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Application of the Chiral Acyl Anion Equivalent, *trans*-1,3-Dithiane 1,3-Dioxide, to an Asymmetric Synthesis of (*R*)-Salbutamol

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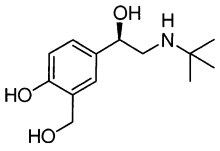
An enantioselective synthesis of (*R*)-salbutamol has been carried out using the chiral, C_2 symmetric acyl anion equivalent, (1*R*,3*R*)-1,3-dithiane 1,3-dioxide, which undergoes addition to an aromatic aldehyde with very high stereocontrol at 0 °C. Pummerer reaction and work-up with lithium ethanethiolate generated the α-hydroxy thiolester in high yield and further transformations led to the target compound with high enantiomeric excess.

Bronchial asthma is an inflammatory disease in which the calibre of the airways is chronically narrowed by oedema and is unstable.[1] The disease is widespread: about 150-million people worldwide currently suffer from asthma.[2]



(*R*)-Salbutamol

Although many pharmaceuticals are available for treatment of asthma, salbutamol (also called albuterol), which was introduced in the late 60's, remains an effective treatment. It is a β_2-adrenoceptor agonist, which produces bronchodilation via the production of cAMP which is presumed to affect calcium levels in the bronchial smooth muscle, causing relaxation.[1] Salbutamol was developed as a racemate, although β_2 agonist activity resides almost exclusively in the (*R*)-enantiomer.[3] The pure (*R*)-isomer, marketed as levalbuterol, was recently approved by the FDA for use in patients in a hospital setting, who often require higher doses of salbutamol.[4]

There are a range of arylethanolamines with potent β_2-adrenoceptor agonist activity (e.g., formoterol, terbutaline, and salmeterol) which have the same basic structure as salbutamol. The asymmetric synthesis of this class of compounds has been achieved by yeast[5] or CBS reduction[6] of iminoketones, azidoketones, or α-bromoketones, by hydrocyanation of an aldehyde,[7] or by chemical resolution.[8]

In this paper we describe the application of our chiral acyl anion equivalent, (1*R*,3*R*)-1,3-dithiane 1,3-dioxide,[9] to an asymmetric synthesis of (*R*)-salbutamol (Scheme 1).

Dithiane dioxide (+)-**1**[9a] was metalated with use of NaHMDS and reacted with aldehyde **2**[10] to give the adduct **3** as a single diastereomer. The relative stereochemistry was determined by X-ray analysis (see the Supporting Information). To obtain high diastereoselectivity it was critical to use the sodium counterion and to operate at 0 °C. These conditions led to rapid equilibration of the sodium alkoxides **4** and **5**, and resulted in high diastereocontrol. Low diastereocontrol was observed under kinetic conditions employing the lithium counterion at low temperature.[11]

Our rationale for the high diastereoselectivity observed is depicted in Scheme 2. Under equilibrating conditions, the thermodynamic stability of the two diastereomeric sodium alkoxides, which can chelate to either the equatorial or axial sulfoxide, need to be considered.[11] It is believed that the metal alkoxides which position the aryl

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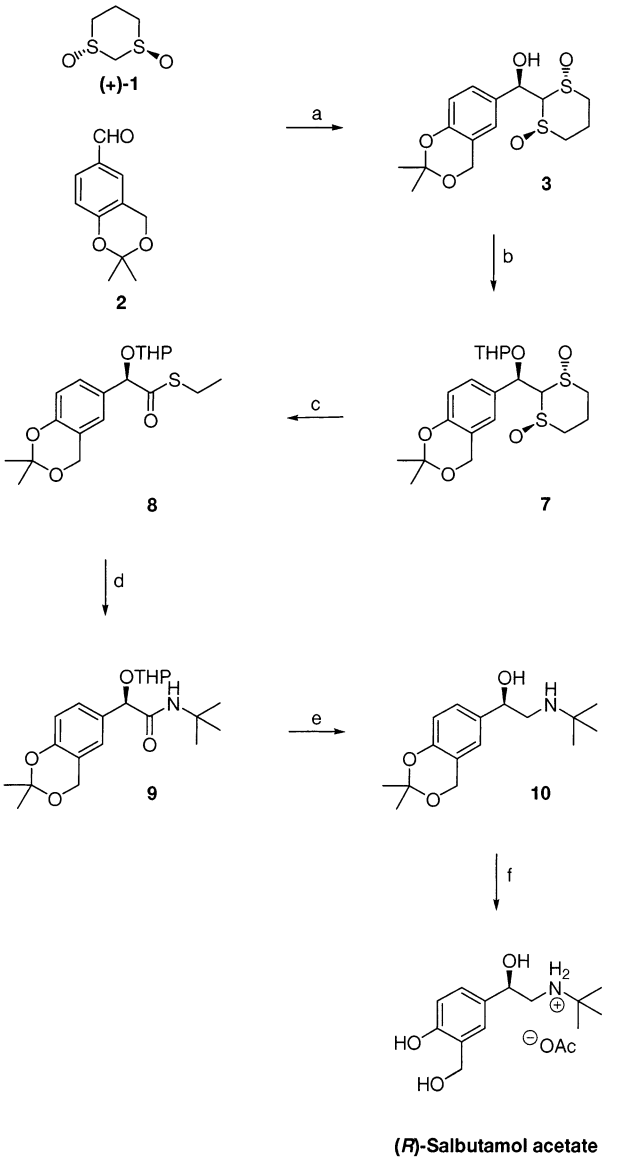
SCHEME 1. Synthesis of (*R*)-Salbutamol[a]

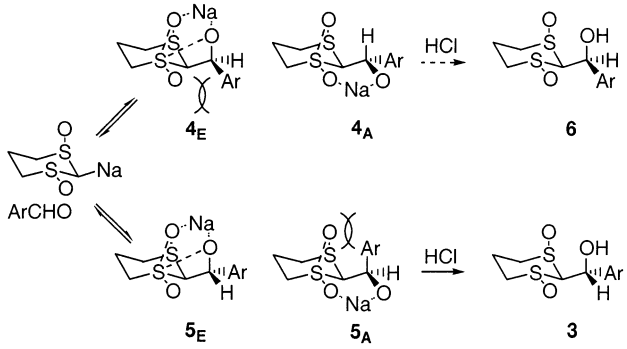


[a] Reagents and conditions: (a) (+)-**1** in Py/THF, NaHMDS, 0 °C, 30 min, then **2**, 0 °C, 2 h, 89%; (b) CH_2Cl_2, DHP, TsOH, 0 °C to rt, 4 h, 88%; (c) CH_2Cl_2, Py, TFAA, 0 °C, 15 min, then EtSH, THF/H_2O, LiOH/H_2O, 0 °C, 1 h then rt 2 h, 83%; (d) CH_3CN, $AgOCOCF_3$, *t*-$BuNH_2$, 40 °C, 4 days, 57%; (e) THF, $LiAlH_4$, 68 °C, 24 h, 37%; (f) AcOH/H_2O, 50 °C, 2 h, quantitative, 89% ee. DHP = 3,4-dihydro-2*H*-pyran, TFAA = trifluoroacetic anhydride

group parallel with the sulfoxide groups ($\mathbf{4_E}$, $\mathbf{5_A}$) are disfavored due to both steric and electronic repulsion (electron-rich sulfoxide and electron-rich aromatic ring).[11] That leaves $\mathbf{4_A}$ and $\mathbf{5_E}$, but we believe that $\mathbf{5_E}$ is favored as both the axial sulfinyl oxygen and alkoxide can stabilize the equatorial sulfoxide through electrostatic interaction. In contrast only one stabilizing interaction is possible with $\mathbf{4_A}$ and so **6** is the minor diastereomer formed. In this case very high diastereoselectivity was obtained and the minor diastereomer was not observed.

To obtain high yields it is necessary to quench the reaction rapidly by adding it to a vigorously stirring mixture of ethanol and aqueous HCl, otherwise significant amounts of starting material are obtained.[11] Following protection of the alcohol as the THP ether **7**,[12] the

SCHEME 2. Model for Diastereocontrol



dithiane dioxide was transformed into the ethyl thiolester **8** by a Pummerer reaction and exchange of thiolesters.[13] The thiolester was converted into the *tert*-butyl amide **9** under silver catalysis[13] and reduced to the amine **10** with $LiAlH_4$. We were surprised to observe concomitant release of the THP group during this step. Loss of the THP group occurred during the reduction and not upon work up of the reaction as evidenced by TLC analysis of the reaction mixture. Finally, mild hydrolysis of the acetonide[8c] gave (*R*)-salbutamol with high enantiomeric excess (89% ee).[14] The small reduction in the enantiomeric excess could arise either during the hydrolysis of the dithiane moiety which generates an easily epimerisable thiolester (base is present when it is formed) or during acid hydrolysis of the acetonide in the final step. Indeed the product salbutamol is known to racemise readily with acid.[7] However, analysis of the product from acid hydrolysis of **10** after a short reaction time (2 h) revealed that it possessed the same ee as the product obtained from prolonged hydrolysis (6 h), which implies that the small degree of racemization probably occurred in the step forming the thiolester **8**. This was confirmed by chiral HPLC analysis of amide **9**, which was found to have the same ee (89%) as the final product. A small degree of racemization had previously been observed during the hydrolysis of related substrates[13a] presumably because, as noted above, the thiolester **8** bearing an α-aryl group (which is especially sensitive to racemization) is generated in the presence of base.

In conclusion, we have extended our dithiane dioxide methodology to a short synthesis of (*R*)-salbutamol. Complete diastereocontrol was achieved in the key carbon−carbon bond-forming step although a small degree of racemization occurred during the hydrolysis of the auxiliary.

Experimental Section

Chemicals were purchased and used as delivered unless otherwise indicated. Dry tetrahydrofuran was obtained by distillation from sodium wire and benzophenone. Anhydrous CH_2Cl_2 and acetonitrile were obtained from a purification

(12) This was found to be the optimum protecting group but of course suffers from the disadvantage of carrying through a mixture of diastereomers at the acetal center.

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(14) Enantiomeric excess was determined by chiral HPLC (Chiralpak AD column using 92% heptane/8% EtOH/0.1% TFA as eluent at 0.5 mL/min, UV detection @ 215 nm).

column composed of activated alumina (A-2).[15] Dry pyridine was obtained by distillation from CaH_2 (after predrying by storage over KOH) and stored over activated molecular sieves. Dihydropyran was obtained, after partial drying with Na_2CO_3, by distillation from Na, until hydrogen was no longer evolved when fresh Na was added. *p*-Toluenesulfonic acid was recrystallized from ethyl acetate and dried under vacuum. Acetone was distilled prior to use as a chromatography eluent. Silica gel, grade 9385, 230−400 mesh, 60 Å was employed. (+)-*trans*-Dithiane dioxide **1**[9a] and the protected aldehyde **2**[10] were prepared as described in the literature.

2-[(1*R*)(2,2-Dimethyl(4*H*-benzo[3,4-*e*]1,3-dioxin-6-yl))-hydroxymethyl]-(1*R*,3*R*)-1,3-dithiane 1,3-Dioxide (3). (+)-*trans*-Dithiane dioxide **1** (1 g, 6.6 mmol) was dissolved in dry pyridine (50 mL) with warming and stirring under a nitrogen atmosphere and then the solution was diluted with THF (30 mL). The mixture was cooled to 0 °C and a solution of NaHMDS (8.6 mL of 1.0 M in THF, 8.6 mmol) was added. After 0.5 h at 0 °C, **2** (1.9 g, 9.7 mmol) was added neat, and the mixture was stirred for a further 2 h at 0 °C to give a clear pale yellow homogeneous solution. The reaction was quenched rapidly by adding it to a vigorously stirred 10% solution of 2.0 M HCl in EtOH (80 mL) that had been precooled. The solvents were evaporated under reduced pressure and the residue was taken up in MeOH and preadsorbed on silica gel. Flash chromatography on silica gel (acetone/EtOH 100:0 → 90:10) gave a single diastereoisomer of the alcohol **3** as a white solid (2.0 g, 89%). R_f 0.37 (10% EtOH/acetone), mp 156 °C dec (MeOH); ν_{max} (KBr) 3266, 2991 cm^{-1}; δ_H (270 MHz, DMSO-d_6) 1.46 (6H, s), 2.17−2.26 (1H, m), 2.52−2.61 (1H, m), 2.73−2.98 (2H, m), 3.05 (1H, ddd, J = 14.9, 13.0, 3.0 Hz), 3.48−3.57 (1H, m), 4.09 (1H, d, J = 4.3 Hz), 4.78 (1H, d, J = 15.5 Hz), 4.87 (1H, d, J = 15.5 Hz), 5.40 (1H, dd, J = 5.0, 4.3 Hz), 6.00 (1H, d, J = 5.0 Hz), 6.81 (1H, d, J = 8.5 Hz), 7.16 (1H, br s), 7.22 (1H, dd, J = 8.5, 2.0 Hz); δ_C (68 MHz, DMSO-d_6) 15.6, 25.2, 46.3, 51.4, 60.8, 68.0, 79.5, 99.9, 116.8, 119.7, 123.8, 126.8, 133.7, 150.7; MS *m*/*z* (EI) 344 (M^+, 12%), 268 (20), 192 (41), 134 (100); HRMS *m*/*z* (EI) calcd for $C_{15}H_{20}O_5S_2$, $[M]^+$ 344.0753, found 344.0753.

2-[(1*R*)(2,2-Dimethyl(4*H*-benzo[3,4-*e*]1,3-dioxin-6-yl))-perhydro-2*H*-pyran-2-yloxymethyl]-(1*R*,3*R*)-1,3-dithiane 1,3-Dioxide (7). 3 (1.5 g, 4.4 mmol) was suspended in dry CH_2Cl_2 (40 mL) under a nitrogen atmosphere and cooled to 0 °C. 3,4-Dihydropyran (2.1 mL, 1.9 g, 22.8 mmol) and *p*-toluenesulfonic acid (35 mg, 0.18 mmol) were added and stirred while warming to room temperature over 4 h. The reaction mixture was poured into aqueous saturated $NaHCO_3$ solution (60 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed with brine (40 mL) and dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using neat acetone as eluent to give **7** as a colorless solid (1.7 g, 88%) and a mixture of diastereomers. R_f 0.35 (acetone), mp 155 °C dec; ν_{max} (KBr) 2940, 1266 cm^{-1}; δ_H (400 MHz, $CDCl_3$) (1:2 mixture of diastereomers) 1.54 (6H, s), 1.56−2.00 (5.6H, m), 2.30−2.45 (1H, m), 2.60−2.75 (1H, m), 2.85−2.98 (2H, m), 3.10−3.23 (1H, m), 3.37 (0.6H, d, J = 4.9 Hz), 3.41 (0.3H, d, J = 4.9 Hz), 3.50−3.74 (2.6H, m), 4.18 (0.6H, ddd, J = 13.7, 10.7, 3.9 Hz), 4.66 (0.6H, br t, J = 3.0), 4.84 (1H, s), 4.85 (1H, s), 5.10 (0.3 H, br t, J = 3.0 Hz), 5.50 (0.3H, d, J = 5.0 Hz), 5.56 (0.6H, d, J = 5.0 Hz), 6.83 (0.35, d, J = 8.3 Hz), 6.85 (0.5H, d, J = 8.3 Hz), 7.08 (0.6H, br s), 7.15 (0.3H, br s), 7.27 (0.6H, br d, J = 8.3 Hz), 7.30 (0.3H, dd, J = 8.3, 1.5 Hz); δ_C (100 MHz, $CDCl_3$) (diastereomeric signals) 13.9, 14.0, 18.3, 18.9, 24.7, 24.8, 24.9, 25.2, 25.4, 29.9, 30.1, 45.4, 45.5, 50.6, 50.8, 60.8, 60.9, 61.6, 62.4, 70.4, 72.6, 80.9, 81.8, 94.0, 99.8, 99.9, 100.0, 117.4, 117.7, 119.5, 119.8, 123.4, 124.4, 126.7, 127.5, 128.2, 130.8, 151.0, 151.7; MS *m*/*z* (FAB) 429 (M + 1, 60%), 345 (62), 327 (100); HRMS *m*/*z* (EI) calcd for $C_{20}H_{28}O_6S_2$ $[M]^+$ 428.1327, found 428.1318.

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(2*R*)-2-(2,2-Dimethyl(4*H*-benzo[3,4-*e*]1,3-dioxin-6-yl))-1-ethylthio-2-perhydro-2*H*-pyran-2-yloxyethan-1-one (8). To a stirred solution of **7** (1.2 g, 2.9 mmol) in dry CH_2Cl_2 (30 mL) and dry THF (30 mL) at 0 °C under a nitrogen atmosphere were successively added dry pyridine (0.93 mL, 907 mg, 11.6 mmol) and trifluoroacetic anhydride (0.50 mL, 735 mg, 3.5 mmol). The mixture was stirred for 15 min before ethanethiol (2.16 mL, 1.8 g, 29 mmol), ca. 3% aqueous THF (31 mL) and lithium hydroxide monohydrate (657 mg, 15.4 mmol) were added sequentially at 0 °C. The resulting heterogeneous solution was stirred to 0 °C for 1 h and at room temperature for 2 h then the resulting pale brown solution was diluted with CH_2Cl_2 (50 mL) and water (50 mL). The layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), and evaporated. The crude product was purified by flash chromatography on silica gel using 10% EtOAc/petrol as eluent to afford **8** as a colorless oil (880 mg, 83%) and a mixture of diastereoisomers. R_f 0.60 (20% EtOAc/petrol); ν_{max} (film) 2941, 1683 cm^{-1}; δ_H (400 MHz, $CDCl_3$) (1:2 mixture of diastereomers) 1.22 (1.5H, t, J = 1.5 Hz), 1.24 (1.5H, t, J = 1.5 Hz), 1.53 (6H, s), 1.55−2.05 (6H, m), 2.82 (1H, q, J = 7.0 Hz), 2.84 (1H, q, J = 7.0 Hz), 3.42−3.48 (0.3H, m), 3.52−3.58 (0.6H, m), 3.62−3.70 (0.3H, m), 3.92−4.02 (0.6H, m), 4.63 (0.6H, br t, J = 7.0 Hz), 4.81 (1H, d, J = 10.3 Hz), 4.85 (1H, d, J = 10.3 Hz), 4.87 (0.3H, br t, J = 7.0 Hz), 5.14 (0.6H, s), 5.18 (0.3H, s), 6.8 (1H, d, J = 8.4), 7.01 (0.6H, d, J = 1.8 Hz), 7.09 (0.3H, d, J = 1.8 Hz), 7.20 (0.6 Hz, dd, J = 8.4, 1.8), 7.28 (0.3H, dd, J = 8.4, 1.8 Hz); δ_C (100 MHz, $CDCl_3$) (diastereomeric signals) 14.4, 18.5, 18.8, 22.7, 23.3, 24.6, 24.7, 24.9, 25.2, 25.4, 26.8, 28.8, 30.0, 30.1, 32.7, 36.9, 60.8, 60.9, 61.9, 62.2, 67.8, 79.5, 81.3, 81.8, 95.0, 98.2, 99.6, 99.7, 117.1, 117.3, 117.4, 119.3, 119.4, 119.7, 123.2, 123.5, 124.2, 126.8, 127.1, 127.4, 128.3, 129.0, 151.3, 151.6, 200.6, 202.1; MS *m*/*z* (CI) 384 ($M^+ + NH_4$, 29%), 277 (6), 242 (100), 193 (48), 85 (43); HRMS *m*/*z* (CI) calcd for $C_{19}H_{26}O_5S$ $[MH^+ - H_2]$ 365.1422, found 365.1422.

(2*R*)-2-(2,2-Dimethyl(4*H*-benzo[3,4-*e*]1,3-dioxin-6-yl))-*N*-(*tert*-butyl)-2-perhydro-2*H*-pyran-2-yloxyacetamide (9). Silver trifluoroacetate (1.9 g, 8.6 mmol) was added to a solution of **8** (570 mg, 1.6 mmol) and *tert*-butylamine (0.66 mL, 460 mg, 6.3 mmol) in dry CH_3CN (20 mL) and the mixture stirred to 40 °C for 4 days under a nitrogen atmosphere. The solvent was evaporated under reduced pressure and the mixture was directly charged onto a silica gel column. Elution with (EtOAc/petrol 15:85 → 50:50) afforded pure *amide* **9** as a colorless viscous oil (336 mg, 57%) and a mixture of diastereoisomers. R_f 0.61 (40% EtOAc/petrol); ν_{max} (film) 3414, 1682 cm^{-1}; δ_H (400 MHz; $CDCl_3$) (1:2 mixture of diastereomers) 1.36 (3H, s), 1.38 (6H, s), 1.53 (6H, s), 1.6−1.8 (6H, m), 3.38−3.90 (2H, m), 4.48 (0.6H, br t, J = 3.0 Hz), 4.75 (0.3H, br t, J = 3.0 Hz), 4.83 (2H, s), 4.94 (0.6H, s), 4.95 (0.3H, s), 6.47 (1H, br s), 6.79 (1H, d, J = 8.3 Hz), 6.98 (0.6H, d, J = 2.0 Hz), 7.05 (0.3H, d, J = 2.0 Hz), 7.13 (0.6H, dd, J = 8.3, 2.0 Hz), 7.24 (0.3H, dd, J = 8.3, 2.0 Hz); δ_C (100 MHz, $CDCl_3$) (diastereomeric signals) 14.2, 19.2, 19.6, 21.0, 24.7, 24.9, 25.0, 25.3, 28.8, 30.4, 30.8, 50.8, 50.9, 60.2, 60.4, 60.9, 62.6, 62.8, 78.6, 95.7, 98.2, 99.6, 99.6, 117.1, 117.2, 117.2, 119.2, 123.5, 124.6, 126.6, 127.1, 151.1, 151.3 169.9, 170.4; MS *m*/*z* (EI) 377 (M^+, 16%), 277 (21), 193 (59), 85 (100); HRMS *m*/*z* (EI) calcd for $C_{21}H_{31}O_5N$ $[M]^+$ 377.2202, found 377.2201.

***(R)*-2-(*N*-*tert*-Butylamino)-1-(2,2-dimethyl-4*H*-benzo-[3,4-*e*]1,3-dioxin-6-yl)ethanol (10).** To a stirred suspension of lithium aluminum hydride (133 mg, 3.5 mmol) in 2.5 mL of dry THF at 0 °C was added a solution of **9** (290 mg, 0.77 mmol) in 2.5 mL of dry THF. The mixture was stirred at 20 °C for 1 h and refluxed overnight under a nitrogen atmosphere. After the mixture was cooled, it was diluted with Et_2O (15 mL) and then water (0.13 mL), 15% NaOH (0.13 mL), and water again (3 × 0.13 mL) were added and the reaction mixture was stirred for 45 min. After the addition of more Et_2O (25 mL), stirring was continued for an additional 30 min. The solid precipitate was removed by filtration and washed with Et_2O. The com-

bined organic phases were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The mixture was purified by flash chromatography on silica gel (EtOAc/petrol/triethylamine 50%:45%:5% → 50%:30%:20%) affording **10** as colorless crystals (79 mg, 37% yield). R_f 0.14 (EtOAc/petrol/triethylamine 50%:45%:5%); δ_H (400 MHz, $CDCl_3$) 1.11 (s, 9 H), 1.53 (3H, s), 1.54 (3H, s), 2.55 (1H, dd, J = 11.7, 9.2 Hz), 2.87 (1H, dd, J = 11.7, 3.5 Hz), 4.49 (1H, dd, J = 9.2, 3.5 Hz), 4.85 (2H, s), 6.79 (1H, d, J = 8.4 Hz), 7.02 (1H, br s), 7.13 (1H, dd, J = 8.4, 1.8 Hz); δ_C (100 MHz, $CDCl_3$) 24.7, 25.0, 29.3, 50.3, 50.4, 61.1, 72.1, 99.5, 117.0, 119.4, 122.1 125.8, 134.8, 150.6. These data are consistent with the literature.[8c]

(*R*)-Salbutamol Acetate. Glacial acetic acid (0.16 mL, 2.9 mmol) was added to a mixture of **10** (35 mg, 0.13 mmol) in H_2O (0.16 mL, 0.16 g, 8.8 mmol). The resulting solution was stirred to 50 °C for 2 h. The solvents were evaporated under reduced pressure to leave a colorless sticky oil that was taken up in absolute ethanol. After evaporation, the procedure was repeated twice more to afford (*R*)-salbutamol acetate (quantitative, 89% ee[14]), $[\alpha]^{22}_D$ −29.8 (*c* 0.15 methanol), 97% ee, $[\alpha]_D$ − 37.9 (*c* 0.5 methanol).[8c] R_f 0.07 (10% EtOH/acetone); δ_H (400 MHz; DMSO-d_6) 1.02 (3H, t), 1.09 (9H, s), 1.83 (3H, s), 2.64 (1H, dd, J = 11.7, 9.5 Hz), 2.67 (1H, dd, J = 11.7, 3.3 Hz), 3.43 (2H, q), 4.45 (2H, s), 4.53 (1H, dd, J = 9.5, 3.3 Hz), 6.70 (1H, d, J = 8.4 Hz), 7.00 (1H, dd, J = 8.4, 2.2 Hz), 7.27 (1H, d, J = 2.2 Hz); δ_C (100 MHz, DMSO-d_6) 19.1, 23.0, 27.6, 50.2, 53.1, 56.6, 58.9, 71.1, 114.7, 125.4, 125.7, 128.6, 134.1, 153.9, 173.0. These data are consistent with the literature.[8c]

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Supporting Information Available: Copies of ^{1}H NMR spectra for compounds **3**, **7**−**10**, and salbutamol acetate, and X-ray data for **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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