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Enantio- and Diastereoselective Synthesis of all Four Stereoisomers of Formoterol

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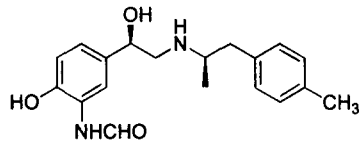
Abstract: Enantioselective syntheses of all four stereoisomers of formoterol are accomplished using asymmetric catalytic borane reductions with chiral oxazaborolidines as reducing agents.

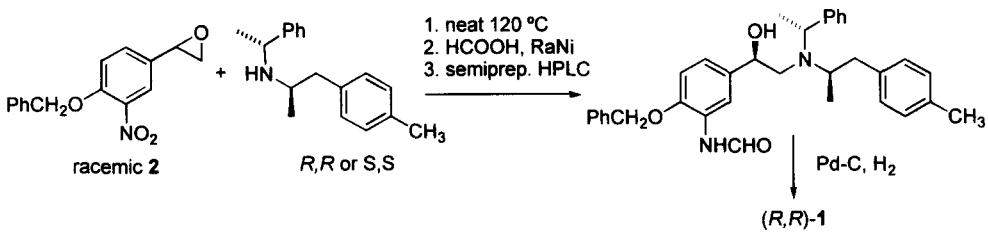
Formoterol (Foradil®) **1** is a long acting, very potent β_2-agonist which is used as a bronchodilator in the therapy of asthma and chronic bronchitis.[1] It is currently marketed as a racemate, as are the β_2-agonists albuterol (Salbutamol), salmeterol, fenoterol or terbutaline. However, it has been shown that single enantiomers of chiral drugs are often more potent or have less side effects compared to their racemates.[2] For formoterol, the (*R,R*)-enantiomer has been shown to be more active than the other stereoisomers (*R,S; S,R; S,S*) of formoterol.[3]



(*R,R*)-**1**

The synthesis of all four stereoisomers of formoterol has been described in the literature via a resolution procedure[3a] and an immolative process (Scheme 1)[3b] which gave low overall yields (2%), involving semipreparative HPLC for the separation of diastereomers.

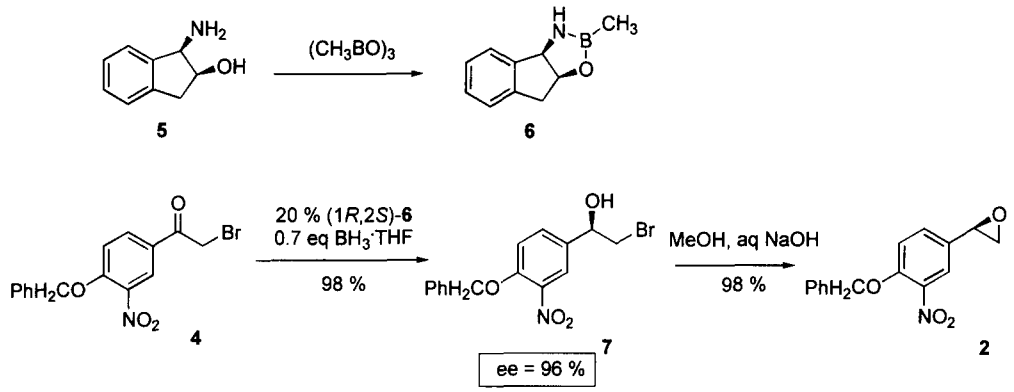
Scheme 1:



We herein wish to report a diastereo- and enantioselective synthesis of formoterol. The procedure involves enantioselective synthesis of the intermediate epoxide **2**,[4] by utilizing the previously developed enantioselective, *cis*-1-amino-2-indanol catalysed borane reduction.[5] In addition, we also describe a new resolution procedure for the intermediate amine **3** using mandelic acid.

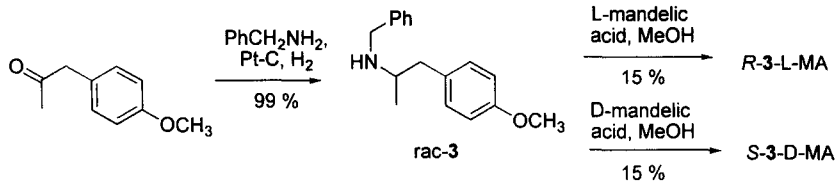
The starting point for the enantioselective reduction is bromoketone **4**[4] and enantiomerically pure *cis*-aminoindanol **5**.[6] First, *cis*-(1*R*, 2*S*)-aminoindanol (0.2 eq) is reacted with trimethylboroxine (0.07 eq) in toluene[7] to give oxazaborolidine **6.** After azeotropic removal of methaneboronic acid, THF and borane (0.2 eq) are added followed by simultaneous addition of more borane (0.7 eq) and a solution of bromoketone (1 eq) in tetrahydrofuran at -15°C.[5a] The product (*R*)-bromohydrin **7** is isolated by extraction from aqueous acid in excellent yield (>98%) and good enantiomeric excess (ee = 95%), determined by HPLC.[8] In a similar experiment using 20 mol % diphenylprolinol derived oxazaborolidine as catalyst (CBS),[9] bromohydrin **7** is prepared with an ee of 88%. (*R*)-bromohydrin **7** is converted to (*R*)-epoxide **2** in quantitative yield in the presence of an aqueous base.[10] Likewise, (*S*)-epoxide **2** is obtained via the same synthetic sequence by using *cis*-(1*S*, 2*R*)-aminoindanol derived oxazaborolidine in the reduction step.

Scheme 2:



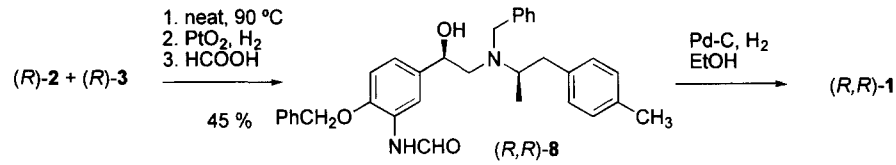
Although synthesis of amine **3** is described via reductive benzylation of 4-methoxyamphetamine[11] in the literature,[3a] we find it more convenient to prepare **3** by catalytic reductive amination from benzylamine and p-methoxyphenylacetone in the presence of Pt-C in ethanol (Scheme 3).[12] A resolution procedure is developed using L-mandelic acid (MA) in methanol to give optically pure (*R*)-**3** L-MA (ee > 99%) after 2-3 crystallizations from methanol. Partially enriched (*S*)-**3** is recovered from the mother liquor and crystallized as D-mandelate to give optically pure (*S*)-**3**-D-MA.

Scheme 3:



Epoxide ring opening between (*R*)-**2** and (*R*)-**3** followed by nitro reduction and formylation are straightforward (Scheme 4).[13] The three step sequence gives the dibenzyl protected formoterol precursor **8** in reasonable yields (45%) containing 2-3% of (*S,R*)-diastereomer, stemming from the minor enantiomer in epoxide **2.**

Scheme 4:



The debenzylation of precursor (*R,R*)-**8** with Pd-C, H_2 in ethanol gives (*R,R*)-formoterol in good chemical purity containing 2-3% of undesired diastereomer. Crystallization of (*RR*)-formoterol with L-tartaric acid (TA) in aqueous isopropanol (85%) finally affords the pure diastereomer.[14] This is an interesting result compared to the resolution procedure in the literature,[3a] which uses D-tartaric acid to give the diastereomerically pure (*R,R*)-formoterol-D-tartrate. Likewise, (*R,S*)-, (*S,R*)-, (*S,S*)-formoterol-tartrates are obtained via the same synthetic sequence by reacting the appropriate epoxide with the appropriate amine. The chemical and stereoisomeric purities, determined by HPLC[15] are listed the table below.

Table: Chemical and Stereoisomeric Purities of Formoterol Tartrate

Entry	**Chem. Purity (% area)**	**(*R,R*) (%)**	**(*R,S*) (%)**	**(*S,R*) (%)**	**(*S,S*) (%)**	α (c=1, H_2O)
(*R,R*)-**1**-L-TA	98.9	**99.9**	0.0	0.1	0.0	-29.1
(*R,S*)-**1**-L-TA	99.5	0.0	**96.8**	0.0	3.2	+5.0
(*S,R*)-**1**-D-TA	99.3	1.7	0.0	**98.3**	0.0	-5.2
(*S,S*)-**1**-D-TA	99.3	0.0	0.1	0.0	**99.9**	+29.0

In conclusion, we have synthesized all four stereoisomers of formoterol by applying the enantioselective, *cis*-1-amino-2-indanol catalysed borane reduction, and have thus demonstrated the applicability of this method in the synthesis of a complex chiral molecule. Furthermore, we have developed a new resolution procedure for N-Benzyl-4-methoxyamphetamine **3**.

References and Notes:

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5. (a) Hong, Y.; Gao, Y.; Nie, X, Zepp, C. M. *Tetrahedron Lett.* **1994**, *35*, 6631. (b) Hong, Y.; Gao, Y.; Nie, X, Zepp, C. M. *Tetrahedron Lett.* **1994**, *35*, 5551. (c) Di Simone, B.; Savoia, D; Tagliavini, E.; Umani-Ronchi, A. *Tetrahedron: Asymmetry* **1995**, *6*, 301
6. The asymmetric synthesis of optically pure *cis*-1-amino-2-indanols will be addressed in a separate paper. Also see: Senanayake, C. H.; Roberts, F. E.; DiMichele, L. M.; Ryan, K. M.; Liu, J.; Fredenburgh, L. E.; Foster, B. S.; Douglas, A. W., Larsen, R. D.; Verhoven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 3993.
7. Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Carrol, J. D.; Corley, E. G.; Grabowski, E. J. *J. Org,. Chem.* **1993**, *58*, 2880.
8. Chiracel OJ, 10 μm, 25 cm x 4.6 mm (Daicel); mobile phase hexane/ ethanol = 7 / 3, ambient temperature, flow rate 1.0 ml/min, retention times (*R*) = 21 min, (*S*) = 23.5 min.
9. (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.
10. (*R*)-(-)-4-Benzyloxy-3-nitrostyrene oxide: To a solution of (*R*)-bromohydrin (35.2 g, 0.1 mol) in methanol an aqueous solution of sodium hydroxide is added and stirred for 30 min. The solvent is evaporated and the residue extracted with dichloromethane. The organic phase is dried over sodium sulfate and evaporated to give the product as a yellow solid melting at . $[\alpha]_D^{25}$ = -10.5° (c = 1, $CHCl_3$) ee = 96%.
11. In the USA 4-Methoxyamphetamine is a schedule 1 controlled substance DEA 7411.
12. M. Freifelder in "Practical Catalytic Hydrogenation", Wiley-Interscience, New York, 1970.
13. (a) Murase, K.; Mase, T.; Ida, H.; Takahashi, K.; Murakami, M. *Chem. Pharm. Bull.* **1977**, *25*, 1368; (b) Trofast, J. W.; Jakupovic, E.; Månsson, L. K.; PCT Int. Appl. WO 92/05147.
14. While the (*R,S*) and (*S,R*) diastereomers of the free base are crystalline solids (see ref 3a), the (*R,R*) and (*S,S*) diastereomers are amorphous solids and could not be crystallized without salt formation.
15. Chiracel OJ, 10 μm, 25 cm x 4.6 mm (Daicel); mobile phase hexane/ ethanol/ Et_2NH = 85 / 15 / 0.1, ambient temperature, flow rate 1.0 ml/min, retention times (*R,R*) = 17.0 min, (*R,S*) = 19.2 min, (*S,R*) = 23.6, (*S,S*) = 26.8 min.

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