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Enantioselective Synthesis of Salmeterol via Asymmetric Borane Reduction

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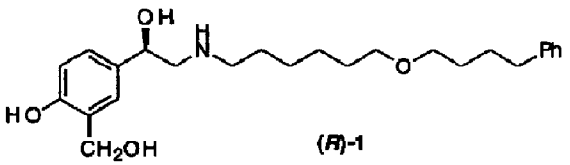
Abstract: Enantioselective syntheses of both enantiomers of salmeterol are accomplished using asymmetric borane reductions with chiral oxazaborolidines as catalysts.

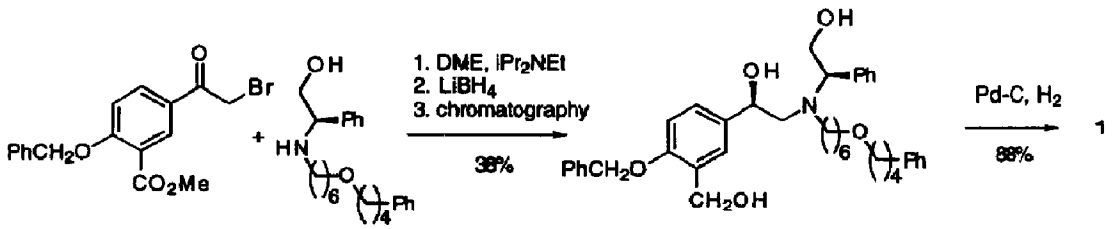
Salmeterol (Serevent®) is a long acting, very potent β-agonist and is used in the therapy of asthma and chronic bronchitis.[1] It is marketed, like many other chiral drugs, as a racemate. However, it is well established, that single enantiomers are often much more potent and have reduced side effects compared to their racemates.[2] For many β-agonists, the active isomer is the (*R*)-enantiomer.



(*R*)-1

Despite some elegant, recently reported syntheses of other β-agonists,[3] the synthesis of non-racemic salmeterol has been published only in the patent literature and involved a resolution to give chiral oxirane **4** as an intermediate[4] or the use of a chiral auxiliary[5] as shown in Scheme 1. The disadvantages of this latter route are the low yield and the destruction of the chiral auxiliary upon hydrogenolysis.

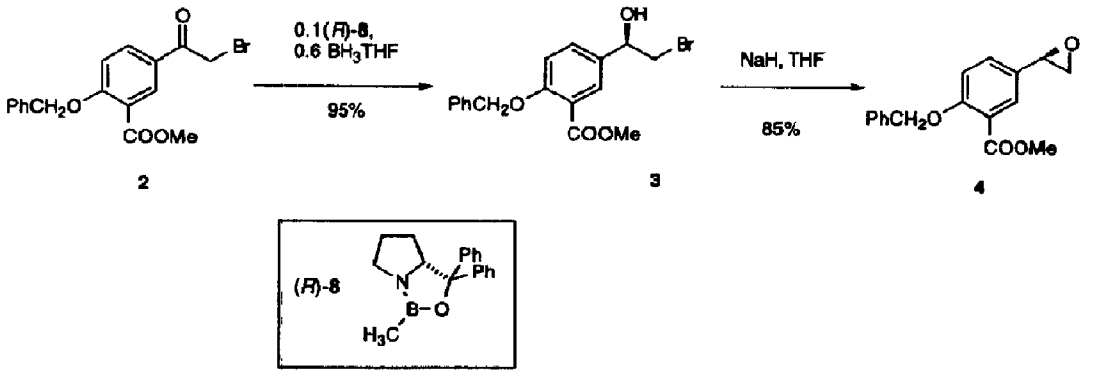
Scheme 1:



We herein wish to report enantioselective syntheses of both enantiomers of salmeterol. The key step in each synthesis is asymmetric borane reduction catalyzed by chiral oxazaborolidine catalysts developed by Corey *et al.*[6,7] (CBS-reduction).

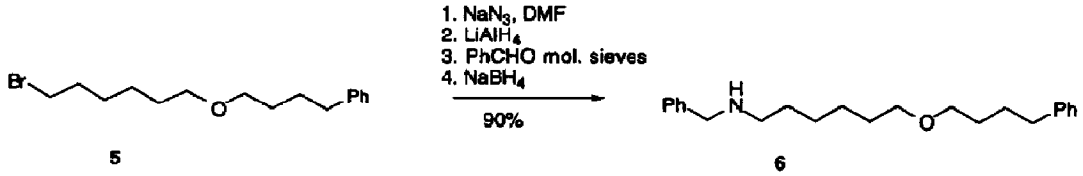
The synthesis starts with bromoketone **2** (Scheme 2), which is synthesized by bromination ($CHCl_3$, Br_2) of the parent ketone. Enantioselective reduction of **2** with borane and a catalytic amount of oxazaborolidine (*R*)-**8** or (*S*)-**8** gives bromohydrin **3** in almost quantitative yield. The synthesis of the catalyst[8] and then the reductions are performed as described by Corey *et al.* using 10 mol % oxazaborolidine and 0.6 equiv. borane.[6c,9] We have not tested recent modifications of this procedure.[10] The bromohydrin is purified by chromatography or, on larger scale, by crystallization from ethyl acetate /hexane . The (*S*)-catalyst gives (*S*)-**3**, and the (*R*)-catalyst gives (*R*)-**3**. The e.e. of bromohydrin **3** was not determined directly. However, it can be concluded to be at least 94%, which is the value we obtained by HPLC analysis of the later intermediate **7**. It is noteworthy that the reaction is apparently not influenced by the other functional groups of **2**, which could also coordinate to the catalyst and thus decrease the chiral induction. Treatment of bromohydrin **3** with a sodium hydride suspension in THF generates epoxide **4** as an oil with an optical purity of > 95% ($[\alpha]_D^{25}$ = -18.9° (c = 0.75, C_6H_6)[4].

Scheme 2:



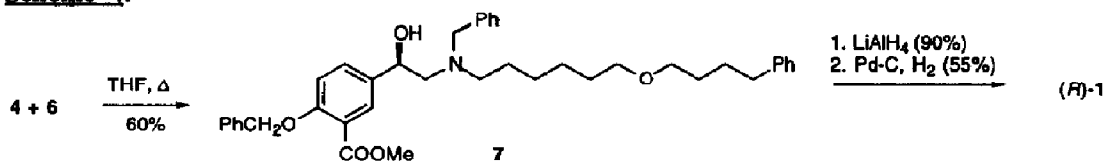
The synthesis of the amine portion starts with **5** which is obtained from 1,6-dibromohexane and 4-phenylbutanol in 60% yield. Bromoether **5** is purified by distillation and is thus separated from the bis-ether byproduct. Transformation of **5** into benzyl amine **6** is straightforward (Scheme 3). First, the bromide is substituted with azide, followed by reduction with lithium aluminum hydride to give the primary amine. Reaction with benzaldehyde in the presence of molecular sieves and subsequent reduction with sodium borohydride in ethanol affords **6**. This benzyl amine is obtained without chromatography in high purity and high yield as an oil, but it did solidify to form a wax, when prepared on a 50 g scale.

Scheme 3:



Regioselective epoxide ring opening is observed in the reaction of **4** and **6** to give the desired aminoalcohol **7** in 60% yield after purification by chromatography (Scheme 4). The e.e. of this product is 94% based upon HPLC analysis[11]. Ester reduction and removal of the two benzyl groups affords (*R*)-salmeterol **1** in reasonable yield and purity as a very thick oil[12]. Likewise, (*S*)-salmeterol is obtained via the series of enantiomeric intermediates originating with the use of the (*S*)-oxazaborolidine catalyst in the initial asymmetric step.

Scheme 4:



The ester reduction of **7** may also be done as part of a one-pot procedure whereby the reaction mixture after the epoxide ring opening is diluted with THF and lithium aluminum hydride is added carefully. Attempts to obtain **7** more directly by reaction of bromo alcohol **3** with the benzyl amine **6** gave only poor yields.

For meeting higher standards of chemical and enantiopurity, (*R*)- and (*S*)-salmeterol may be crystallized as their hydroxynaphthoic acid salts from ethyl acetate/hexane to give enantiomerically pure products as white powders[13].

In conclusion, we have synthesized (*R*)- and (*S*)-salmeterol by applying asymmetric borane reductions, and we have thus demonstrated the applicability of this method to a more complex haloketone than reported previously. Furthermore, we have developed a new, more practical synthesis of the amine portion **6**.

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References and Notes:

1. Anderson, G. P. in "New Drugs in Allergy and Asthma", Birkhäuser Verlag, Basel, 1993.
2. Millership, J. S.; Fitzpatrick, A. *Chrality* **1993**, *5*, 573.
3. (a) Hong, Y.; Gao, Y.; Nie, X, Zepp, C. M. *Tetrahedron Lett.* **1994**, *35*, 5551. (b) Solladié-Cavallo, A.; Simon-Wermeister, M.-C.; Farkhani, D. *Helv. Chim. Acta* **1991**, *74*, 390. (c) Corey, E. J.; Link, J. O. *J. Org. Chem.* **1990**, *56*, 442.
4. Skidmore, I. F.; Lunts, L. H. C.; Finch, H.; Naylor, A. U.S. Patent 4,992,474.

5. Evans, B. Eur. Pat. Appl. 0 422 889 A2.
6. (a) Corey, E. J.; Bakshi, R. K.; Shibita, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibita, S. J.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (c) Corey, E. J.; Shibita, S. J. ; Bakshi, R. K.*J. Org Chem.* **1988**, *53*, 2861.
7. For leading reviews: (a) Singh, V. K. *Synthesis* **1992**, 605. (b) Wallbaum, S.; Martens, J. *Tetrahedron : Asymmetry* **1992**, *3*, 1475.
8. The catalyst "MeCBS" is now commercially available as a 1M solution in toluene from Callery Chemical Company.
9. Procedure (*S*)-Diphenylprolinol (288 mg, 1.14 mmol) and methaneboronic acid (69 mg, 1.14 mmol) in toluene (3 ml) were stirred in the presence of molecular sieves (4 Å, 2 g) for 8 h. Filtration over Celite and evaporation of the solvent gave 290 mg of a syrup that was dissolved in dry THF (10 ml) to give a 0.1 M catalyst solution. Bromoketone 2 (360 mg, 1 mmol) was placed in THF (3 ml) and the catalyst solution was added (1 ml, 0.1 mmol) followed by a 1 M solution of BH_3-THF (0.6 ml). After 1 h (no more gas evolution; TLC) methanol (1 ml) was added, and the solvent was evaporated. The residue was filtered over silica gel using ethyl acetate/hexane 1:2. Evaporation of the filtrate gave the pure alcohol as an oil (363 mg), which crystallizes from EtOAc/hexane to give colorless crystals: mp = 66-68°C; TLC: Rf = 0.45 (E/H = 1/2); $[\alpha]_D^{25}$ = +25.2° (c = 4, CH_2Cl_2); ^{1}H-NMR (300-MHz, $CDCl_3$) δ 7.83 (d, *J* = 2 Hz, 1 H), 7.5-7.25 (m, 7 H, Ph, Ar), 7.01 (d, *J* = 8.7 Hz, 1 H), 5.18 (s, 2 H, $PhCH_2O$), 4.87 (dd, *J* = 8.4, 3 Hz, 1 H, CHOH), 3.90 (s, 3 H, CH_3O), 3.39 (dd, *J* = 10, 3 Hz, 1 H, CHH'Br), 3.50 (dd, *J* = 10, 8.7 Hz, 1 H, CHH'Br) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) 166.37, 158.02, 136.44, 132.47, 130.97, 129.51, 128.52, 127.80, 126.73, 120.62, 113.96, 72.86. 70.58, 65.80, 52.09, 39.85 ppm.
10. (a) Mathre, D. J.; Thomoson, A. S.; Douglas, A. W.; Carrol, J. D.; Corley, E. G.; Grabowski, E. J. *J. Org,. Chem.* **1993**, *58*, 2880. (b) Corey, E. J; Link, J. O. *Tetrahedron Lett.* **1993**, *29*, 4141. (c) Quallich, G. J.; Woodall, T. M. *Synlett* **1993**, 929.
11. Chiracel OD, 10 µm, 25 cm x 4.6 mm (Daicel); mobile phase hexane/ i-propanol = 75 / 25, ambient temperature, flow rate 1.0 ml/min, retention times (*R*) = 16.7 min, (*S*) = 20.9 min.
12. The compounds obtained showed correct ^{1}H-NMR spectra; ee = 92% determined on a Chirex (*S*)-ICA and (*R*)-NEA, 10 µm, 25 cm x 4.6 mm (Phenomex); mobile phase: hexane/dichloromethane/methanol/TFA = 480/280/40/2; ambient temperature; flow rate 1.0 ml/min, retention times (*R*) = 38.2 min, (*S*) = 31.0 min.
13. For (*S*): [α] = + 22.4 ° (c = 0.5, MeOH), ee = 97.6% determined as in (12), mp = 92°C; for (*R*): [α] = - 22.8° (c = 0.5, MeOH), ee > 99.9%, mp = 92°C.

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