Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 19, pp. 2279-2280, 1996

0960-894X/96 $15.00 + 0.00

PII: S0960-894X(96)00413-1

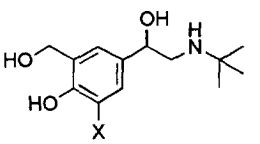
A CONCISE SYNTHESIS OF 1-(3-HYDROXYMETHYL-4,5-DIHYDROXY-PHENYL)-2-*tert*-BUTYLAMINO-ETHANOL (5-HYDROXYALBUTEROL)

Nathan K. Yee,* Larry J. Nummy, and Gregory P. Roth

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals Inc.
900 Ridgebury Rd./P.O. Box 368, Ridgefield, Connecticut 06877-0368 USA

Abstract: An efficient synthesis of 5-hydroxyalbuterol is described starting from 2,3-dihydroxybenzoic acid. The key step utilizes the Stille cross-coupling reaction to install the side-chain functionality.

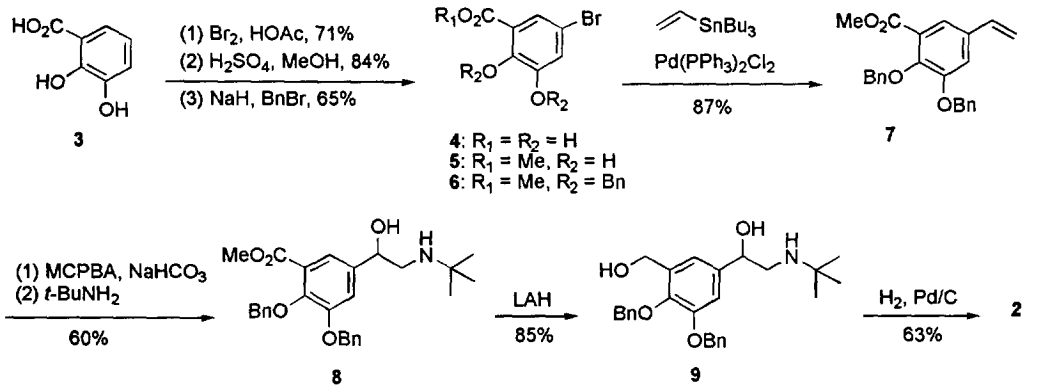
Albuterol (**1**) is a potent β-adrenoceptor stimulant effective as a bronchial smooth muscle relaxant.[1] The structurally related arylethanolamine-type drugs such as terbutaline, isoproterenol, and sotalol are well known in the treatment of asthma, glaucoma, and cardiovascular disease.[1] In our research program, the previously unknown 5-hydroxyalbuterol (**2**), 1-(3-hydroxymethyl-4,5-dihydroxyphenyl)-2-*tert*-butylamino-ethanol, was isolated as a degradation product derived from prolonged storage under ambient atmosphere and was identified by spectroscopic methods. In addition, a family of similar hydroxylated aromatic products have also been shown to be metabolites of structurally related drugs, for example, dilevalol.[2] An efficient synthesis of **2** was required in order to confirm its identity and to prepare quantities for toxicological evaluation.



1 X = H, Albuterol
2 X = OH, 5-Hydroxyalbuterol

The synthesis of 5-hydroxyalbuterol (**2**) is illustrated in the following scheme. Commercially available 2,3-dihydroxybenzoic acid provides the required 1,2,3-trisubstituted phenyl moiety. This synthetic strategy takes advantage of the Stille coupling reaction[3] to install the side-chain functionality. Direct bromination (Br_2, HOAc, rt, 20 h)[4] of the acid **3** gave the bromide **4** in 71% yield. The regioselectivity of the bromination is apparent from the ^1H NMR spectrum of **4** that exhibits two doublets attributable to the aromatic protons at δ 7.31 and 7.12 with J = 2.4 Hz . Esterification (H_2SO_4, MeOH, reflux, 16 h, 84%) and dibenzylation (BnBr, NaH, DMF, 0 °C to rt, 18 h, 65%) provided the fully protected bromide **6**.

Following the standard protocol, palladium-catalyzed cross-coupling of bromide **6** and tributylvinyltin proceeded smoothly at 96 °C in toluene using 5 mol % $Pd(PPh_3)_2Cl_2$ as catalyst. This afforded styrene **7** in 87% yield after silica gel column chromatography. Epoxidation of this olefin was carried out using *m*-chloroperoxybenzoic acid in an aqueous $NaHCO_3$-CH_2Cl_2 two-phase system (0 °C to rt, 18 h). The opening of the crude epoxide was achieved by refluxing with excess *t*-butylamine in isopropanol. The desired amino-alcohol **8** was obtained by silica gel column chromatography in 60% overall yield from styrene **7**. Hydride reduction (LAH, THF, 0 °C to rt, 3 h, 85%) of ester **8** followed by catalytic hydrogenolysis (5%Pd/C, MeOH, rt, 6 h) gave 5-hydroxyalbuterol (**2**) in 63% yield after crystallization from isopropanol.



The product was fully characterized by IR, ^1H and ^{13}C NMR, MS, combustion analysis,[5] and its purity was determined to be 99% by HPLC. The spectral characterization of the **2** prepared as described herein is identical to that obtained from the isolated degradation product. Thus, the identity of the degradation product as hydroxyalbuterol (**2**) is unequivocally established.

In summary, albuterol and its derivatives possess unique chemical and physical properties resulting from their reactive and multifunctional nature. This imposes special design challenges for synthesis. We have developed a straightforward route to 5-hydroxyalbuterol (**2**) that makes multigram quantities readily accessible. In addition, the synthetic strategy described above appears to be general and useful in the synthesis of other arylethanolamine-type compounds.

Acknowledgment: We thank Dr. Vittorio Farina for helpful discussions.

References and Notes:

1. (a) Collin, D. T.; Hartley, D.; Jack, D.; Lunts, L. H. C.; Press, J. C.; Ritchie, A. C.; Toon, P. *J. Med. Chem.* **1970**, *13*, 674. (b) Main, B. G.; Tucker, H. in *Medicinal chemistry, 2nd Ed.*; Genellin, C. R.; Roberts, S. M. Eds; Academic Press: London, New York; **1993**, pp. 187-208. (c) Lunts, L. H. C. *ibid.* pp. 210-226.
2. Tulshian, D. B.; Bercovici, A. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2073.
3. (a) Stille, J. K. *Angew. Chem.* **1986**, 508; (b) Mitchell, T. N. *Synthesis* **1992**, 803.
4. Pettit, G. R.; Piatak, D. M. *J. Org. Chem.* **1960**, *25*, 721.
5. IR (cm^{-1}, KBr): 3452, 3104, 2971, 2874, 1598, 1481, 1447, 1295, 1235, 1144, 891, 865; ^1H NMR (270 MHz, DMSO-d_6) δ 6.74 (s, 1H, Ar*H*), 6.68 (d, 1H, J = 1.7 Hz, Ar*H*), 4.46 (s, 2H, CH_2OH), 4.41 (br. t, 1H, J = 6.1 Hz, $CHCH_2$), 2.55-2.65 (m, 2H, CH_2NH), 1.06 (s, 9H, CH_3); ^{13}C NMR (67.9 MHz, DMSO-d_6) δ 144.8, 141.5, 134.5, 128.8, 115.5, 111.7, 72.4, 58.8, 50.8, 50.5, 28.7; CIMS: MH^+ 256; Anal. calcd. for $C_{13}H_{21}NO_4$: C: 61.16; H: 8.29; N: 5.49. Found: C: 60.84; H: 8.15; N: 5.15.

(*Received in USA* 25 *July* 1996; *accepted* 27 *August* 1996)