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Large-Scale Synthesis of Enantio- and Diastereomerically Pure (*R*,*R*)-Formoterol†

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Abstract:

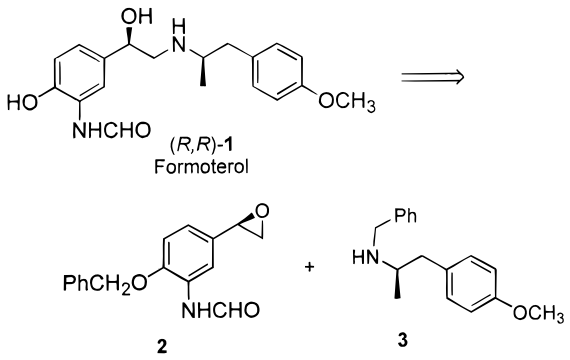
(*R*,*R*)-Formoterol (1) is a long-acting, very potent β_2-agonist, which is used as a bronchodilator in the therapy of asthma and chronic bronchitis. Highly convergent synthesis of enantio- and diastereomerically pure (*R*,*R*)-formoterol fumarate is achieved by a chromatography-free process with an overall yield of 44%. Asymmetric catalytic reduction of bromoketone 4 using as catalyst oxazaborolidine derived from (1*R*, 2*S*)-1-amino-2-indanol and resolution of chiral amine 3 are the origins of chirality in this process. Further enrichment of enantio- and diastereomeric purity is accomplished by crystallizations of the isolated intermediates throughout the process to give (*R*,*R*)-formoterol (1) as the pure stereoisomer (ee, de >99.5%).

Introduction

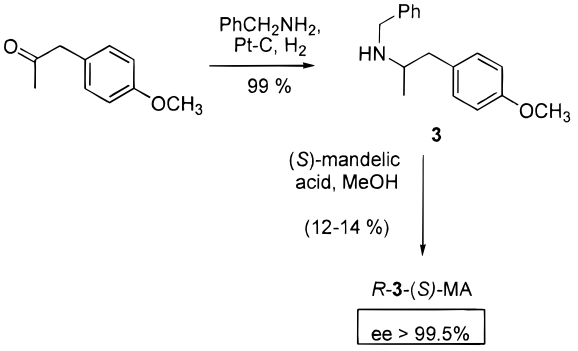
Bronchodilators, in particular β_2-adrenoceptor agonists, are recognized as very effective drugs to treat asthma and other bronchospastic conditions.[1] Important characteristics for these drugs are activity, selectivity, duration of action, and onset. While the first-generation drugs (e.g., isoprenaline or terbutaline) were relatively unselective and short-acting, the current drugs have either a fast onset but only a short duration of action of about 4 h (albuterol)[2] or a slow onset (20 min) with a longer duration of action (salmeterol).[3a,b] Formoterol (**1**) (IUPAC name: 3-formamido-4-hydroxy-α-[[*N*-(*p*-methoxy-α-methylphenethyl)amino]methyl]benzyl alcohol) is unique in that it not only is extremely potent and selective but also has a duration of up to 12 h and a rapid onset of 1−5 min. Most β_2-adrenoceptor agonists are currently marketed as racemates despite regulatory preference and different biological activity of pure enantiomers.[4] In the case of formoterol it has been shown that the (*R*,*R*)-isomer is 1000 times more active than the (*S*,*S*)-isomer.[5]

To date, there are three published synthetic entries to enantiomerically pure formoterol (**1**). The first procedure utilizes a resolution of diastereomerically pure racemic formoterol using tartaric acid with a 5% yield.[6] The second procedure utilizes (phenylethyl)amine as the chiral source in an immolative process, involving semipreparative HPLC for the separation of minor diastereomers, to give stereochemically pure formoterol in yields of 2%.[5] These procedures are neither practical nor efficient because of the lack of crystalline intermediates, the necessary chromatography purifications, and the low overall yields. The third procedure, our initial approach to formoterol, includes enantioselective catalytic borane reduction and opening of the related epoxide with an optically pure amine.[7] We now report a highly improved, more convergent and practical version of this approach involving only crystalline intermediates (no chromatography), with an overall yield of 44%.

Scheme 1. **Retrosynthetic analysis of formoterol**



Scheme 2. **Synthesis of enantiomerically pure amine 3**



Results and Discussion

The disconnection of formoterol suggests two synthetic subunits: chiral epoxide **2** and chiral amine **3** (Scheme 1). Optically pure (*R*)-**3** is synthesized by reductive amination followed by crystallization of its (*S*)-mandelic acid salt as described earlier (Scheme 2).[7] The free amine is generated in situ concurrently with the formation of the epoxide **2** in

† Dedicated to Prof. Carl R. Johnson on the occasion of his 60th birthday.

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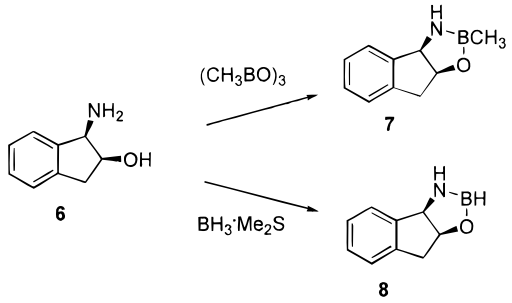
Table 1. **Enantioselective outcome of the asymmetric reduction of bromo ketone 4[a]**

catalyst	mol %	temp °C	ee (%)
7	20	−15	95.0
7	20	0	93.4
7	20	25	90.0
8	20	0	82.0
8	20	25	90.0
8	10	25	89.4
8	5	25	88.6
8	1	25	86.8

[a] All reactions were run at a concentration of 0.3 M in THF, with simultaneous addition of the ketone and the reducing agent (0.7 equiv BH_3·Me_2S) to the catalyst over 2 h. Enantiomeric excesses determined by HPLC [Chiracel OJ column with 30% EtOH in hexane at 1 mL/min, UV detection at 230 nm, (*R*) 21 min, (*S*) 23 min].

Scheme 3. **Synthesis of oxazaborolidines from (1*R*,2*S*)-1-amino-2-indanol**



the last step, but may also be isolated as an oil by neutralization with NaOH and extraction with methyl *tert*-butyl ether (MTBE).

The starting point for the synthesis of epoxide **2** is the catalytic enantioselective reduction of bromo ketone **4** to give bromohydrin **5,** using 1-amino-2-indanol (**6)** derived oxazaborolidine as catalyst.[8] In our initial synthesis 20 mol % *B*-methyloxazaborolidine **7** was used as the catalyst and BH_3·THF (0.7 equiv) as the reducing agent. This particular catalyst needs to be prepared by reacting (1*R*,2*S*)-1-amino-2-indanol (**6)** with trimethylboroxin followed by an azeotropic distillation with toluene[9] (Scheme 3). The cost of these reagents and the additional handling prompted us to study the reduction with in situ generated oxazaborolidine **8** as catalyst. Selected results of this study are summarized in Table 1.

While the highest selectivities are achieved by using catalyst **7** at −15 °C, the enantiopurities were only slightly lower (i.e., 90% vs 95%) when in situ prepared **8** was used. However, the catalyst **8** is easier to handle, the preparation is less time-consuming, and no expensive reagents are involved. In addition, the optimal reaction temperature for catalyst **8** is 25 °C rather than the −15 °C for catalyst **7,** and bromohydrin **5** is isolated by crystallization and thereby enriched in its enantiopurity. Therefore, we chose catalyst **8** as the reducing agent for the synthesis of **5**.

A typical preparation on a 120-g scale is carried out with 5 mol % of catalyst **8** with an addition time of 3 h (Scheme 4). An extractive workup with diluted acid removes aminoindanol **6** and the product is crystallized from the concentrated organic phase by the addition of heptane. The isolated yield is 84%, and the product **5** has an ee of 94%. Further crystallization of **5** from toluene/heptane with enrichment up to >99.5% can be done, but is not necessary for achieving high stereochemical purities of the final product **1**.

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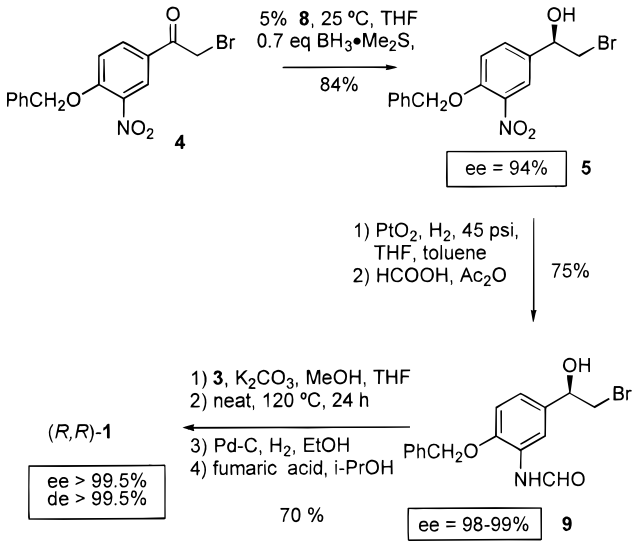
Scheme 4. **Enantio- and diastereoselective synthesis of (*R*,*R*)-formoterol 1**



In the next step, the nitro group of **5** is cleanly reduced by hydrogenation in the presence of Adams catalyst (PtO_2) in quantitative yield. The resulting aniline can be isolated by simple removal of the solvent. However, to avoid autoxidation, it is treated with a mixture of formic acid and acetic anhydride immediately after the removal of the platinum catalyst. Bromohydrin **9** crystallizes from the reaction mixture upon concentration in good yields (75%) and with an increased enantiopurity (ee = 98.6%). It is further enriched to ee > 99.5%, by a single crystallization from ethyl acetate.

The last step, which comprises several reactions without isolation of the intermediates, starts by reacting bromohydrin **9** with K_2CO_3 to form epoxide **2**. At the same time, the amine salt (*R*)-**3**-(*S*)-MA is freed up. An aqueous workup removes salts and mandelic acid and sets the stage for the epoxide opening. Alternatively these steps can be done separately and the crystalline epoxide **2** can be isolated from toluene/heptane and then reacted with free amine **3**. The epoxide opening is performed at 120 °C, and the highest conversion rates are observed without a solvent. The subsequent deprotection of the benzyl groups by catalytic hydrogenation affords an ethanolic solution of formoterol (**1**), which is subsequently crystallized as its fumarate salt. (*R*,*R*)-Formoterol fumarate (**1**) is thus isolated in a yield of 70% (44% from **4**) with a stereochemical purity higher than 99.5%.

Likewise the other stereoisomers of **1** could be prepared by reacting the appropriate bromohydrin **9** and amine **3**, following the given synthetic protocol for (*R*,*R*)-**1**.

In summary, (*R*,*R*)-formoterol (**1**) is synthesized by a highly selective, practical and convergent process in an overall yield of 44%. Enantioselective catalytic (1*R*, 2*S*)-1-amino-2-indanol derived oxazaborolidine reduction of **4** and resolution of chiral amine **3** are the origins of chirality in this process. Further enrichment of enantio- and diastereomeric purity is accomplished by crystallizations throughout the process to give (*R*,*R*)-formoterol (**1**) as the pure stereoisomer (ee, de >99.5%).

Experimental Section

General Procedures. All reactions are carried out under a nitrogen or an argon atmosphere. Solvents and reagents were obtained from commercial sources and used without further treatment or purification.

Materials. 2-Bromo-4′-(benzyloxy)-3′-nitroacetophenone (**4**) is prepared according to a previously reported procedure.[10] (1*R*,2*S*)-1-Amino-2-indanol, in larger quantities, is prepared following published methods[11] and is now also commercially available.

(*R*)-(*N*−Benzyl-2-amino)-1-(4-methoxyphenyl)propane (*S*)-Mandelic Acid Salt [(R)-3-(S)-MA]. A Parr hydrogenator is charged with Pt/C (5% Pt, 6.6 g) and a solution of *N*-benzylamine (214 g, 2 mol) and (4-methoxyphenyl)acetone (328 g, 2 mol) in MeOH (800 mL) which is cooled to ambient temperature before charging, to avoid sparks. This mixture is then hydrogenated at 45−55 psi until the hydrogen uptake is completed (6−10 h). The reaction mixture is filtered through a pad of Celite and diluted with MeOH (4.2 L), and (*S*)-mandelic acid (304 g, 2 mol) is added. The mixture is heated to reflux until a clear solution is formed. It is cooled to ambient temperature and stirred for 2−3 h. The crystals are filtered off and recrystallized twice from MeOH (c = 0.4 M) to give (*R*)-**3**-(*S*)-MA (100−110 g, 12−14%) as white crystals: mp = 164 °C; $[\alpha]^{20}_D$ = +21.5 (c = 1, MeOH); 99.0% ee; ^{1}H NMR (300 MHz, DMSO-d_6), δ(ppm): 7.16−7.46 (m, 10 H), 7.04 (d, 2 H, J = 8.7 Hz), 6.85 (d, 2 H, J = 8.7 Hz), 4.71 (s, 1 H), 4.08 (d, 1 H, J = 12.9 Hz), 4.01 (d, 1 H, J = 12.9 Hz) 3.72 (s, 3 H), 3.08 (m, 2H), 2.50 (m, 1 H + DMSO-d_6) 1.03 (d, 3 H, J = 6.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 175.0, 157.9, 142.8, 135.0, 130.2, 129.6, 129.4, 128.4, 128.0, 127.6, 126.5, 126.4, 113.8, 73.3, 55.0, 54.2, 48.1, 16.3. Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.69; H, 7.17; N, 3.44. Found: C, 73.35; H, 7.18; N, 3.36.

(*S*)-**3** is obtained by concentrating the mother liquor, extraction from NaOH/MTBE, and subsequent crystallization from MeOH using (*R*)-mandelic acid as described above.

The free base is obtained as an oil from NaOH/MTBE extraction. The racemic amine is obtained by concentration of the methanolic solution or precipitation as the hydrochloride.

(*R*)-2-Bromo-1-[4-(benzyloxy)-3-nitrophenyl]ethanol (5). A 2-L three-necked flask, equipped with a magnetic stir bar, a nitrogen inlet, and an internal temperature monitor, is charged with (1*R*,2*S*)-1-aminoindan-2-ol (2.5 g, 17 mmol, 5 mol %) and anhydrous THF (50 mL). During cooling with an ice bath, BH_3·Me_2S (10 M, 3.4 mL, 34 mmol) is slowly added at such a rate that the internal temperature remains below 20 °C. After the addition is complete and no more gas evolution is observed (10 min), a solution of bromo ketone **4** (120 g, 0.34 mol) in anhydrous THF (950 mL) and more BH_3·Me_2S (10 M, 24 mL, 0.24 mol, 0.7 equiv) are added simultaneously over a period of 3 h at 20−25 °C. Following this addition, the mixture is stirred for 15 min and cooled with an ice bath, and then MeOH (100 mL) is added (gas evolution!) at such a rate that the internal temperature remains below 20 °C. The reaction mixture is concentrated in vacuo (Me_2S is trapped and oxidized with household bleach) to a volume of 200 mL and the residue dissolved in toluene (650 mL). The solution is washed with H_2SO_4 (0.2 M, 100 mL) and water (100 mL), dried (Na_2SO_4), and concentrated to a weight of ca. 250 g. The product is crystallized by the addition of heptane (100 mL), filtered off, washed with 1:1 heptane/toluene, and dried to give (*R*)-**5** (100 g, 83%) as an off-white powder: mp = 69−70 °C; $[\alpha]^{20}_D$ = −17.7 (c = 1, EtOH); 94% ee; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.86 (d, 1H, J = 2 Hz), 7.4 (m, 6H), 7.10 (d, 1 H, J = 8.7 Hz), 5.20 (s, 2 H), 4.88 (dd, 1 H, J = 3.5, 8.4 Hz), 3.58 (dd, 1 H, J = 3.5, 10.8 Hz), 3.46 (dd, 1 H, J = 8.4, 10.8 Hz), 2.95 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 151.79, 139.85, 135.45, 133.34, 131.83, 128.82, 128.39, 127.07, 123.50, 115.34, 72.21, 71.30, 39.44. Anal. Calcd for $C_{15}H_{14}BrNO_4$: C, 51.16; H, 4.01; N, 3.98. Found: C, 51.32; H, 3.99; N, 3.99.

(*R*)-2-Bromo-1-[4-(benzyloxy)-3-(formylaminophenyl]-ethanol (9). A Parr hydrogenator is charged with PtO_2 (1 g) and a solution of **5** (100 g, 0.28 mol) in THF (200 mL) and toluene (200 mL). This mixture is then hydrogenated at 45−55 psi until the hydrogen uptake ceases (6−10 h). The reaction mixture is filtered through a pad of Celite, and a mixture of formic acid (21.5 g, 0.48 mol) and acetic anhydride (33 g, 0.32 mol) is added at such a rate that the internal temperature remains below 15 °C. After 20 min the reaction mixture is concentrated to 300 mL, while the product (*R*)-**9** crystallizes to give 75 g of white crystals (75%): mp = 131 °C; $[\alpha]^{20}_D$ = −25.3 (c = 1, $CHCl_3$); 98% ee; ^{1}H NMR (300 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 8.77 (d), 8.4 (dd), 8.35 (d), 8.19 (br s), 7.90 (m), 7.4 (m), 7.13 (m), 6.96 (m), 5.11 (m), 4.85 (m), 4.70 (m), 4.30 (d), 4.23 (d), 3.56 (m); ^{13}C NMR(75 MHz, $CDCl_3$) δ (ppm) 158.9, 147.0, 135.9, 133.5, 128.9, 128.7, 128.0, 127.8, 127.2, 121.7, 118.4, 111.5, 73.5, 71.1, 40.3. Anal. Calcd for $C_{16}H_{16}BrNO_3$: C, 54.87; H, 4.60; N, 4.00. Found: C, 54.82; H, 4.60; N, 3.96.

(*R*)-[4-(Benzyloxy)-3-(formamino)phenyl]oxirane (2). A 2-L three-necked flask, equipped with a mechanical stirrer, is charged with (*R*)-**9** (30 g, 86 mmol), K_2CO_3 (16 g, 0.11 mol), THF (175 mL), and MeOH (175 mL). This suspension is stirred at 25 °C for 1−2 h (monitored by TLC or HPLC)

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and then concentrated to remove MeOH and THF. The residue is partitioned between toluene (300 mL) and water (300 mL). The organic layer is separated, dried (Na_2SO_4), and concentrated to a volume of 100 mL. To this solution is slowly added heptane (50 mL), while the mixture is stirred mechanically. The product is filtered off and dried to give an off-white powder: mp = 67 °C; $[\alpha]^{20}_D = +3.9$ ($c = 1$, EtOH); 99% ee; ^{1}H NMR (300 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 8.80 (d), 8.35 (br d), 7.85 (br s), 7.40 (m), 7.0 (m), 5.14 (s, 2 H), 3.87 (m, 1 H), 3.15 (m, 1 H), 2.84 (m, 1 H). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.20; H, 5.61; N, 5.14. Found: C, 71.36; H, 5.61; N, 5.20.

(*R*,*R*)-Formoterol Fumarate (1). A 2-L three-necked flask equipped with a mechanical stirrer is charged with (*R*)-**9** (70 g, 0.2 mol), (*R*)-**3**-(*S*)-MA (76.5 g, 0.19 mol), fine powdered K_2CO_3 (70 g, 0.5 mol), THF (400 mL), and MeOH (400 mL). This suspension is stirred at 25 °C for 1−2 h (monitored by TLC or HPLC) and then concentrated to remove MeOH and THF. The residue is partitioned between toluene (600 mL) and water (600 mL). The organic layer is separated, dried (Na_2SO_4), and concentrated to a weight of ca. 110 g. This oily residue is then heated at 120 °C for 24 h to achieve the epoxide opening. The hot mixture is dissolved in EtOH (400 mL), cooled to 25 °C, and hydrogenated in a Parr apparatus at 45 psi in the presence of Pd/C (10% Pd, 50% wet, 10 g) until the hydrogen uptake is complete (2−3 h). The reaction mixture is filtered through a pad of Celite and washed with ^{i}PrOH (200 mL). Fumaric acid (10.8 g, 0.5 equiv) is added to the filtrate, and the mixture is heated to reflux, while being stirred with a mechanical stirrer. The clear solution is allowed to cool to 25 °C over 1 h and then stirred for another 2 h to complete the crystallization. The product is filtered off and dried to give (*R*,*R*)-formoterol fumarate (53.5 g, 70%) as white crystals: mp = 139 °C dec; $[\alpha]^{20}_D = -45.5$ ($c = 1$, H_2O); ee, de > 99.5%; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 9.64 (s), 9.35 (d), 8.55 (d), 8.29 (s), 8.15 (s), 7.14 (d, 2 H), 7.0 (m), 6.95 (d, 2 H), 6.51 (s, 1 H), 4.82 (m, 1 H), 3.72 (s, 3 H), 3.35 (m, 1 H), 3.10 (m, 3 H), 2.58 (m, 1 H), 2.50 (br s, 2 H), 1.06 (d, 3 H). Anal. Calcd for $C_{42}H_{52}N_4O_{12}$: C, 62.67; H, 6.51; N, 6.96. Found: C, 62.34; H, 6.57; N, 6.85.

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