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Synthesis of a salbutamol dimer†

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Abstract—First synthesis of the diastereomeric mixture of Salbutamol dimer (**2**) is described. The synthesis provides access to multi-gram quantities of **2** for reference supplies and further analytical and toxicology investigations. It also confirmed the proposed structure by comparison to authentic sample.

Salbutamol (**1**), a potent β_2-adrenoceptor agonist, is effective as a bronchial smooth muscle relaxant. Currently it is considered, in its racemic form, as one of the most prescribed bronchodilators for the treatment of bronchial asthma.[1] Since its development in the late 1960's, the continuous effort for the separation and structure determination of related impurities,[2,3] obtained during the synthesis or upon prolonged storage of the drug, is still of interest. Special attention was focused on the mixture of its dimeric 'side-by-side' impurities[2] **2**, usually detected in ca. 0.05–0.1% in salbutamol batches. To the best of our knowledge, there are neither reported synthesis nor unambiguous structure determination of these proposed dimeric structures (Fig. 1).

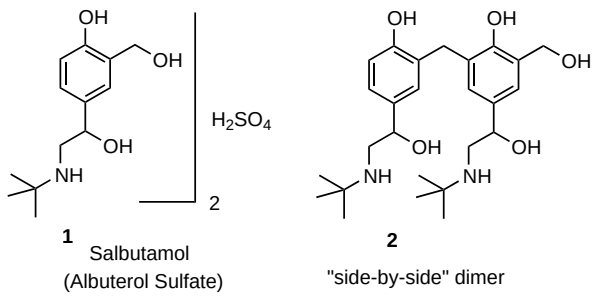
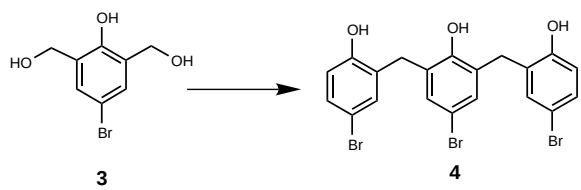


Figure 1.

In order to confirm the structures **2** and also provide an easy access to these compounds for reference supplies, further analytical and toxicology investigations, a synthesis of the diastereomeric mixture was desirable. Herein, we describe the first synthesis of **2**.

Initial efforts focused on the direct preparation of **2** via dimerization of Salbutamol under a variety of acidic conditions (HCl, pTsOH, CSA with different solvents and temperatures).[4,5] Unfortunately, no traces of the desired product could be detected by HPLC upon comparison to authentic sample. The following synthesis of **2** was then developed.

Two approaches were examined for the preparation of the key starting material **6**: (a) Coupling of bromophenol with the commercially available triol **3** under acidic conditions. Unfortunately, double condensation product **4** and triol **3** were the major compounds detected in these attempts (Scheme 1); (b) Baekelite condensation of *p*-bromophenol with formaldehyde provided **5** in 94% yield.[5a] Treatment of **5** with paraformaldehyde and NaOH provided **6** in 38% isolated yield.[5b] Acetate protection of the triol was expected to hold and to increase the solubility of the intermediates throughout the synthesis. Treatment of **6** with acetic anhydride provided **7** in 94% yield.



Scheme 1.

Stille coupling[3,6] of **7** with *tri-n*-butylvinyltin afforded **8** in 50% isolated yield. Direct epoxidation of **8** with MCPBA was first examined and resulted in low yield of the desired bis-epoxide **10**. Alternatively, **10** was prepared upon treatment of **8** with NBS in wet DMSO[7] to

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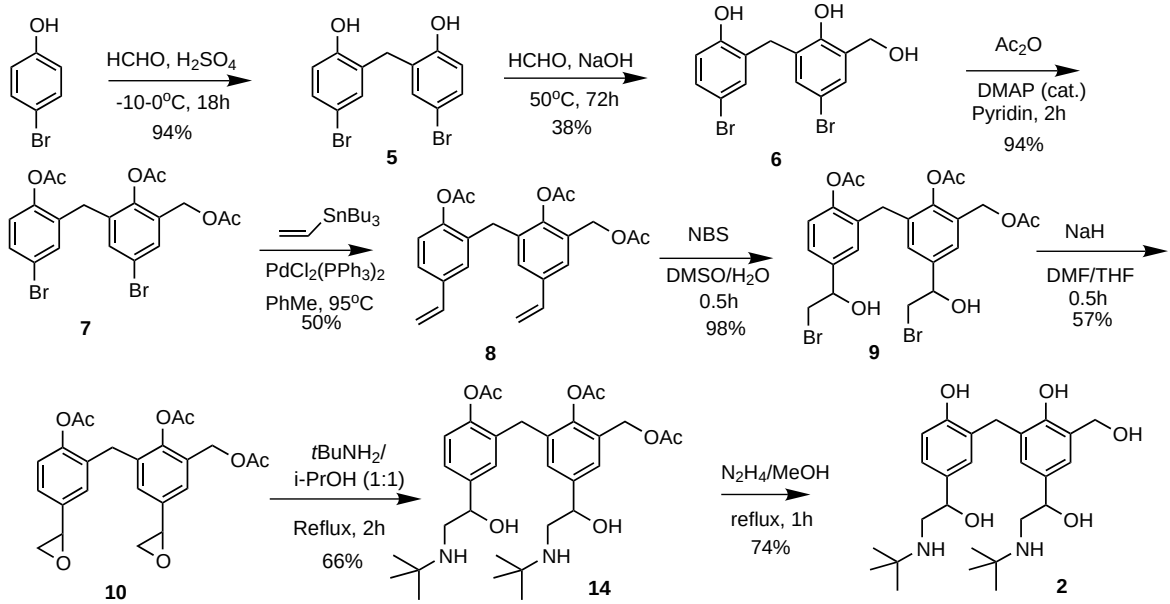
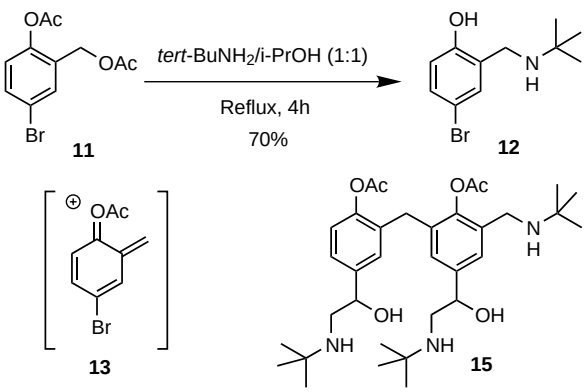


Scheme 2.

give **9** in 98% yield, followed by cyclization with NaH to give **10** in 57% yield (Scheme 2).

A regioselective addition of tBuNH$_2$ to the epoxide was expected.[3,8] However, it should be noted that treatment of **11** with tBuNH$_2$ in isopropanol under reflux for 4 h provided **12** in 70% isolated yield, presumably via intermediate **13** (Scheme 3). Interestingly, treatment of **10** with tBuNH$_2$ in isopropanol (1:1) under reflux for 2 h, provided **14** in 66% isolated yield with no detectable amount of **15** by NMR.



Scheme 3.

Hydrolysis of the acetate groups was examined under a variety of conditions including K_2CO_3, NaOH, Al_2O_3, KCN, Mg/MeOH and $NaBH_4$, in all cases the product could not be isolated in sufficient yield. However, reflux of **14** with hydrazine/MeOH afforded the desired final product (**2**) in 74% isolated yield after purification on C18-preparative column followed by crystallization from EtOAc.[9]

The NMR spectra of **2** was recorded in D_2O and almost complete overlap of chemical shifts of the diastereomers was obtained. Careful comparison with authentic sample was carried out by ^{1}H NMR, MS and HPLC. Complete match was obtained in all these experiments, providing for the first time unambiguous confirmation of the chemical structure of **2**.

Acknowledgements

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9. All new compounds were characterized by ^{1}H, ^{13}C NMR, and MS spectroscopy. Dimer **2**: ^{1}H NMR (500.1325 MHz, D_2O) δ: 1.34 (18H, s), 3.19 (3H, s), 3.86 (2H, s), 4.62 (2H, s), 4.81 (2H, d, $J=6.5$ Hz), 6.74 (1H, d, $J=8.64$ Hz), 7.08 (1H, d, $J=7.7$ Hz), 7.13 (1H, s), 7.26 (1H, s), 7.29 (1H, s); ^{13}C NMR (125.7574 MHz, $CDCl_3$) δ: 27.7, 35.5, 50.4, 60.0, 63.2, 72.3 (×2), 120.7, 127.5, 128.7, 129.9, 130.5, 131.5, 131.7, 131.8, 133.2, 133.4, 159.2, 161.7; HRMS calcd for $(M+H)^+$ $C_{26}H_{41}N_2O_5$: 461.3020, found 461.3015.