Synthesis of 2,6-Bis(trifluoromethyl)phenol and Its Elaboration Into "Metabolism-Resistant" Analogs of Tebufelone

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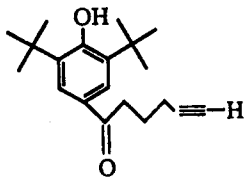
Received December 10, 1992

The primary biliary metabolic pathways in rats for the antiinflammatory drug tebufelone (1) involve hydroxylation of a *tert*-butyl group[2] and modification (including hydroxylation) at the propargylic position. With the goal of producing a longer acting and more potent antiinflammatory derivative, we became interested in synthesizing analogs of 1 which cannot participate in these in vivo



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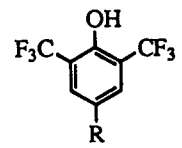


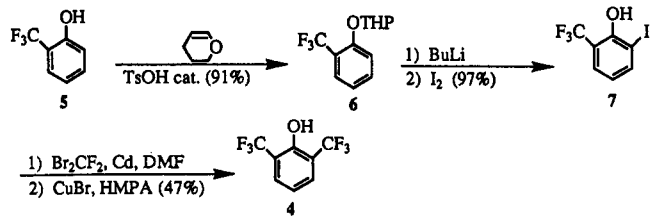
2: R= - C(=O)(CH$_2$)$_3$C≡CH

3: R= - C(=O)(CH$_2$)$_2$C(CH$_3$)$_2$C≡CH

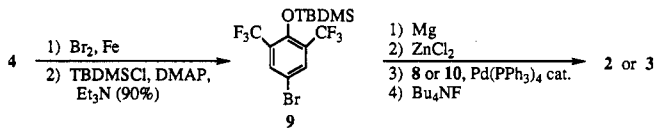
transformations. This Note describes the synthesis of two "metabolism resistant" derivatives of 1, the first of which (2) has the *tert*-butyl groups replaced by trifluoromethyl groups, while the second (3) possesses this modification together with a *gem*-dimethyl blocked propargylic position.

The key intermediate from which we envisioned synthesizing both 2 and 3 was 2,6-bis(trifluoromethyl)phenol (4), a compound whose preparation had not been previously reported.[3] As outlined in Scheme I, 4 was readily prepared from the commercially available 2-(trifluoromethyl)phenol (5) in a three-step sequence. Thus, the phenolic moiety in 5 was first protected as the corresponding tetrahydropyranyl ether 6. Ortho-directed lithiation[4] of 6 using BuLi, followed by iodination, then yielded the deprotected aryl iodide 7 in a single step. Finally, transformation of 7 into 2,6-bis(trifluoromethyl)phenol (4) was accomplished in good yield using "F_3CCu", prepared via Burton's methodology.[5] To illustrate this last step, a mixture of Cd metal in DMF was treated with Br_2CF_2 and the (trifluoromethyl)-cadmium reagent obtained was transmetalated with cuprous bromide to yield "(trifluoromethyl)copper". The coupling reaction of "F_3CCu" with 7 was then carried out in the same reaction vessel in the presence of HMPA at

Scheme I



Scheme II



60 °C, and the desired 2,6-bis(trifluoromethyl)phenol (4) was obtained cleanly in 47% yield.[6] It is important to utilize equal volumes of DMF and HMPA for this coupling reaction, in addition to carefully controlling the reaction temperature below ca. 70 °C, since decomposition of the (trifluoromethyl)copper reagent into a (perfluoroethyl)-copper species can occur and leads to the corresponding F_5C_2-alkylated phenol. Small amounts of this impurity are, however, readily separated from the desired trifluoromethylated compound by either distillation or flash chromatography.

The pathway outlined in Scheme II was utilized for the transformation of 4 into the tebufelone derivatives 2 and 3. Unfortunately, direct Friedel–Crafts acylation of 4 using 5-hexynoyl chloride (8)[8] with a variety of Lewis acids did not take place at low temperature, and, upon warming, cyclization of the acid chloride to 3-chloro-2-cyclohexenone occurred.[2] As an alternative, 4 was brominated selectively in the 4-position (Br_2/Fe) and then protected as its phenolic TBDMS ether 9. Generation of the aryl Grignard reagent of 4 proceeded readily upon immersing the reaction flask in an ultrasonic bath at room temperature. Interestingly, formation of the Grignard reagent from the corresponding TMS-protected phenol was not straightforward, producing considerable 2,6-bis(trifluoromethyl)-4-(trimethylsilyl)-phenol upon hydrolysis. Transmetalation of the Grignard reagent derived from 9 to the respective arylzinc halide using $ZnCl_2$, followed by Pd-catalyzed acylation[9] at room temperature with 8 provided the TBDMS ether of 2 in 42% isolated yield. Deprotection using TBAF in THF then afforded the desired target compound 2 in high yield (88%).

Essentially the same route was utilized for the preparation of the *gem*-dimethylated derivative 3 from 9, with the acylation and desilylation steps proceeding in slightly lower isolated yields (32 and 78%, respectively). The requisite acid chloride, 4,4-dimethyl-5-hexynoyl chloride (10), was prepared in seven steps from 2-methyl-3-butyn-2-ol as illustrated in Scheme III.

The methodology described herein for the synthesis of 2,6-bis(trifluoromethyl)phenol (4) allows for its facile

(1) Present address: Exxon Chemical Co., Basic Chemicals Technology, P.O. Box 4900, Baytown, TX 77522-4900.

(2) Miller, J. A.; Matthews, R. S. *J. Org. Chem.* **1992**, *57*, 2514.

(3) Although the title compound 4 has been claimed previously as a copolymer component with formaldehyde [Eglin, S. B.; Eisenbraun, E. W. U.S. Patent 3658758 (1972)], its synthesis as a pure entity has not been previously described.

(4) Stern, R.; English, J., Jr.; Cassidy, H. G. *J. Am. Chem. Soc.* **1957**, *79*, 5797. Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1.

(5) Burton, D. J.; Wiemers, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 5014. Wiemers, D. M.; Burton, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 832.

(6) Attempts to convert 7, as well as its phenoxy-protected derivatives, into 4 via Pd-catalyzed trifluoromethylation[7] with CF_3ZnI were unsuccessful.

(7) Kitazume, T.; Ishikawa, N. *Chem. Lett.* **1982**, 137. Ishikawa, N.; Kitazume, T. U.S. Patent 4,484,993 (1984).

(8) Earl, R. A.; Vollhardt, K. P. C. *J. Org. Chem.* **1984**, *49*, 4786.

(9) Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181. Grey, R. A. *J. Org. Chem.* **1984**, *49*, 2288.

(10) Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier: Amsterdam, 1981; p 219.

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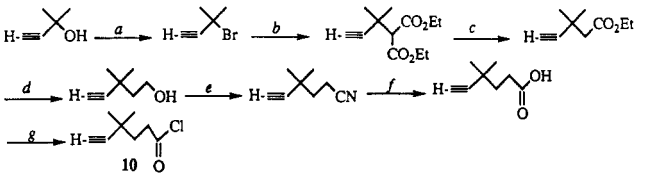
Scheme III[a]



[a] (a) PBr_3, 0 °C → 25 °C (56%);[10] (b) Na, $CH_2(CO_2Et)_2$, EtOH, 50 °C (39%);[11] (c) NaCl, DMSO, H_2O, 175 °C (65%);[12] (d) $LiAlH_4$, ether, 0 °C, then H_3O^+ (83%); (e) MsCl, Et_3N, 0 °C (96%), then NaCN, DMSO, 60 °C (81%); (f) 40% KOH, diethylene glycol, 90 °C, then H_3O^+ (90%); (g) $(COCl)_2$, CH_2Cl_2, 25 °C (80%).

preparation from a commercially available starting material. This ready access to **4** now makes available a new class of sterically hindered phenols which possess chemical properties quite different from BHT and other important 2,6-di-*tert*-butylphenolic derivatives.

Experimental Section

General Procedures. 5-Hexynoyl chloride was prepared from 5-hexyn-1-ol (Farchan Laboratories) as described in the literature.[8] 2-(Trifluoromethyl)phenol and dibromodifluoromethane were purchased from Aldrich Chemical Co. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Dimethylformamide (DMF) was distilled from calcium hydride prior to use. Hexamethylphosphoric triamide (HMPA) was treated with a small amount of triphenylmethane and then to it added BuLi until the red color of lithium triphenylmethide persisted. The dry HMPA was then distilled under reduced pressure and stored under nitrogen. Zinc chloride was flame-dried in vacuo. Tetrakis(triphenylphosphine)palladium was prepared according to the procedure described in the literature.[13] All other materials were obtained from commercial sources and were used without further purification. Distilled products were ≥97% pure by GLC analysis.

2-Iodo-6-(trifluoromethyl)phenol (7). To a solution of 2-(trifluoromethyl)phenol (**5**; 12.2 g, 75.0 mmol) and dihydropyran (27.3 mL, 300 mmol) in diethyl ether (250 mL) was added a few crystals of *p*-TsOH·H_2O. The mixture was refluxed for 18 h, cooled to room temperature, and then poured into saturated $NaHCO_3$. The aqueous layer was extracted with ether, and the combined extract was washed with saturated NaCl and then dried ($MgSO_4$). Flash chromatography through silica gel (5% ethyl acetate/hexane containing 0.5% triethylamine; R_f = 0.29) afforded 16.8 g (91%) of **6**. This entire product was dissolved in THF (200 mL) and treated at −78 °C with BuLi (2.80 M, 29.4 mL, 82.0 mmol). After stirring at −78 °C for 30 min, the reaction mixture was treated with a solution of iodine (25.1 g, 99.0 mmol) in THF (75 mL), stirred for 10 min, and then allowed to warm to room temperature. The mixture was poured into 20% Na_2SO_3 and vigorously shaken. The aqueous portion was extracted with ether, and the combined extract was washed with saturated NaCl and then dried ($MgSO_4$). Concentration and short-path distillation gave 19.1 g (97%, based on **6**) of **7**: bp 85 °C (0.25 Torr); IR (film) 3480 (m), 1600 (m), 1445 (s), 1320 (s), 1140 (s), 785 (m), 740 (m), 675 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.85 (s, 1 H), 6.80 (t, 1 H), 7.60 (d, 1 H), 7.85 (d, 1 H).

2,6-Bis(trifluoromethyl)phenol (4). A mixture of Cd powder (21.0 g, 187 mmol) in DMF (83 mL) was treated at 0 °C with Br_2CF_2 (11.5 mL, 125 mmol) at a rate which maintained the temperature below 40 °C. The mixture was stirred at room temperature for an additional 30 min and was then diluted with HMPA (83 mL). The reaction mixture was cooled to 0 °C and to it added CuBr (8.96 g, 62.5 mmol), causing an exotherm to ca. 18 °C. The mixture was then warmed to room temperature and stirred for 10 min. The resultant mixture of "F_3CCu" was treated with **4** (6.00 g, 20.8 mmol) and then heated at 60 °C for 90 min. The reaction mixture was cooled to room temperature and poured into a mixture of 3 N HCl and ether (200 mL each), and then the solids were removed from the mixture by filtration. The aqueous phase was extracted with ether, and the combined extract was washed with saturated NaCl and then dried ($MgSO_4$). The volatiles were distilled from the crude product, which was then isolated by distillation to furnish 2.37 g (47%) of **4**: bp 70 °C (30 Torr); IR (CCl_4) 3615 (s), 1605 (m), 1465 (m), 1330 (m), 1290 (s), 1255 (m), 1140 (s), 1060 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.85 (broad s, 1 H), 6.90 (t, 1 H), 7.50 (d, 2 H).

TBDMS Ether of 2,6-Bis(trifluoromethyl)-4-bromophenol (9). To a mixture of **4** (2.87 g, 12.5 mmol) and Fe powder (0.88 g, 15.6 mmol) in CCl_4 (25 mL) was added at room temperature Br_2 (0.98 mL, 18.8 mmol). The reaction was heated at 60 °C for 2 h, cooled to room temperature, and poured into a mixture of saturated $NaHCO_3$ and ether (75 mL of each). The aqueous phase was extracted with ether, and the combined extract was washed with saturated NaCl, dried ($MgSO_4$), and concentrated. The crude 2,6-bis(trifluoromethyl)-4-bromophenol thus obtained was dissolved in THF (60 mL) and to it sequentially added *tert*-butyldimethylsilyl chloride (2.37 g, 15.6 mmol), 4-(dimethylamino)pyridine (0.38 g, 3.12 mmol), and triethylamine (5.10 mL, 37.2 mmol). The solution was stirred at room temperature for 2 h, and then was poured into a mixture of water and petroleum ether (75 mL of each). The aqueous phase was extracted with petroleum ether, and the combined extract was washed with saturated NaCl and then dried ($MgSO_4$). The crude, concentrated solution was passed through a short column of silica gel, eluting with 2% ethyl acetate/hexane directly into a round-bottomed flask. Removal of the solvents followed by distillation using a Kugelrohr apparatus (120 °C, 0.5 Torr) provided 4.75 g (90%) of **9**: IR (film) 2930 (m), 2860 (m), 1595 (m), 1460 (s), 1345 (s), 1290 (s), 1255 (s), 1180 (s), 1140 (s), 825 (s), 810 (s), 785 (m), 715 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.15 (s, 6 H), 0.85 (s, 9 H), 7.80 (s, 2 H).

1-[3,5-Bis(trifluoromethyl)-4-hydroxyphenyl]-5-hexyn-1-one (2). A mixture of Mg turnings (0.274 g, 11.3 mmol) in THF (12 mL) was treated with 3–4 drops of 1,2-dibromomethane and heated at 45 °C for 10 min. To the reaction mixture was then added **9** (2.38 g, 5.61 mmol), and the flask was placed in an ultrasonic cleaning bath and irradiated at room temperature for 1 h. The solution of Grignard reagent thus produced was added at 0 °C to a solution of $ZnCl_2$ (1.03 g, 7.45 mmol) in THF (15 mL) and the resultant mixture stirred at 25 °C for 15 min. The reaction mixture containing the arylzinc derivative of **9** was treated sequentially with tetrakis(triphenylphosphine)palladium (0.31 g, 5 mol%) and 5-hexynoyl chloride (0.748 g, 5.75 mmol) and then stirred for 1 h at room temperature. The reaction was poured into a mixture of saturated NH_4Cl and petroleum ether (75 mL of each), and the layers were separated. The aqueous portion was extracted with petroleum ether, and the combined organic phases were washed with saturated NaCl and then dried ($MgSO_4$). Flash chromatography through silica gel (3% ethyl acetate/hexane, R_f = 0.30) afforded 1.04 g (42%) of the TBDMS ether of **2** as an oil which solidified in the refrigerator overnight. This entire product was then dissolved in THF (20 mL) and treated at room temperature with $Bu_4NF·3H_2O$ (1.60 g, 5.00 mmol). After stirring at room temperature for 1 h, the reaction mixture was poured into a mixture of 0.1 N HCl and ether (50 mL of each). The layers were separated and the aqueous phase was extracted with ether. The combined extract was washed with saturated NaCl and then dried ($MgSO_4$). Flash chromatography through silica gel (20% ether/hexane containing 1% formic acid, R_f = 0.26) gave 0.674 g (88% yield based on the starting TBDMS ether) of **2**. Recrystallization of this product was achieved using hexane–benzene: mp 64.5–65.5 °C; IR ($CHCl_3$) 3600 (m), 3305 (m), 2110 (w), 1685 (m), 1610 (s), 1305 (s), 1270 (s), 1140 (s), 645 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.9–2.6 (m, 5 H), 3.20 (t, 2 H), 6.90 (broad s, 1 H), 8.45 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 17.617, 22.524,

(11) The corresponding chloride, 3-chloro-3-methyl-1-butyne, has been reported to undergo a similar alkylation with sodium diethylmalonate: Behrens, O. K.; Corse, J.; Huff, D. E.; Jones, R. G.; Soper, Q. F.; Whitehead, C. W. *J. Biol. Chem.* **1948**, *175*, 771. Cope, A. C.; Holmes, H. L.; House, H. O. *Org. React.* **1957**, *9*, 107.

(12) The methodology used for this transformation was developed by Krapcho, et al.: Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, 957. Krapcho, A. P.; Jahngen, E. G. E., Jr.; Lovey, A. J. *Tetrahedron Lett.* **1974**, 1091. Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138.

(13) Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.

36.475, 69.390, 83.303, 119.896 (quartet, J = 31.3 Hz), 122.864 (quartet, J = 273.0 Hz), 128.129, 130.742, 156.949, 196.676.

4,4-Dimethyl-5-hexynoyl Chloride (10). To a solution of 4,4-dimethyl-5-hexynoic acid (9.66 g, 69.0 mmol) in CH_2Cl_2 (140 mL) was added at room temperature oxalyl chloride (9.00 mL, 103 mmol). The reaction solution was stirred at 25 °C for 4 h and then was heated to 40 °C and concentrated under reduced pressure (25 Torr). Distillation of the crude product provided 8.74 g (80%) of **10**: bp 46 °C (1.7 Torr): IR (film) 3300 (s), 2960 (s), 2100 (w), 1795 (s), 960 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 6 H), 1.7–2.0 (m, 2 H), 2.15 (s, 1 H), 3.0–3.3 (m, 2 H).

1-[3,5-Bis(trifluoromethyl)-4-hydroxyphenyl]-4,4-dimethyl-5-hexyn-1-one (3). In a procedure similar to that described above for the preparation of **2**, the arylzinc derivative was prepared from **9** (2.38 g, 5.61 mmol) and treated sequentially with tetrakis(triphenylphosphine)palladium (0.31 g, 5 mol%) and 4,4-dimethyl-5-hexynoyl chloride (0.911 g, 5.75 mmol). The reaction was stirred at room temperature for 1 h and then worked up as described above. Flash chromatography through silica gel (2% ethyl acetate/hexane, R_f = 0.34) furnished 0.846 g (32%) of the TBDMS ether of **3**. This entire product was then dissolved in THF (20 mL) and treated at room temperature with $Bu_4NF{\cdot}3H_2O$ (1.22 g, 3.80 mmol). After stirring for 1 h, the reaction solution was worked up in a manner similar to that described above in the preparation of **2**. Flash chromatography through silica gel (15% ether/hexane containing 1% formic acid, R_f = 0.26) delivered 0.502 g (78% yield based on the starting TBDMS ether) of **3** as a white solid: mp 83–84 °C; IR ($CHCl_3$) 3590 (m), 3300 (m), 2100 (w), 1685 (m), 1610 (m), 1270 (s), 1150 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 6 H), 1.75–1.95 (m, 2 H), 2.19 (s, 1 H), 3.05–3.25 (m, 2 H), 6.80 (broad s, 1 H), 8.39 (s, 2 H); ^{13}C NMR ($CDCl_3$, 10% CD_3OD) δ 28.973, 30.816, 34.904, 36.976, 69.053, 90.533, 119.155 (quartet, J = 31.3 Hz), 122.898 (quartet, J = 273.4 Hz), 129.290, 131.076, 155.493, 196.957.

Supplementary Material Available: ^{13}C and/or ^1H NMR spectra of all compounds described in the Experimental Section (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.