A Short Stereoselective Synthesis of (*R*)-Salmeterol

David J. Buchanan,[a] Darren J. Dixon,*[a] Brian E. Looker[b]

[a] School of Chemistry, The University of Manchester, Oxford Road, Manchester, M13 9PL, UK
Fax +44(161)2754939; E-mail: darren.dixon@manchester.ac.uk

[b] GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK

Received 4 May 2005

Abstract: A short, highly stereoselective oxy-Michael approach to the total synthesis of the β_2-agonist, (*R*)-salmeterol is described.

Key words: asymmetric synthesis, oxy-Michael addition, 1,2-amino alcohol, δ-lactol

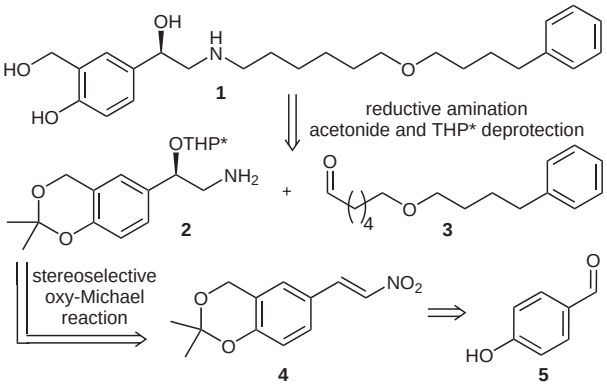
Recently we have developed an effective and practical route to enantiopure vicinal amino alcohols.[1] This new and general method relies on the highly diastereoselective oxy-Michael addition of the 'naked' anion of (*S*)-6-methyltetrahydropyran-2-ol to β-substituted nitroolefins. Subsequent chemical manipulations of the resulting O-protected Henry product, affords a reliable alternative to the existing protocols for the synthesis of biological targets containing the β-substituted ethanolamine motif.[1b]

Herein we wish to report an application of this oxy-Michael reaction to the synthesis of (*R*)-salmeterol (**1**). Salmeterol[2] (Serevent®) induces prolonged bronchodilation, reduced vascular permeability, inhibition of inflammatory mediators, stimulation of ciliary function and modulation of ion and water transport across the bronchial mucosa.[3] This biological activity combined with the key β-aryl ethanolamine skeleton made the asymmetric synthesis of (*R*)-salmeterol, by exploiting our chemistry, an attractive goal.

A range of methods has been used to install the key ethanolamine unit of salmeterol (**1**) in an asymmetric fashion. These include the enzymatic[4] and chemical[5] reductions of ketones, exploitation of solid supported reagents[6] in diastereoselective reductions and the chromatographic separation of enantiomeric[7] and diastereomeric mixtures.[8]

We envisaged a convergent synthesis beginning with aldehyde **5**, which, after transformation into nitroolefin **4**, could partake in the oxy-Michael addition. It was believed that a subsequent nitro group reduction to amine **2**, followed by a reductive amination with aldehyde **3** and an acidic global deprotection would reveal the target molecule (Scheme 1).

The synthesis of the key Michael acceptor required four steps beginning from 4-hydroxybenzaldehyde (**5**). First, chloromethylation using formaldehyde and concentrated hydrochloric acid at 65 °C for 3.5 hours afforded the



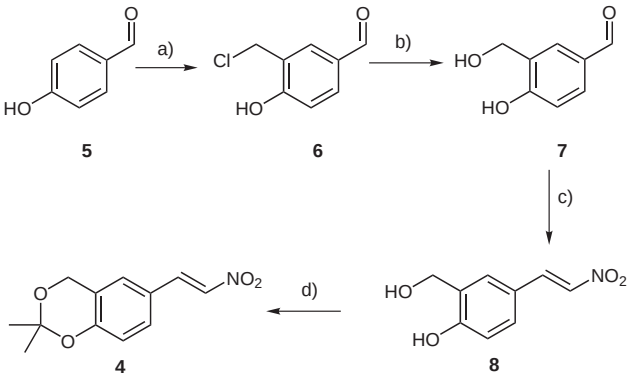
Scheme 1 Retrosynthesis of (*R*)-salmeterol **1**.

chloromethyl arene **6** in 56% yield. Subsequent hydrolysis of the chloride using calcium carbonate in aqueous THF afforded the diol **7**. These two steps, which were subtle but practical modifications of the literature procedures,[9] were performed on multigram scale and the product aldehyde was isolated via trituration of the crude reaction mixture. Attempts to protect the diol as an acetonide at this stage were thwarted by side reactions occurring at the carbonyl group. Accordingly, condensation of **7** with nitromethane was performed prior to protection. The ammonium acetate catalysed condensation method was the one of choice for the formation of nitroolefin **8** and CSA-catalysed *trans*-acetalisation with 2,2-dimethoxypropane (DMP) gave desired **4** in good chemical yield. Overall, **4** was synthesised in 32% yield from the commercially available aldehyde and no chromatography was needed at any stage (Scheme 2).

Aldehyde **3** was cleanly synthesised in three steps following the standard literature procedures.[6]

With Michael acceptor **4** in hand, the key stereoselective oxy-Michael addition with (*S*)-6-methyltetrahydropyran-2-ol (**9**) was investigated with our reported conditions[1a] working optimally. Thus, a THF solution (–78 °C) of (*S*)-6-methyltetrahydropyran-2-ol (**9**, 1.5 equiv) was treated sequentially with KHMDS (1.5 equiv), 18-crown-6 (1.5 equiv) and then **4** (1.0 equiv). After an acetic acid quench the desired oxy-Michael adduct **10** was obtained in quantitative yield and with excellent (>98% de) diastereocontrol. In line with our usual practice, and to aid quantification of the stereocontrol in the reaction an authentic sample of the minor diastereomer, epimeric at the centre

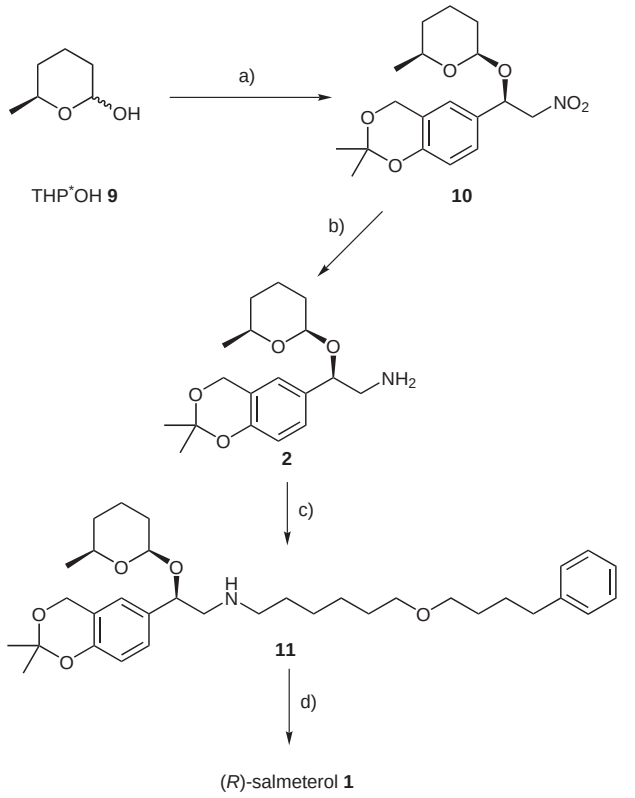
SYNLETT 2005, No. 12, pp 1948–1950
Advanced online publication: 07.07.2005
DOI: 10.1055/s-2005-871927; Art ID: D12405ST



Scheme 2 Synthesis of Michael acceptor **4**. *Reagents and conditions*: a) CH_2O (40% aq), HCl (concd), 65 °C, 3.5 h, 56%; b) $CaCO_3$, THF–H_2O, r.t., 13 h, 87%; c) CH_3NO_2, NH_4OAc, reflux, 3.5 h, 66%; d) DMP, propanone, CSA, r.t., 12 h, 99%.

β to the nitro group, was made by performing the oxy-Michael reaction in the absence of the 18-crown-6 (Scheme 3).

Reduction of the nitro group to the amine was performed using nickel boride,[10] formed in situ by adding sodium borohydride (6 equiv) to a chilled (0 °C) 1:1 MeOH–THF



Scheme 3 Synthesis of (*R*)-salmeterol (**1**). *Reagents and conditions*: a) KHMDS, 18-crown-6, **4**, AcOH, THF, –78 °C, 99%, 98% de; b) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH–THF, 0 °C, 88%; c) **3**, $NaB(O_2CCH_3)_3H$, CH_2Cl_2, 72%; d) SCX-II, NH_3–MeOH, 100%.

solution of Michael adduct **10** and $NiCl_2 \cdot 6H_2O$ (2 equiv). After an alkaline aqueous work up, essentially pure amine product **2** was obtained in 88% yield and used directly in the reductive amination step. Thus, 1.2 equivalents of amine **2** was added to 1 equivalent of aldehyde **3** in CH_2Cl_2 and $NaBH(OAc)_3$ (3.6 equiv) and acetic acid (3.6 equiv) was added to the mixture. Stirring was maintained for 3.0 hours before aqueous work-up afforded the desired secondary amine product **11** in 72% yield. Interestingly, the reductive amination step was initially difficult to master and invariably the tertiary amine product was dominant in the reaction mixtures. After a number of unsuccessful attempts, it was concluded that small amounts of residual nickel salts were facilitating this double alkylation. Accordingly, a thorough alkaline aqueous work up was employed, prior to reductive amination with aldehyde **3**, and the desired secondary amine **11** resulted as the major reaction product.

The final step in the sequence was the global deprotection of the acid labile acetal protecting groups. This was facilitated by ion exchange conditions using a SCX-II cartridge. Elution of the secondary amine **11** onto the stationary phase with methanol, standing for 12 hours and subsequent elution with ammonia-saturated methanol afforded (*R*)-salmeterol in 100% yield and 96% ee, as determined by chiral stationary phase HPLC. The spectroscopic and specific rotation data of **1** were in good agreement with the literature.[11]

In conclusion, the highly diastereoselective oxy-Michael addition of the naked anion of (*S*)-6-methylterahydropyran-2-ol (**9**) has been used as the key step in the total asymmetric synthesis of (*R*)-salmeterol (**1**). The overall yield was 20% commencing from 4-hydroxybenzaldehyde and the longest linear sequence was 8 steps.

Acknowledgment

We gratefully acknowledge GlaxoSmithKline for financial support (DJB), EPSRC National Mass Spectrometry Service Centre (Swansea), Mr E. Hortense for chiral HPLC and Prof. S. V. Ley.

References

(1) (a) Adderley, N. J.; Buchanan, D. J.; Dixon, D. J.; Lainé, D. I. *Angew. Chem. Int. Ed.* **2003**, *42*, 4241. (b) Buchanan, D. J.; Dixon, D. J.; Scott, M. S.; Lainé, D. I. *Tetrahedron: Asymmetry* **2004**, *15*, 195. (c) Buchanan, D. J.; Dixon, D. J.; Hernández-Juan, F. A. *Org. Biomol. Chem.* **2004**, *2*, 2932.

(2) (a) Bradshaw, J.; Brittain, R. T.; Coleman, R. A.; Jack, D.; Kennedy, I.; Lunts, L. H. C.; Skidmore, I. F. *Brit. J. Pharm.* **1987**, *92*, 590P. (b) Ullman, A.; Svedmyr, N. *Thorax* **1988**, *43*, 674.

(3) Johnson, M.; Butchers, P. R.; Coleman, R. A.; Nials, A. T.; Strong, P.; Summer, M. J.; Vardey, C. J.; Whelan, C. J. *Life Sci.* **1993**, *52*, 2131.

(4) (a) Procopiou, P. A.; Morton, G. E.; Todd, M.; Webb, G. *Tetrahedron: Asymmetry* **2001**, *12*, 2005. (b) Goswami, J.; Bezbaruah, R. L.; Goswami, A.; Borthakur, N. *Tetrahedron: Asymmetry* **2001**, *15*, 3343.

(5) (a) Hett, R.; Stare, R.; Helquist, P. *Tetrahedron Lett.* **1994**, *35*, 9375. (b) Coe, D. M.; Perciaccante, R.; Procopiou, P. A. *Org. Biomol. Chem.* **2003**, *1*, 1106. (c) Bream, R. N.; Ley, S. V.; McDermott, B.; Procopiou, P. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2237.
(6) Bream, R. N.; Ley, S. V.; Procopiou, P. A. *Org. Lett.* **2002**, *4*, 3793.
(7) Skidmore, I. F.; Lunts, L. H. C.; Finch, H.; Naylor, A. US 4992474, **1991**.
(8) Evans, B. EP-A 422889, **1991**.
(9) Amann, A.; Koenig, H.; Thieme, P. C.; Giertz, H. Ger. Offen. 2,310,140, **1974**.
(10) (a) Nose, A.; Kudo, T. *Chem. Pharm. Bull.* **1981**, *29*, 1159. (b) Nose, A.; Kudo, T. *Chem. Pharm. Bull.* **1988**, *36*, 1529. (c) Nose, A.; Kudo, T. *Chem. Pharm. Bull.* **1989**, *37*, 816. (d) Osby, J. O.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 6413.
(11) Data for synthetic **1**: $[\alpha]_D^{25}$ –21.1 (*c* 1.48, $CHCl_3$), [lit.[6] $[\alpha]_D^{25}$ –20.6 (*c* 1.46, $CHCl_3$)]. ^{1}H NMR (400 MHz, CD_3OD, lit.[5c]): δ = 7.29 (1 H, s, Ar-C*H*), 7.23 (2 H, m, Ar-C*H*), 7.17–7.11 (4 H, m, Ar-C*H*), 6.75 (1 H, d, *J* = 8.1 Hz, Ar-C*H*), 4.68 (1 H, dd, *J* = 8.7, 4.2 Hz, C*H*CH_2NH), 4.65 (2 H, s, CH_2OH), 3.44–3.39 (4 H, m, CH_2OCH_2), 3.35 (1 H, s, NH), 3.31 (2 H, s, 2 × OH), 2.77 (1 H, dd, *J* = 12.1, 8.8 Hz, CHC*H*HNH), 2.71 (1 H, dd, *J* = 12.1, 4.3 Hz, CHCH*H*NH), 2.61 (4 H, m, *J* = 6.8 Hz, CH_2CH_2Ph and NHC$H_2$$CH_2$), 1.71–1.56 (8 H, m, 4 × CH_2), 1.37–1.29 (4 H, m, 2 × CH_2). ^{13}C NMR (100 MHz, CD_3OD): δ = 154.5 (OAr-1), 142.3 (Ar), 133.6 (Ar), 128.1 (Ar), 128.0 (Ar), 127.9 (Ar), 127.1 (Ar), 125.7 (Ar), 125.3 (Ar), 114.5 (Ar-5), 71.6 (*C*HCH_2NH), 70.4 (*C*H_2 °CH_2), 70.3 (CH_2OCH_2), 59.7 (Ar*C*H_2), 56.4 (CH*C*H_2NH), 50.2 (NH*C*$H_2$$CH_2$), 35.2 ($CH_2$*C*$H_2$Ph), 30.3 ($CH_2$), 29.2 ($CH_2$), 28.9 ($CH_2$), 27.9 ($CH_2$), 26.7 ($CH_2$), 25.7 ($CH_2$). IR (film): ν_{max} = 3675 (OH), 2987, 2901, 1452, 1406, 1394 cm^{-1}. HRMS (ES+): m/z calcd for $C_{25}H_{38}NO_4$ $[M + H]^+$: 416.2795; found: 416.2796. Chiral HPLC was performed on a Sumichiral OA-4100 column (25 cm × 4.6 mm) eluting with hexane–EtOH–CH_2Cl_2–TFA (240:30:130:1), at a flow rate of 1 mL/min, detecting at 276 nm; t_R = 19.26 min, 2.0% [*S*-isomer]; t_R = 21.84 min, 98.0% [*R*-isomer].