found: C, 79.87; H, 8.64.

Preparation of 4,4′-Di-*tert*-butyl-2-methylbiphenyl (4a). The reduction of **3** with $LiAlH_4$–LiH[18] was carried out according to the reported method[9] to afford **4a** in 72.7% yield as colorless prisms (EtOH): mp 60–63 °C; NMR (CCl_4) δ 1.34 [18 H, s, $C(CH_3)_3$], 2.23 (3 H, s, CH_3), and 7.02–7.37 (7 H, m, aromatic protons). Anal. Calcd for $C_{21}H_{28}$: C, 89.94; H, 10.06. Found: C, 89.70; H, 10.10.

Preparation of 2-Bromo-4,4′-di-*tert*-butylbiphenyl (4b). To a solution of 12.55 g (50 mmol) of **2** in 50 mL of CCl_4 was added at 5–8 °C a solution of 8.8 g (55 mmol) of Br_2 in 10 mL of CCl_4 in the presence of a small amount of Fe powder. After the reaction mixture was stirred at 15 °C for 3 h, it was poured into a large amount of water. The organic layer was extracted with ether, and the ether solution was washed with 10% NaOH solution and water, dried over Na_2SO_4, and evaporated in vacuo to give 15.0 g (73.3%) of **4b**: colorless prisms (EtOH); mp 76–78 °C; NMR (CCl_4) δ 1.27 [18 H, s, $C(CH_3)_3$], and 7.15–7.56 (7 H, m, aromatic protons). Anal. Calcd for $C_{20}H_{25}Br$: C, 69.56; H, 7.30. Found: C, 69.57; H, 7.37.

Preparation of 2-Iodo-4,4′-di-*tert*-butylbiphenyl (4d). After a mixture of 12.55 g (50 mmol) of **2**, 2.31 g of $HIO_4 \cdot 2H_2O$, 5.09 g of I_2, 25.5 mL of AcOH, 4.5 mL of H_2O, 0.9 mL of concentrated H_2SO_4, and 20 mL of CCl_4 was warmed at 80 °C for 3 h, it was cooled to room temperature and extracted with ether. The ether solution was washed with $NaHSO_3$ solution and water, dried over Na_2SO_4, and evaporated in vacuo to afford 18.3 g (97.1%) of **4d**: colorless needles (EtOH); mp 92–93 °C; IR (KBr) 2940, 1490, 1370, 1350, 1260, 1250, 840, and 820 cm^{-1}; NMR (CCl_4) δ 1.31 [9 H, s, $C(CH_3)_3$], 1.34 [9 H, s, $C(CH_3)_3$], and 6.99–7.85 (7 H, m, aromatic

(18) J. E. Johnson, *J. Am. Chem. Soc.*, **70**, 3664 (1948).

protons). Anal. Calcd for $C_{20}H_{25}I$: C, 61.23; H, 6.42. Found: C, 61.22; H, 6.39.

Preparation of 2-Nitro-4,4′-di-*tert*-butylbiphenyl (4e). To a solution of 5.02 g (20 mmol) of **2** in 100 mL of Ac_2O was added at room temperature a solution of 3 mL of fuming HNO_3 (d = 1.5) and 5 mL of AcOH. The reaction mixture was stirred for 1 h and poured into a large amount of water. The precipitated crystaline product was filtrated to give 5.9 g (99.7%) of **4e**: pale yellow prisms; mp 106–107 °C; IR (KBr) 2950, 1520, 1330, and 825 cm^{-1}; NMR (CCl_4) δ 1.34 [9 H, s, $C(CH_3)_3$], 1.37 [9 H, s, $C(CH_3)_3$], and 7.03–7.10 (7 H, m, aromatic protons). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09; N, 4.49. Found: C, 77.11; H, 7.95; N, 4.71.

Preparation of 2-Amino-4,4′-di-*tert*-butylbiphenyl (4f). To a solution of 2.96 g (10 mmol) of **4e** and 20 mL of concentrated HCl in 50 mL of EtOH was gradually added 2.37 g of Sn powder. After the reaction mixture was refluxed for 30 min, it was poured into a large amount of ice–water, basified with 10% NaOH solution, and extracted with ether. The ether solution was washed with water, dried over Na_2SO_4, and evaporated in vacuo to give 2.6 g (97.7%) of **4f**: colorless prisms (EtOH); mp 125–126 °C; IR (KBr) 3370, 3250, 2910, 1590, 1490, 1400, 820, and 725 cm^{-1}; NMR (CCl_4) δ 1.28 [9 H, s, $C(CH_3)_3$], 1.22 [9 H, s, $C(CH_3)_3$], 3.45 (2 H, s, NH_2), and 6.58–7.28 (7 H, m, aromatic protons). Anal. Calcd for $C_{20}H_{27}N$: C, 85.35; H, 9.67; N, 4.98. Found: C, 84.96; H, 9.67; N, 5.09.

Preparation of 2,2′-Dibromo-4,4′-di-*tert*-butylbiphenyl (7a). To a solution of 2.51 g (10 mmol) of **2** in 10 mL of CCl_4 was added a solution of 12.0 g (30 mmol) of Br_2 in 2 mL of CCl_4 in the presence of small amount of Fe powder. The reaction mixture was stirred at 30 °C for 3 h, and it was treated and worked up as described above to give 3.82 g (90%) of **7a**: colorless prisms (EtOH); mp 157–158 °C; NMR (CCl_4) δ 1.35 [18 H, s, $C(CH_3)_3$] and 6.96–7.55 (6 H, m, aromatic protons). Anal. Calcd for $C_{20}H_{24}Br_2$: C, 56.62; H, 5.70. Found: C, 56.41; H, 5.52.

Preparation of 2,2′-Dichloro-4,4′-di-*tert*-butylbiphenyl (7b). To a mixture of 12.55 g (50 mmol) of **2** in 50 mL of CCl_4 and a small amount of Fe powder was added slowly Cl_2 gas for 1 h, and then the reaction mixture was poured into large amount of water. The organic layer was extracted with ether. The ether solution was washed with 10% NaOH solution and water, dried over Na_2SO_4, and evaporated in vacuo to give 11.2 g (70%) of **7b**: colorless prisms (EtOH); mp 120–122 °C; NMR (CCl_4) δ 1.35 [18 H, s, $C(CH_3)_3$] and 7.00–7.39 (6 H, m, aromatic protons). Anal. Calcd for $C_{20}H_{24}Cl_2$: C, 71.64; H, 7.22. Found: C, 71.61; H, 7.24.

The formation of **4c** was detected by GLC analysis but it could not be isolated in pure form.

Preparation of 2,2′-Dinitro-4,4′-di-*tert*-butylbiphenyl (7d). To a solution of 5.02 g (20 mmol) in 100 mL of Ac_2O was gradually added a mixture of 5 g of fuming HNO_3 and 5 g of concentrated H_2SO_4. After the reaction mixture was stirred for 1 h, it was treated and worked up as described above to afford 6.6 g (96.7%) of **7d**: pale yellow prisms (EtOH); mp 180–182 °C; IR (KBr) 2950, 1500, 1330, and 830 cm^{-1}; NMR (CCl_4) δ 1.40 [18 H, s, $C(CH_3)_3$] and 7.00–8.10 (6 H, m, aromatic protons). Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.39; H, 6.79; N, 7.86. Found: C, 67.35; H, 6.81; N, 7.77.

Preparation of 2,2′-Diamino-4,4′-di-*tert*-butylbiphenyl (7e). To a solution of 3.41 g (10 mmol) of **7d** and 20 mL of concentrated HCl in 50 mL of EtOH was added 4.74 g of Sn powder. The reaction mixture was treated and worked up as described above to give 2.53 g (90%) of **7e**: colorless prisms (EtOH); mp 195–197 °C; IR (KBr) 3440, 3340, 2950, 1610, 1410, 1300, and 805 cm^{-1}; NMR (CCl_4) δ 1.30 [18 H, s, $C(CH_3)_3$], 3.55 (4 H, s, NH_2), and 6.73–7.20 (6 H, s, aromatic protons). Anal. Calcd for $C_{20}H_{28}N_2$: C, 81.03; H, 9.52; N, 9.45. Found: C, 80.75; H, 9.58; N, 9.34.

Preparation of 4-*tert*-Butyl-2-iodotoluene (10a). The iodonation of 4-*tert*-butyltoluene (**9a**)[15] was carried out according to the reported method[14] to afford **10a** in 94.3% yield. **10a**: mp 139–142 °C (3 mm); colorless liquid; IR (NaCl) 3030, 2960, 1485, 1460, 1375, 1260, 1040, and 820 cm^{-1}; NMR (CCl_4) δ 1.26 [9 H, s, $C(CH_3)_3$], 2.34 (3 H, s, CH_3), and 7.06–7.77 (3 H, m, aromatic protons). Anal. Calcd for $C_{11}H_{15}I$: C, 48.19; H, 5.52. Found: C, 48.36; H, 5.54.

Preparation of 3-Iodo-5-*tert*-butyl-*o*-xylene (10b). Similarly **10b** was obtained in 93% yield from 4-*tert*-butyl-*o*-xylene (**9b**)[15] by the same iodonation. **10b**: colorless liquid; bp 107–108 °C (3 mm). Anal. Calcd for $C_{12}H_{17}I$: C, 50.01; H, 5.95. Found: C, 49.93; H, 5.93.

Preparation of 2-Iodo-5-*tert*-butyl-*m*-xylene (10c). Similar iodonation of 5-*tert*-butyl-*m*-xylene (**9c**)[15] afforded **10c** in 93% yield as colorless prisms (EtOH): mp 55–56 °C (lit.[19] mp 59–60 °C).

Preparation of 2,2′-Dimethyl-5,5′-di-*tert*-butylbiphenyl (11a). A mixture of 20 g (73 mmol) of **10a** and 20 g of Cu powder (100 mesh) was heated at 300 °C with stirring for 3 h. After the reaction mixture was cooled to room temperature, it was dissolved in benzene. Unreacted Cu powder and insoluble materials were filtered off, and the benzene solution was evaporated in vacuo and distilled under reduced pressure to afford 7.3 g (68%) of **11a**: colorless liquid; bp 132–134 °C (3 mm); IR (NaCl) 2950, 2860, 1490, 1360, 1260, and 820 cm^{-1}; NMR (CCl_4) δ 1.30 [18 H, s, $C(CH_3)_3$], 2.00 (6H, s, CH_3), and 7.00–7.12 (6H, m, aromatic protons). Anal. Calcd for $C_{22}H_{30}$: C, 89.73; H, 10.27. Found: C, 89.53; H, 10.11.

Preparation of 2,2′,3,3′-Tetramethyl-5,5′-di-*tert*-butylbiphenyl (11b). Similarly 20 g of **10b** was treated and worked up as described above to afford 6.2 g (56%) of **11b**: colorless prisms (EtOH); mp 106–107 °C; IR (KBr) 2950, 2850, 1470, 1450, 1350, 1275, and 860 cm^{-1}; NMR (CCl_4) δ 1.30 [18 H, s, $C(CH_3)_3$], 1.86 (6 H, s, CH_3), 2.29 (6 H, s, CH_3), 6.84–7.04 (4 H, m, aromatic protons). Anal. Calcd for $C_{24}H_{34}$: C, 89.73; H, 10.63. Found: C, 88.94; H, 10.59.

Preparation of 2,2′,6,6′-Tetramethyl-4,4′-di-*tert*-butylbiphenyl (11c). Similarly 20 g of **10c** was treated and worked up as described above to afford 3.0 g (27%) of **11c**: colorless prisms (EtOH); mp 121–122 °C; IR (KBr) 2950, 1470, 1360, 1230, 1010, and 870 cm^{-1}; NMR (CCl_4) δ 1.32 [18 H, s, $C(CH_3)_3$], 1.88 (12 H, s, CH_3), and 6.99 (4 H, s, aromatic protons). Anal. Calcd for $C_{24}H_{34}$: C, 89.37; H, 10.63. Found: C, 88.87; H, 10.66.

Preparation of 2-Methylbiphenyl (12). To a solution of 2.65 g (10 mmol) of **4a** in 60 mL of benzene was added $AlCl_3$–CH_3NO_2 catalyst (264 mg/0.5 mL) at 50 °C. After the reaction mixture was stirred for 4 h and quenched with water, the organic layer was extracted with ether. The ether solution was dried over Na_2SO_4 and evaporated in vacuo to leave the residue, which was distilled under pressure to afford 1.34 g (80%) of **12** and 1.34 g (75%) of **13**. **12**: colorless liquid; bp 120–123 °C (18 mm) [lit.[19] bp 255 °C (760 mm)].

Preparation of 2-Bromo-4-*tert*-butylbiphenyl (14). (a) The $AlCl_3$–CH_3NO_2 Catalyzed Trans-*tert*-butylation of 4b. To a solution of 3.30 g (10 mmol) of **4b** in 60 mL of benzene was added $AlCl_3$–CH_3NO_2 catalyst (2.64 g/5 mL) at 50 °C. After the reaction mixture was stirred for 6 h, it was treated and worked up as described above to give 1.0 g (75%) of **13** and 23.8 g (87%) of **14**: colorless liquid; bp 140–143 °C (3 mm); IR (NaCl) 2960, 1480, 1380, 760, and 700 cm^{-1}; NMR (CCl_4) δ 1.32 [9 H, s, $(CH_3)_3$], 7.13–7.55 (8 H, m, aromatic protons). Anal. Calcd for $C_{16}H_{17}Br$: C, 66.44; H, 5.93. Found: C, 66.23; H, 5.79.

(b) From 22. When diazonium salt which was prepared from **22** by usual manner was treated with CuCl, **4b** was also obtained.

Preparation of 2-Bromobiphenyl (15). (a) From 4b. Similarly a solution of 3.30 g (10 mmol) of **4b** in 60 mL was treated with 132 mg (1 mmol) of $AlCl_3$ and worked up as described above to afford 1.9 g (82%) of **15**: colorless liquid; bp 90–91 °C (3 mm) [lit.[21] bp 298 °C (760 mmHg)].

(b) From 14. Similarly 2.74 g (10 mmol) of **14** was treated and worked up as described above to give 2.0 g (86%) of **15**.

Preparation of 2-Iodo-4-*tert*-butylbiphenyl (16). (a) From 4d. Similarly 3.92 g (10 mL) of **4d** was treated with $AlCl_3$–CH_3NO_2 catalyst (2.64 g/5 mL) and worked up as described above [bp 165–167 °C (3 mmHg)] to give 2.0 g (60%) of **16** together with formation of iodobenzene (**17**) and **1** as well as **13**. The relative yields are shown in Table I. **16**: colorless liquid; IR (NaCl) 3080, 3040, 2960, 1610, 1480, 1260, 840, 765, and 700 cm^{-1}; NMR (CCl_4) δ 1.32 [9 H, s, $C(CH_3)_3$], 7.13–7.85 (8 H, m, aromatic protons).

(19) N. Campbell and M. Wang, *J. Chem. Soc.*, 2186 (1949).
(20) C. S. Marvel, E. Ginsberg, and M. B. Meuller, *J. Am. Chem. Soc.*, **61**, 77 (1939).
(21) W. E. Bachmann and H. T. Clarke, *J. Am. Chem. Soc.*, **49**, 2094 (1927).

Anal. Calcd for $C_{16}H_{17}I$: C, 57.16; H, 5.10. Found: C, 57.37; H, 5.14.

(b) From 22. Also **16** was obtained from **22** via its diazonium salt by the usual manner.

The $AlCl_3$ Catalyzed Trans-*tert*-butylation of 4d. **4d** was treated with $AlCl_3$ catalyst and worked up as described above to give only a small amount of 1-iodobiphenyl (**18**) with formation of a large amount of **1**, **13**, and **17**. The relative yields are shown in Table I.

Preparation of Tetra-*tert*-butyl-*o*-quaterphenyl (19). A mixture of 10 g (26.5 mmol) of **4d** and 10 g of Cu powder was heated at 300 °C for 4 h, and it was treated and worked up as described above to afford 4.0 g (60.3%) of **19**: colorless prisms (EtOH); mp 254–255 °C; IR (KBr) 2950, 1475, and 830 cm^{-1}; NMR (CCl_4) δ 1.08 [18 H, s, $C(CH_3)_3$], 1.28 [18 H, s, $C(CH_3)_3$], 6.85–7.25 (14 H, m, aromatic protons). Anal. Calcd for $C_{40}H_{50}$: C, 90.85; H, 9.15. Found: C, 90.93; H, 9.52.

Preparation of *o*-Quaterphenyl (20). To a solution of 500 mg (1 mmol) of **19** in 10 mL of benzene was added 26.4 mg (0.2 mmol) of $AlCl_3$ at 50 °C. The reaction mixture was stirred for 3 h and treated as described above to give 220 mg (80%) of **20**: colorless crystalline powder (EtOH–benzene); mp 116–118 °C (lit.[21] mp 118–119 °C).

Preparation of 2-Nitro-4-*tert*-butylbiphenyl (21). (a) From 4a. To a solution of 5.42 g (20 mmol) of **4e** in 120 mL of benzene was added 5.32 g (40 mmol) of $AlCl_3$. After the reaction mixture was stirred for 4 h, it was treated and worked up to afford 3.36 g (70%) of **21**: pale yellow prisms (hexane); mp 93–94 °C; IR (KBr) 3060, 2960, 1520, 1360, 830, 775, and 700 cm^{-1}; NMR (CCl_4) δ 1.38 [9 H, s, $C(CH_3)_3$] and 7.23–7.70 (8 H, m, aromatic protons). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.03; H, 6.77; N, 5.47.

(b) From 25 and 17. After a mixture of 5.16 g (20 mmol) of **25**, 8.16 g (40 mmol) of **17**, and 15 g of Cu powder was refluxed (at 250 °C) for 5 h, it was treated and worked up as described above to give 1.0 g (21%) of **21**: mp 93–94 °C.

Preparation of 2-Amino-4-*tert*-butylbiphenyl (22). (a) From 4f. To a solution of 266 mg (1 mmol) of **4f** in 6 mL of benzene was added 264 mg (2 mmol) of $AlCl_3$. The reaction mixture was treated and worked up as described above to give 165 mg (80%) of **22**: colorless prisms (hexane); mp 110–112 °C; IR (KBr) 3400, 3300, 3040, 2960, 1610, 1410, 1300, 800, 765, and 700 cm^{-1}; NMR (CCl_4) δ 1.30 (9 H, s, *t*-Bu), 3.45 (2 H, s, NH_2), and 6.60–7.30 (8 H, m, aromatic protons). Anal. Calcd for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22. Found: C, 85.17; H, 8.49; N, 6.54.

(b) From 21. The reduction of **21** with Sn powder and concentrated HCl in ethanol by the manner as described above afforded **22**: mp 112 °C.

Preparation of 2,2′-Dibromo- (26a) and 2,2′-Dichlorobiphenyl (26b). To a solution of 5 mmol of **7a** or **7b** in 23.4 g (300 mmol) of benzene was added 132 mg (1 mmol) of $AlCl_3$ at 50 °C. After the reaction mixture was stirred for 1 h, it was treated and worked up as described above to give 0.80 g (77%) or 1.1 g (74%) of **26a** or **26b**, respectively. **26a**: colorless needles (hexane); mp 57–58 °C (lit.[22] mp 59 °C). **26b**: colorless needles (hexane); mp 79–80 °C (lit.[23] mp 80–81 °C).

Preparation of Polymethylbiphenyls (27). To a solution of 1.4 mmol of **11a** or **11b** in 8 mL of benzene was added $AlCl_3$–CH_3NO_2 catalyst (62 mg/2 mL). After the reaction mixture was stirred for 4 h, it was treated and worked up as described above to afford **27a** or **27b** in 90 or 92.2% yields, respectively. Similarly **27c** was obtained in 80% yield from **11c**; however, 93 mg of $AlCl_3$ was used as a catalyst. **27a**: colorless liquid; mp 130–132 °C (18 mmHg) [lit.[24] 135 °C (135 mmHg)]. **27b**: colorless needles (EtOH); mp 114–115 °C; IR (KBr) 2900, 1440, 995, 780 cm^{-1}; NMR (CCl_4) δ 1.90 (6 H, s, CH_3), 2.30 (6 H, s, CH_3), 6.80–7.04 (6 H, m, aromatic protons). Anal. Calcd for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.04; H, 8.67. **27c**: colorless prisms (EtOH); mp 63–64 °C (lit.[25] 64–65 °C).

Registry No. **1**, 92-52-4; **2**, 1625-91-8; **3**, 70728-88-0; **4a**, 69386-38-5; **4b**, 70728-89-1; **4c**, 70728-90-4; **4d**, 70728-91-5; **4e**, 69386-34-1; **4f**, 70728-92-6; **7a**, 70728-93-7; **7b**, 70728-94-8; **7c**, 70728-95-9; **7d**, 70728-96-0; **7e**, 70728-97-1; **9a**, 98-51-1; **9b**, 7397-06-0; **9c**, 98-19-1; **10a**, 70728-98-2; **10b**, 5122-21-4; **10c**, 5122-20-3; **11a**, 70728-99-3; **11b**, 70729-00-9; **11c**, 35132-98-0; **12**, 643-58-3; **13**, 98-06-6; **14**, 70729-01-0; **15**, 2052-07-5; **16**, 70729-02-1; **17**, 591-50-4; **18**, 2113-51-1; **19**, 70729-03-2; **20**, 641-96-3; **21**, 69386-37-4; **22**, 70729-04-3; **25**, 70729-05-4; **26a**, 13029-09-9; **26b**, 13029-08-8; **27a**, 605-39-0; **27b**, 7495-46-7; **27c**, 4036-43-5; chloromethyl methyl ether, 107-30-2; 2,6-di-*tert*-butyl-*p*-cresol, 128-37-0.

(22) J. J. Dobbie, *J. Chem. Soc.*, **99**, 1619 (1911).
(23) F. H. Case, *J. Am. Chem. Soc.*, **61**, 3487 (1939).
(24) E. A. Johnson, *J. Chem. Soc.*, 4155 (1957).
(25) K. Ishizu, H. Hasegawa, H. Chibaki, H. Nishiguchi, and Y. Deguchi, *Kogyo Kagaku Zasshi*, **68**, 210 (1965).

An Approach to the Total Synthesis of Chlorothricolide: The Synthesis of the Top Half

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An efficient synthesis of the top half of chlorothricolide (I) is described. The top half **1** was prepared in 14 steps from tartaric acid. The utility of **1** as a potential intermediate in the total synthesis of chlorothricolide was demonstrated by connection to bottom half models. The selective deprotection of the α-hydroxytetronic acid dimethyl ether, necessary for closure of the macrolactone, is also described.

Chlorothricin (I), a chlorine containing macrolide antibiotic active against Gram positive bacteria, was isolated from a strain of *Streptomyces antibioticus* in 1969.[1] In contrast to a majority of macrolide antibiotics which generally function by inhibiting protein biosynthesis, chlorothricin was shown to act as an antagonist to CoASAc, by inhibiting the reaction catalyzed by pyruvate carboxylase.[2] The aglycone portion, chlorothricolide methyl ester (II), was found to retain part of the activity of the intact antibiotic, while the other methanolysis product, α-methyl-2-deoxy-3-*O*-(5′-chloro-2′-methoxy-6′-methylbenzoyl)-D-rhamnoside, showed a lack of activity.[3]

(1) (a) W. Keller-Schierlein, R. Muntwyler, W. Pache, and H. Zähner, *Helv. Chim. Acta*, **52**, 127 (1969); (b) R. Muntwyler, J. Widmer, and W. Keller-Schierlein, *ibid.*, **53**, 1544 (1970); (c) R. Muntwyler and W. Keller-Schierlein, *ibid.*, **55**, 2071 (1972); (d) M. Brufani, S. Cerrini, W. Fedeli, F. Mazza, and R. Muntwyler, *ibid.*, **55**, 2094 (1972).

(2) (a) P. W. Schindler and H. Zaehner, *Arch. Microbiol.*, **82**, 66 (1972); (b) W. Pache and D. Chapman, *Biochem. Biophys. Acta*, **255**, 348 (1972); (c) P. W. Schindler and H. Zaehner, *Eur. J. Biochem.*, **39** 591 (1973); (d) P. W. Schindler, *ibid.*, **51**, 579 (1975).

(3) P. W. Schindler and M. C. Scrutton, *Eur. J. Biochem.*, **55**, 543 (1975).

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