

Synthesis of the β_2 Agonist (*R*)-Salmeterol Using a Sequence of Supported Reagents and Scavenging Agents

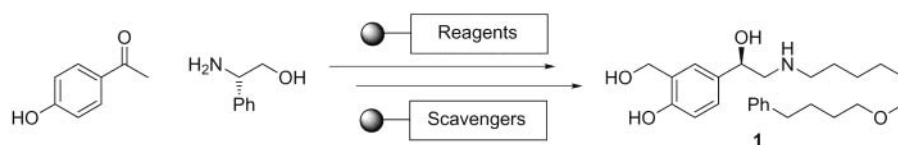
Robert N. Bream,[†] Steven V. Ley,^{*,†} and Panayiotis A. Procopiou[‡]

University Chemical Laboratory, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK, and GlaxoSmithKline Research and Development Ltd. Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, U.K.

svl1000@cam.ac.uk

Received July 8, 2002

ABSTRACT



The enantioselective synthesis of (*R*)-salmeterol has been achieved by using a sequence of supported reagents and sequestering agents. The saligenin core was installed by a regiospecific alkylation and a chiral auxiliary approach was employed to introduce the desired stereochemistry via a diastereoselective reduction.

Much recent attention has been focused on the development of reagents and catalysts bound to solid supports which combine many of the advantages of supported-substrate reactions and traditional solution-phase chemistry.¹ Excess reagent may be used to drive reactions to completion while purification requires only simple filtration and evaporation. In addition, conventional analytical techniques (NMR, TLC, HPLC) are available to monitor formation of the product, which remains in the solution phase.

Recent syntheses of both arrays of drug-like molecules and natural products have clearly demonstrated the advantages of combining sequences of polymer-supported reagents and scavengers to provide complex molecules in a clean and efficient manner.^{2,3} However, the paucity of enantioselective

reactions achieved thus far with supported reagents has precluded their extensive exploitation in synthesis.⁴ We now wish to report the synthesis of a single enantiomer of salmeterol **1**, using a chiral auxiliary approach. Supported reagents have been employed to effect the key steps and purification has been achieved by simple filtration, or by the use of scavenging techniques to remove byproducts.

Salmeterol (Serevent) is a potent and long-acting β_2 adrenoceptor agonist used as a bronchodilator for the prevention of bronchospasm in patients with asthma and chronic obstructive pulmonary disease.⁵ Previous syntheses have employed a yeast⁶ or the CBS-oxazaborolidine reagent⁷

(2) (a) Baxendale, I. R.; Brusotti, G.; Matsuoka, M.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **2002**, 143. (b) Baxendale, I. R.; Ley, S. V. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1983. (c) Ley, S. V.; Massi, A. *J. Comb. Chem.* **2000**, *2*, 104.

(3) (a) Habermann, J.; Ley, S. V.; Scott, J. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1253. (b) Ley, S. V.; Schucht, O.; Thomas, A. W.; Murray, P. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1251. (c) Baxendale, I. R.; Lee, A.-L.; Ley, S. V. *Synlett* **2001**, 1482.

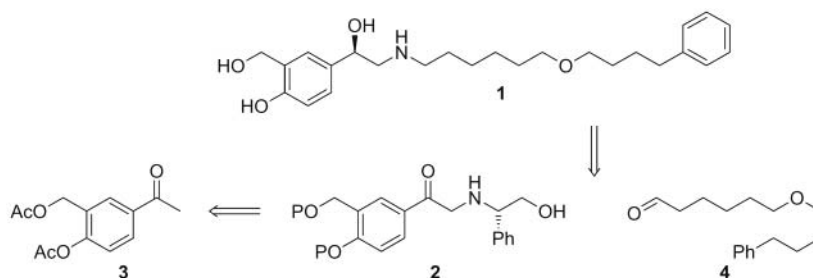
(4) For recent examples see: (a) de Miguel, Y. R.; Brule, E.; Margue, R. G. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1857. (b) Jonsson, C.; Hallmann, K.; Andersson, H.; Stemme, G.; Malkoch, M.; Malmstrom, E.; Hult, A.; Moberg, C. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1857.

[†] University of Cambridge.

[‡] GlaxoSmithKline Research and Development Ltd. Medicines Research Centre.

(1) For example see: (a) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815. (b) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650. (c) Clapham, B.; Reger, T. S.; Janda, K. D. *Tetrahedron* **2001**, *57*, 4637.

Scheme 1. Retrosynthetic Analysis

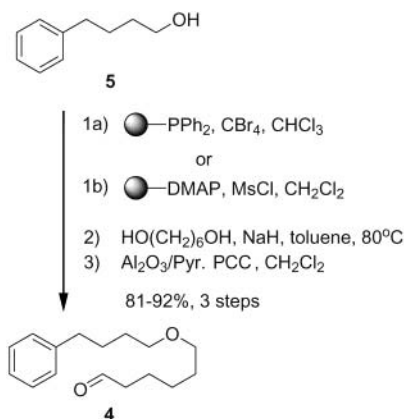


to install the desired benzylic alcohol enantioselectively. Alternative approaches have involved resolution or chromatographic separation of diastereomeric mixtures.^{8,9} A related example demonstrates the capture/release purification of ethanolamines with acidic ion-exchange resin.¹⁰

We envisaged that a diastereoselective reduction of benzylic ketone **2**, available from the saligenin derivative **3**, with borohydride exchange resin (BER) directed by a labile *N*-linked chiral auxiliary, would afford the desired amino alcohol. Completion of the synthesis could then be achieved by a reductive amination with aldehyde **4** and cleavage of the auxiliary by hydrogenolysis (Scheme 1).

Aldehyde **4** was synthesized cleanly in three steps from 4-phenylbutanol **5** in excellent overall yield. Bromination or mesylation was readily achieved by known procedures^{11,3a} and the resultant leaving group displaced with excess water-soluble hexane 1,6-diol to prevent dimerization. Oxidation with alumina-supported pyridinium chlorochromate then quantitatively afforded aldehyde **4** (Scheme 2).

Scheme 2. Synthesis of Aldehyde 4



Initial attempts to form ketone **3** via a condensation of 4-hydroxyacetophenone **6** with formaldehyde,¹² or a stab-

ilized formaldehyde adduct,¹³ proved unsuccessful. We therefore investigated the possibility of aminomethylation followed by displacement of dimethylamine with an oxygen nucleophile to furnish the desired diol motif. Work by Ungaro et al. showed that phenols could be condensed with Eschenmoser's salt catalyzed by potassium carbonate to yield exclusively the *ortho*-substituted products (Scheme 3, eq 1).¹⁴ However, distillation or recrystallization were generally required to purify the products. We envisaged that condensation of 4-hydroxyacetophenone **6** with a resin-bound methyleneiminium salt would eliminate the need for purification, and acid-catalyzed displacement from the resin with acetic anhydride would cleanly furnish the protected diol **3**. Thus, 4-hydroxyacetophenone **6** was added to a stirred suspension of resin-bound piperazinomethylpolystyrene¹⁵ and formaldehyde. Filtration yielded a resin which, when refluxed with *p*TSA and acetic anhydride in toluene, released diacetate **3** in 14% yield (Scheme 3, eq 2). Attempted optimization of the reaction conditions and the use a range of commercially available secondary amine resins failed to improve the initial yield.

We then investigated the use of a polymeric base to catalyze the condensation. Treatment of **6** with Eschenmoser's salt and carbonate exchange resin cleanly afforded the desired tertiary amine **7** after filtration and evaporation without the need for further purification (Scheme 3, eq 3). Interestingly, alkylation of a range of other substituted phenols (Table 1) under identical conditions yielded exclusively the mono-*ortho*-substituted products, suggesting a tight ion pair intermediate. Even in the case where both *ortho* positions were blocked, no *para* substitution was observed (Table 1, entry 8).

Displacement of dimethylamine from **7** with acetic anhydride and catalytic sulfonic acid resin followed by a highly selective monobromination with polyvinylpyridinium bromide perbromide resin furnished diacetate protected α -bromoketone **8** in good yield (Scheme 4).¹⁶ Treatment of **8** with

(5) Nials, A. T.; Coleman, R. A.; Johnson, M.; Vardey, C. *J. Am. Rev. Resp. Dis.* **1994**, *149*, A481.

(6) Procopiou, P. A.; Morton, G. E.; Todd, M.; Webb, G. *Tetrahedron: Asymmetry* **2001**, *12*, 2005.

(7) Hett, R.; Stare, R.; Helquist, P. *Tetrahedron Lett.* **1994**, *35*, 9375.

(8) Skidmore, I. F.; Lunts, L. H. C.; Finch, H.; Naylor, A. patent US4992474, February 12, 1991.

(9) Evans, B. patent EP-A 422889, April 17, 1991.

(10) Shuker, A. J.; Siegel, M. G.; Matthews, D. P.; Weigel, L. O. *Tetrahedron Lett.* **1997**, *37*, 6149.

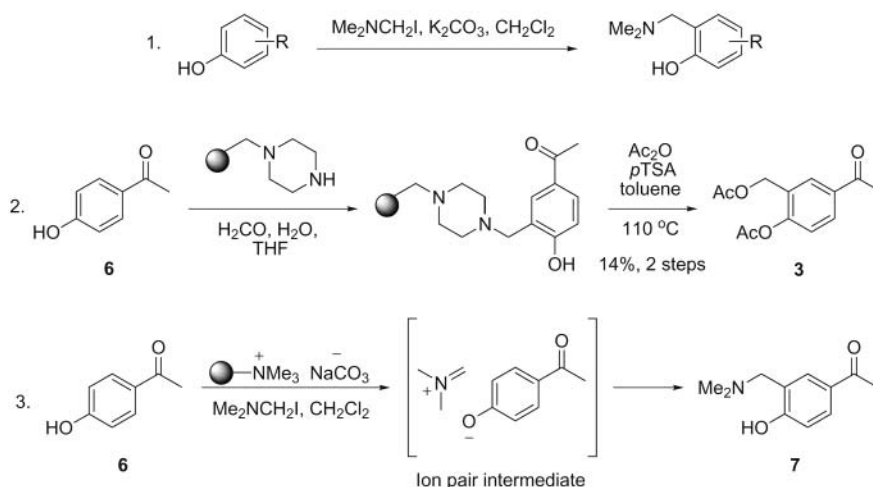
(11) Hodge, P.; Khoshdel, E. *J. Chem. Soc., Perkin Trans. 1* **1984**, 195.

(12) Schlosser, M.; Jenny, T.; Guggisberg, Y. *Synlett* **1991**, 704.

(13) Maruoka, K.; Concepcion, A. B.; Murase, N.; Oishi, M.; Hirayama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 3943.

(14) Pochini, A.; Puglia, G.; Ungaro, R. *Synthesis* **1983**, 906.

Scheme 3. Aminomethylation of 4-Hydroxyacetophenone **6**



(*S*)-phenylglycinol afforded a high proportion of undesired dialkylated by-product, hence the acetate groups were removed under HBr catalysis to preserve the α -bromoketone functionality. Reprotection of the diol as the acetonide was efficiently achieved by using 2-methoxypropene catalyzed by sulfonic acid resin, conditions under which all byproducts are volatile. *N*-Alkylation then proceeded without any observed dialkylation to furnish α -aminoketone **9**. Treatment of **9** with calcium chloride at 0 °C followed by the addition of BER pleasingly delivered the desired amino alcohol **10** as a 10:1 mixture of diastereomers favoring the desired (*R*)-alcohol. Recrystallization from acetonitrile afforded enantiomerically pure **10** in 76% yield. The reduction is thought to proceed via a chelated intermediate where the phenyl substituent points away from the crowded center.¹⁷ Approach of the reductant then occurs preferentially from the convex face of the complex.

Initially, it was envisaged that the imine formed from the condensation of amine **10** and aldehyde **4** could be hydrogenated under palladium catalysis, with concomitant removal of the chiral auxiliary. However, we found that imine reduction was sluggish compared to the rate of auxiliary cleavage, and that doubly alkylated tertiary amine **11** was the major product. The desired reductive amination was accomplished by using polymer-supported cyanoborohydride¹⁸ activated by acetic acid. Filtration and evaporation afforded a mixture of the desired tertiary amine product **12** and its acetate salt, which was conveniently converted to the free base after being stirred briefly with carbonate resin. The auxiliary was then chemoselectively cleaved with Pearlmann's catalyst. Application of the crude product to an acidic SCX-2 cartridge,¹⁹ eluting with methanol, allowed

removal of the phenethyl alcohol byproduct. Elution with 2 *N* ammonia in methanol then released the product with

Table 1. *Ortho*-Alkylation of Phenols^a

entry	substrate	product	yield / %
1			97
2			81
3			82
4			97
5			90
6			87
7			86
8		-	No Reaction

^a Conditions: 1 equiv of Me₂NCH₂I, 2 equiv of carbonate exchange resin, CH₂Cl₂ 16 h.

simultaneous removal of the acetonide group to afford (*R*)-salmeterol **1** in 87% yield for two steps. Enantioselectivity (*es*) was determined by chiral HPLC to be 97.4%.

(19) SCX-2 (alkylsulfonic acid) cartridge, available from Jones Chromatography, catalogue no. 532-0100-C.

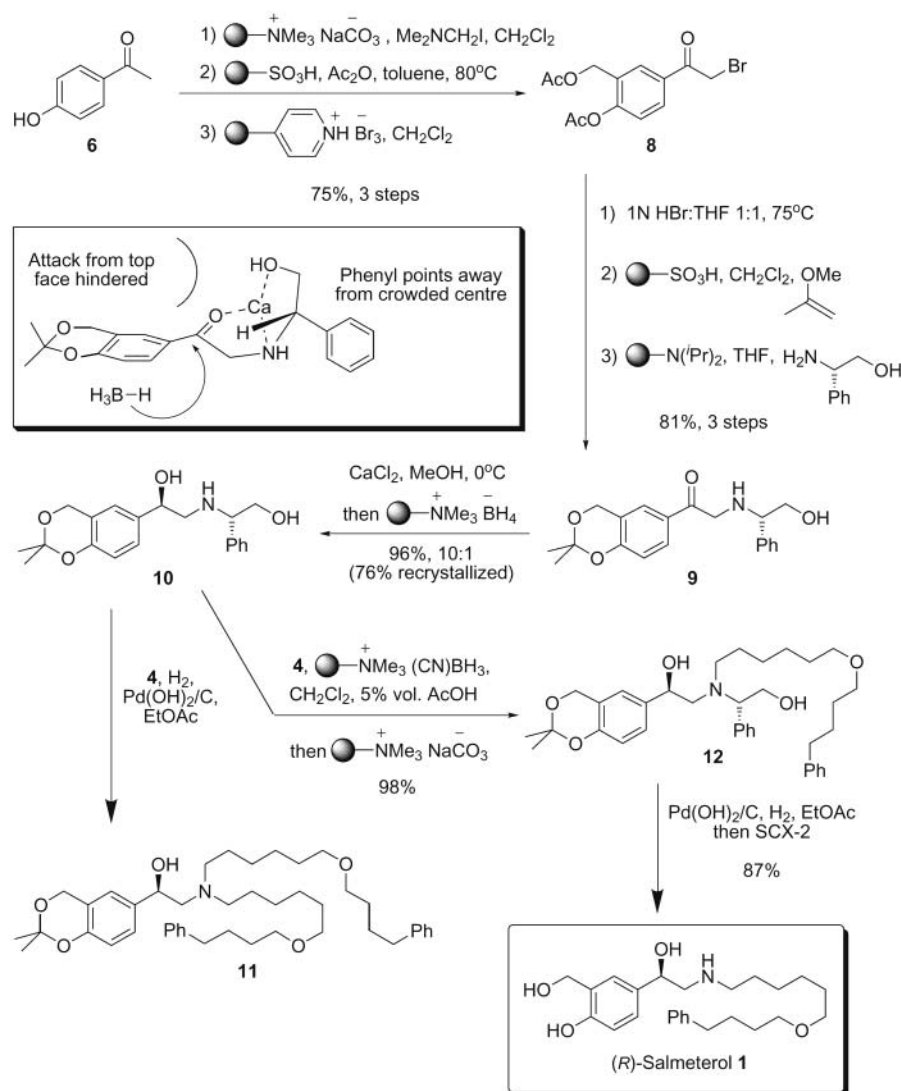
(15) Piperazinomethyl polystyrene, available from Novabiochem, catalogue no. 01-64-0310.

(16) Polyvinylpyridinium bromide perbromide, available from Fluka, catalogue no. 82795.

(17) Bream, R. N.; Ley, S. V.; McDermott, B.; Procopiou, P. A. *J. Chem. Soc., Perkin Trans. 1*. Submitted for publication.

(18) (Polystyrylmethyl)trimethylammonium cyanoborohydride, available from Novabiochem, catalogue no. 01-64-0337.

Scheme 4. Synthesis of (*R*)-Salmeterol 1



In summary, (*R*)-salmeterol **1** was cleanly synthesized in high enantioselectivity and 39% overall yield over nine linear steps without recourse to silica gel chromatography. A rapid synthesis of the saligenin core from 4-hydroxyacetophenone **6** was achieved via a tertiary amine intermediate, and the chiral alcohol was introduced by a chiral auxiliary-mediated diastereoselective reduction. The methodology described provides the opportunity for the rapid synthesis of chiral amino alcohols found in many other drug molecules.

Acknowledgment. We thank EPSRC and GSK (grants to R.N.B.) and Novartis (Research Fellowship to S.V.L.) for funding. We thank Eric Hortense (GSK) for help with final es determination.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL020128G