CHEMOENZYMATIC DYNAMIC KINETIC RESOLUTION AS A KEY STEP IN THE ENANTIOSELECTIVE SYNTHESIS OF (*S*)-SALBUTAMOL

Annika Träff[a1], Carmen E. Solarte[b] and Jan-E. Bäckvall[a2],*

[a] *Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, 106 91 Stockholm, Sweden; e-mail: [1] annika@organ.su.se, [2] jeb@organ.su.se*

[b] *Deparment of Chemistry, Lleida University, 25198 Lleida, Spain; e-mail: solarte@quimica.udl.cat*

Dedicated to Professor Pavel Kočovský on the occasion of his 60th birthday.

The synthesis of (*S*)-salbutamol is described. By utilizing DKR in the enantiodetermining step, employing *Burkholderia cepacia* lipase (PS-IM), (*S*)-acetate ((*S*)-**6**) was obtained in excellent enantiomeric excess (98%). The subsequent transformations yielded the salt of (*S*)-salbutamol with retained stereochemistry.

Keywords: Dynamic kinetic resolution; Kinetic resolution; Enzymatic catalysis; Racemization; Asymmetric synthesis.

Asthma is a chronic disease of the airway that affects 300 million people of all ages worldwide. Treatment options include reliever and controller medication[1]. β_2-Agonist drugs are the most commonly used bronchodilators applied in treatment of bronchospasm[2]. Salbutamol is a relatively selective inhaled short-acting β_2-adrenoreceptor agonist (SABAs) with rapid relief[1,3]. It is a chiral drug that is commonly used as a racemic mixture. Studies have shown that the (*R*)-enantiomer of salbutamol (levosalbutamol) is the therapeutically active isomer and it has been available on the international market since the last few years. Until recently (*S*)-salbutamol was considered inert, but recent studies have shown that the (*S*)-enantiomer may rather have some deleterious effects[2]. However, most of the published studies were supported by pharmaceutical companies involved in production or marketing of levosalbutamol. Therefore large multicenter trials are required to prove the therapeutic superiority of levosalbutamol over racemic salbutamol[2]. This, together with the requirement from the FDA that each single enantiomer of a potential drug must be characterized for their individual

physiological action[4], has increased the demand for efficient preparation of both enantiomers with high degree of purity. Today, separating enantiomers through resolution of a racemic mixture is the most commonly used technique in industry[5]. This process suffers from two major disadvantages being (i) the limitation of 50% maximum yield and (ii) the separation of the product from the remaining starting material[6]. In dynamic kinetic resolution the non-desired enantiomer is continuously racemized during resolution and thereby the limitation of a normal kinetic resolution is overcome. In a chemoenzymatic DKR a transition metal-catalyzed racemization reaction is coupled with enzymatic kinetic resolution to give the enantiomerically pure product in 100% theoretical yield (Fig. 1)[7].
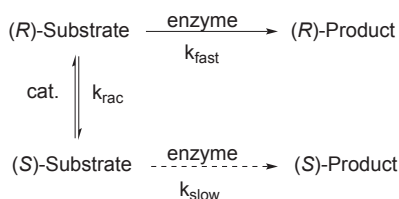

Fig. 1
Schematic picture of dynamic kinetic resolution

In 2004, we reported on a new efficient racemization catalyst, ruthenium complex **1**, which gives fast and efficient reactions at room temperature and has been applied in several DKR processes (Fig. 2)[8].
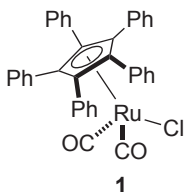

Fig. 2
Ruthenium complex employed as efficient racemization catalyst

Salbutamol belongs to the family of arylethanolamines, with potent β_2-adrenoceptor agonist activity, which all have the same basic structure. Asymmetric synthesis of arylethanolamine can be achieved by CBS reduction[9], enzymatic reduction[10], asymmetric transfer hydrogenation[11], or chemical resolution[12] to mention a few techniques. Herein we report on the total synthesis of (S)-salbutamol where we apply chemoenzymatic DKR

of a chlorohydrin to give a key intermediate in high *ee* from simple starting materials (Scheme 1).
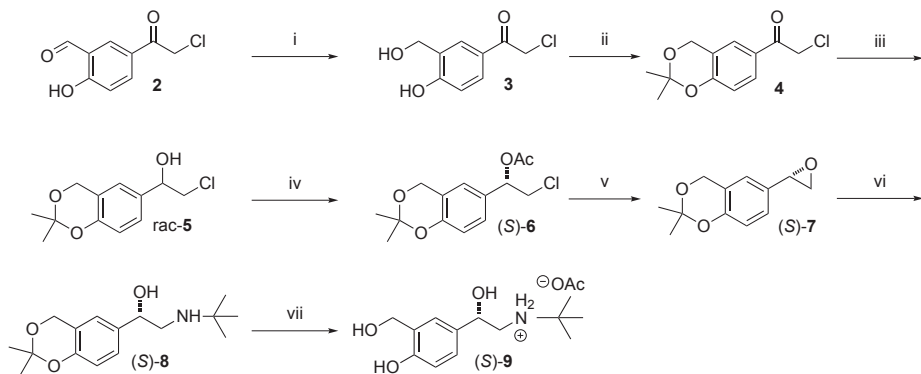
SCHEME 1

Reagents and conditions: i: NaBH$_4$, HOAc, r.t., 88%. ii: CH$_3$C(OCH$_3$)$_2$CH$_3$, PTSA, CH$_2$Cl$_2$, r.t., 85%. iii: NaBH$_4$, MeOH, r.t., 64%. iv: Ru(CO)$_2$Cl(η^5C$_5$Ph$_5$) (1), PS-IM, Na$_2$CO$_3$, toluene, *t*-BuOK, isopropenyl acetate, 40 °C, 98% *ee*, 69%. v: LiOH, EtOH, NaHCO$_3$, r.t., 98% *ee*, quantitative. vi: *t*-BuNH$_2$, 70 °C, 65 %. vii: AcOH, H$_2$O, 50 °C, quantitative

RESULTS AND DISCUSSION

The synthesis starts with Friedel-Crafts acylation of readily available salicylaldehyde in the presence of aluminium trichloride to give **2** following a published procedure[13]. Regioselective NaBH$_4$ reduction of **2** in acetic acid afforded α-chloroketone **3** in 88% yield[14]. Protection of the hydroxy groups by ketal formation with 2,2-dimethoxypropane followed by NaBH$_4$ reduction of ketone **4** gave the desired β-chloroalcohol, **5**, in 55% yield over two steps. Attempts to reduce the aldehyde and ketone in the same step gave a mixture of compounds and even though the synthesis applied has one additional step it was found to be more efficient.

Previously our group has shown that DKR can be successfully carried out on a wide range of β-chlorohydrine derivatives[15]. Screening of different enzymes to investigate the selectivity towards β-chloroalcohol **5** was done (Table I).

Burkholderia cepacia lipase (previously *Pseudomonas cepacia* lipase) has previously been shown to have an excellent enantioselectivity for β-chlorohydrines and shows the same result in this study. PS-IM (*Burkholderia cepacia* lipase immobilized on diatomaceous earth) as well as PS-C1 (*Burkholderia cepacia* lipase immobilized on ceramic particles) showed excellent selectivity, with an *E*-value above 200, as well as good activity (entries

1 and 3). CALB (*Candida antarctica* lipase B immobilized on acrylic resin, Novozyme 435®) and AH-SD showed good selectivity but rather low activity (entries 2 and 4). Lipase AK (*Pseudomonas fluorescens* lipase) showed moderate selectivity and activity (entry 5) while lipase TL (*Thermomyces lanuginosus* lipase) showed the highest activity of the enzymes investigated with good selectivity as well (entry 6). Lipase AYS and F-AP-15 did not show any activity at all (entries 7 and 8). PS-IM (*Burkholderia cepacia* lipase) was employed for the enantioselective resolution in the DKR. However, it was noticed that, while the racemization was still active giving a 1:1 ratio of the (*R*)- and (*S*)-alcohol (**5**), the DKR was very slow showing only 73% ^{1}H NMR yield of the (*S*)-acetate (**6**; 99% *ee*) after 24 h. It was also observed that the substrate was difficult to dissolve in toluene. By optimizing the conditions by increasing the amount of enzyme and acyl donor and diluting the reaction, the DKR was successfully run at 40 °C and gave full conversion within 48 h with (*S*)-**6** isolated in 69% yield and 98% *ee*. Ring-closing formation of the epoxide was performed by treating the acetate with LiOH in EtOH. Care

TABLE I
Investigating the selectivity of different enzymes in kinetic resolution of β-chloro alcohol **5**^{a}
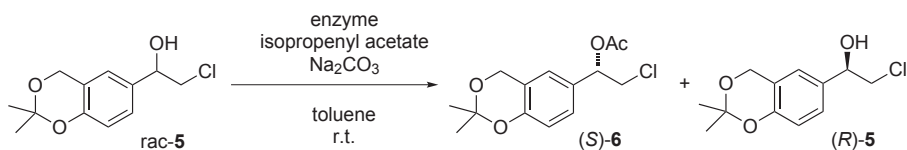
Entry	Enzyme	Time h	conv (**5**)^b %	% ee (*R*)-**5**^{c}	% ee (*S*)-**6**^{c}	E^b
1	PS-IM	3	21	26	>99	>200
2	AH SD	24	10	11	>99	>200
3	PS-C1	3	14	16	>99	>200
4	CALB	24	34	50	>99	>200
5	Lipase AK	24	23	28	95	51
6	Lipase TL	1	40	64	98	192
7	Lipase AYS	24	1	–	–	–
8	Lipase F-AP-15	24	1	–	–	–

^{a} 0.1 mmol **5**, 0.1 mmol Na$_2$CO$_3$, 5 mg enzyme (50 mg/mmol), 0.2 ml toluene, 0.2 mmol isopropenyl acetate. ^{b} Calculated values. ^{c} Measured by chiral GC.

was taken so that the hydroxyether or the diol was not formed. By carefully monitoring the reaction the epoxide was obtained in quantitative yield with retained stereochemistry (98% *ee*). The epoxide was then opened with *tert*-butyl amine. The desired regioisomer was the major one with a selectivity of ~85:15 between (S)-**8** and *iso*-**8**, and the product, (S)-**8**, was isolated in 65% yield. The final step of deprotection in acetic acid/water yielded the acetate salt of (S)-salbutamol in quantitative yield[16].

CONCLUSION

We have here reported an efficient and straightforward synthesis of (S)-salbutamol. By employing DKR in the enantiodetermining step with PS-IM (*Burkholderia cepacia* lipase immobilized on diatomaceous earth) as an enantioselective catalyst and ruthenium catalyst **1** for racemization the limitation of a normal KR was circumvented. By optimizing the conditions, DKR was run to completion within 48 h yielding (S)-**6** in 98% *ee*. The following synthetic alterations yielded the salt of (S)-salbutamol, in 21% overall yield over 7 steps, with retained enantiomeric excess[16].

EXPERIMENTAL

DKR reactions were carried out under dry argon atmosphere using standard Schlenk technique. The β-chloroalcohol **5** was dried over MS (4Å) before used in DKR. Isopropenyl acetate was dried over $CaCl_2$ and distilled before use. Dry THF and toluene were obtained from VAC solvent purifier provided by the Vacuum Atmosphere co. Dry DCM was obtained by distilling it over $CaCl_2$. All other chemicals and solvents were used as purchased. The enantiomeric excess of the compounds was determined by chiral GC/HPLC using racemic compounds as references. Racemic acetate **6** was obtained from the alcohol **5** by standard acylation. Silica column chromatography was performed with Davisil chromatographic silica media for separation and purification applications (35–70 micron).

GC samples were run on GC Varian 3800 with an auto sampler equipped with a CP_Chirasil_Dex CB column (25 m × 0.32 mm × 0.25 μm), carrier gas H_2, flow 1.8 ml min^{-1}. HPLC samples were run on HPLC Waters 2695 equipped with a Waters 996 Photodiode Array detector. ^1H and ^{13}C NMR (δ in ppm; *J* in Hz) were recorded with Bruker 400 or Bruker 500. Optical rotation (10^{-1} deg cm^2 g^{-1}) was measured with a Perkin–Elmer 241 polarimeter equipped with a Na-lamp. HR-MS was recorded with Bruker MicroTOF ESI. $Ru(CO)_2Cl(\eta^5C_5Ph_5)$ (**1**)[8b] and 5-(chloroacetyl)-2-hydroxybenzaldehyde (**2**)[13] were synthesized according to literature procedures.

Synthesis of 2-Chloro-1-(4-hydroxy-3-(hydroxymethyl)phenyl)ethanone (**3**)

Sodium borohydride (294 mg, 7.8 mmol) was added portionwise to a solution of 5-(chloroacetyl)-2-hydroxybenzaldehyde **2** (1.50 g, 7.5 mmol) in acetic acid (38 ml) stirred at 5 °C (ice/water bath) under argon. The mixture was brought to room temperature and the

stirring was continued until the reaction was complete. After the reaction was complete water (40 ml) was added and the mixture was neutralized with a saturated solution of Na_2CO_3. The mixture was extracted with ethyl acetate (4 × 50 ml). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated to give a light red oil that turned solid upon standing. The crude was purified by column chromatography (silica gel, pentane–ethyl acetate, gradient from 9:1 to 2:8) and afforded a light pink solid product (1.33 g, 6.6 mmol, 88% yield). ^{1}H NMR (400 MHz, DMSO-d_6): 10.53 s, 1 H (OH); 7.97 d, 1 H, J = 2.0 (Ar-H); 7.76 dd, 1 H, J = 8.4, 2.4 (Ar-H); 6.87 d, 1 H, J = 8.4 (Ar-H); 5.15 br s, 1 H (OH); 5.04 s, 2 H (CH$_2$OH); 4.50 s, 2 H (CH$_2$Cl). ^{13}C NMR (125 MHz, DMSO-d_6): 190.3, 159.9, 129.7, 129.6, 128.5, 126.0, 114.8, 58.2, 47.5. HR-MS (ESI): calculated for $C_9H_8ClO_3^-$: 199.0167; found [M – H]$^-$: 199.0163.

Synthesis of 2-Chloro-1-(2,2-dimethyl-4*H*-benzo[1,3]dioxin-6-yl)ethanone (**4**)

To a suspension of 2-chloro-1-(4-hydroxy-3-(hydroxymethyl)phenyl)ethanone (**3**) (1.33 g, 6.6 mmol) and *p*-toluenesulfonic acid (0.0061 g, 0.035 mmol) in 33 ml of dichloromethane was added dropwise 2,2-dimethoxypropane (0.763 g, 7.3 mmol) in dichloromethane (17 ml). The suspension was stirred vigorously until it became homogeneous (light yellow). The reaction mixture was washed with saturated NaHCO$_3$ solution. The organic phase was separated and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give **4** as a yellow oil (1.35 g, 5.6 mmol, 85% yield). ^{1}H NMR (400 MHz, CDCl$_3$): 7.79 dd, 1 H, J = 8.6, 2.2 (Ar-H); 7.68 d, 1 H, J = 2.0 (Ar-H); 6.88 d, 1 H, J = 8.8 (Ar-H); 4.89 s, 2 H (CH$_2$O); 4.63 s, 2 H (CH$_2$Cl); 1.57 s, 6 H (C(CH$_3$)$_2$). ^{13}C NMR (100 MHz, CDCl$_3$): 189.7, 156.4, 129.2, 126.7, 126.2, 119.6, 117.4, 100.8, 60.6, 45.5, 24.8. HR-MS (ESI): calculated for $C_{12}H_{13}ClNaO_3^+$: 263.0445; found [M + Na]$^+$: 263.0445.

Synthesis of 2-Chloro-1-(2,2-dimethyl-4*H*-benzo[1,3]dioxin-6-yl)ethanol (**5**)

2-Chloro-1-(2,2-dimethyl-4*H*-benzo[1,3]dioxin-6-yl)ethanone (**4**) (1.35 g, 5.6 mmol) was dissolved in MeOH (34 ml). The solution was cooled to 0 °C then NaBH$_4$ (0.148 g, 3.9 mmol) was added in small portions. Stirring was continued for 30 min at 0 °C, after which the temperature of the reaction mixture was allowed to reach room temperature and stirring was continued. After 3 h the reaction was completed and the solvent was evaporated. Saturated NH$_4$Cl (aq.) solution (25 ml) was added after which the aqueous phase was extracted with ethyl acetate (4 × 25 ml). The organic portions were combined and washed with water (1 × 75 ml) and brine (1 × 75 ml). The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by flash column chromatography (silica gel, pentane–ethyl acetate, 9:1) to give a colorless oil (87 mg, 3.6 mmol, 64% yield). ^{1}H NMR (400 MHz, CDCl$_3$): 7.16 dd, 1 H, J = 8.4, 1.7 (Ar-H); 7.03 d, 1 H, J = 1.5 (Ar-H); 6.82 d, 1 H, J = 8.4 (Ar-H); 4.84 s, 2 H (CH$_2$O); 4.84–4.80 m, 1 H (C**H**CH$_2$); 3.70 dd, 1 H, J = 11.2, 3.4 (CHC**H**$_2$); 3.60 dd, 1 H, J = 11.2, 9.0 (CHC**H**$_2$); 2.60 d, 1 H, J = 2.8 (OH); 1.54 s, 3 H (C(CH$_3$)$_2$); 1.53 s, 3 H (C(CH$_3$)$_2$). ^{13}C NMR (100 MHz, CDCl$_3$): 151.4, 131.7, 126.0, 122.4, 119.6, 117.3, 99.7, 73.7, 60.9, 51.0, 24.8, 24.6. HR-MS (ESI): calculated for $C_{12}H_{15}ClNaO_3^+$: 265.0602; found [M + Na]$^+$: 265.0591.

General procedure for KR of 2-chloro-1-(2,2-dimethyl-4H-benzo[1,3]dioxin-6-yl)ethanol (**5**): Enzyme (5 mg, 50 mg/mmol of **5**) and Na$_2$CO$_3$ (10.6 mg, 0.1 mmol) was added to a μW-vial. 2-Chloro-1-(2,2-dimethyl-4H-benzo[1,3]dioxin-6-yl)ethanol (24.27 mg, 0.1 mmol) dissolved in dry toluene (0.2 ml) was added to the vial, and stirred. After a few min isopropenyl ace-

tate (22 μl, 0.2 mmol) was added to the reaction. Samples for GC analysis were collected with a syringe after 1, 3 and 24 h. GC gradient 110 °C, 0 min; 15 °C/min to 150 °C, 5 min; 2 °C/min to 200 °C, 2 min. t_{R1} = 19.4 min ((*R*)-**6**); t_{R2} = 19.7 min ((*S*)-**6**); t_{R3} = 20.6 min ((*S*)-**5**); t_{R4} = 21.0 min ((*R*)-**5**).

Synthesis of (*S*)-2-Chloro-1-(2,2-dimethyl-4*H*-benzo[1,3]dioxin-6-yl)ethyl Acetate ((*S*)-**6**)

Complex **1** (16 mg, 0,025 mmol), PS-IM (50 mg; 100 mg/mmol substrate) and Na$_2$CO$_3$ (53 mg, 0.5 mmol) were added to a Schlenk-tube. Dry toluene (0.5 ml) was added and the resulting yellow solution was stirred. *t*-BuOK (60 μl, 0.030 mmol, 0.5 M in dry THF) was added to the reaction. The reaction turned orange-brown. After approximately 5 min of stirring, 2-chloro-1-(2,2-dimethyl-4*H*-benzo[1,3]dioxin-6-yl)ethanol (**5**) (121 mg, 0.5 mmol) dissolved in dry toluene (1.0 ml) was added to the reaction mixture. After an additional 5 min isopropenyl acetate (165 μl, 1.5 mmol) was added. The reaction was heated to 40 °C. After 48 h the reaction mixture was filtered and concentrated. Purification by column chromatography (silica gel, pentane–EtO$_2$, 8:2) afforded (*S*)-2-chloro-1-(2,2-dimethyl-4*H*-benzo[1,3]-dioxin-6-yl)ethyl acetate ((*S*)-**6**) in 69% yield (99 mg, 0.35 mmol) with 98% *ee* (determined by chiral GC). ^{1}H NMR (400 MHz, CDCl$_3$): 7.14 dd, 1 H, *J* = 8.6, 2.2 (Ar-H); 6.97 d, 1 H, *J* = 2.0 (Ar-H); 6.80 d, 1 H, *J* = 8.4 (Ar-H); 5.86 dd, 1 H, *J* = 8.2, 4.6 (C**H**CH$_2$); 4.83 s, 2 H (CH$_2$O); 3.76 dd, 1 H, *J* = 11.8, 8.2 (CHC**H**$_2$); 3.67 dd, 1 H, *J* = 11.6, 4.8 (CHC**H**$_2$); 2.11 s, 3 H (COC**H**$_3$); 1.57 s, 6 H (C(C**H**$_3$)$_2$). ^{13}C NMR (100 MHz, CDCl$_3$): 169.8, 151.6, 128.9, 126.4, 123.3, 119.5, 117.3, 99.7, 74.7, 60.7, 46.3, 24.7, 24.6, 20.9. HR-MS (ESI): calculated for C$_{14}$H$_{17}$ClNaO$_4^+$: 307.0708; found [M + Na]$^+$: 307.0713. $[\alpha]_D^{20}$ +73.5 (*c* 1.15, MeOH). GC gradient 110 °C, 0 min; 15 °C/min to 150 °C, 5 min; 2 °C/min to 200 °C, 2 min. t_{R1} = 19.4 min ((*R*)-**6**); t_{R2} = 19.7 min ((*S*)-**6**).

Synthesis of (*S*)-2,2-Dimethyl-6-(oxiran-2-yl)-4*H*-benzo[1,3]dioxin ((*S*)-**7**)

LiOH (27 mg, 1.1 mmol) was added in portions to a solution of acetate (*S*)-**6** (91 mg, 0.32 mmol) in 4 ml EtOH (99%) and stirred. The reaction was quenched by addition of NaHCO$_3$ (192 mg, 2.3 mmol) after 1 h. EtOH was carefully evaporated. To the residue was added brine (20 ml) and the resulting mixture was extracted with Et$_2$O (5 × 20 ml). The combined organic phases were dried over MgSO$_4$, filtered and concentrated under vacuum to give the corresponding epoxide in 98% crude yield (64.1 mg, 0.31 mmol) with 98% *ee* (determined by chiral HPLC). The colorless oil was used without further purification. ^{1}H NMR (400 MHz, CDCl$_3$): 7.08 dd, 1 H, *J* = 8.4, 2.0 (Ar-H); 6.88 d, 1 H, *J* = 1.9 (Ar-H); 6.80 d, 1 H, *J* = 8.4 (Ar-H); 4.82 s, 2 H (CH$_2$O); 3.79 dd, 1 H, *J* = 3.8, 2.8 (C**H**CH$_2$); 3.11 dd, 1 H, *J* = 5.3, 4.0, 1 H (CHC**H**$_2$); 2.79 dd, 1 H, *J* = 5.3, 2.6 (CHC**H**$_2$), 1.53 s, 6 H (C(C**H**$_3$)$_2$). ^{13}C NMR (100 MHz, CDCl$_3$): 151.3, 129.2, 125.6, 121.8, 119.6, 117.2, 99.6, 60.8, 52.2, 51.0, 24.8, 24.6. HR-MS (ESI): calculated for C$_{12}$H$_{15}$O$_3^+$: 207.1016; found [M + H]$^+$: 207.1009. HPLC: Chiralpak AS column, *i*-PrOH–*i*-hexane (1:99), 25 °C, flow rate 1 ml min^{-1}, λ = 230 nm, t_{R1} = 32.1 min (*R*)-**7**, t_{R2} = 38.9 min (*S*)-**7**.

Synthesis of (*S*)-2-(*tert*-Butylamino)-1-(2,2-dimethyl-4*H*-benzo[1,3]dioxin-6-yl)-ethanol ((*S*)-**8**)

A mixture of (*S*)-2,2-dimethyl-6-(oxiran-2-yl)-4*H*-benzo[1,3]dioxin ((*S*)-**7**) (64 mg, 0.31 mmol) and *tert*-butylamine (7 ml) were placed in a Schlenk and refluxed for 5 days. After cooling to

room temperature the excess of *tert*-butylamine was removed under reduced pressure. Chromatographic purification (silica gel, dichloromethane–methanol–triethylamine, 95:5:0.1) afforded (*S*)-**8** (56.7 mg, 0.20 mmol, 65% yield) as a light yellow oil that crystallized upon standing. Spectral data were in accordance with those reported in the literature[12b]. ^1H NMR (400 MHz, CDCl$_3$): 7.12 dd, 1 H, *J* = 8.4, 1.8 (Ar-H); 7.01 d, 1 H, *J* = 1.4 (Ar-H); 6.79 d, 1 H, *J* = 8.4 (Ar-H); 4.84 s, 2 H (CH$_2$O); 4.50 dd, 1 H, *J* = 9.0, 3.6 (CH**CH**$_2$); 2.85 dd, 1 H, *J* = 11.8, 3.6 (CHC**H**$_2$); 2.55 dd, 1 H, *J* = 11.8, 9.0 (CHC**H**$_2$), 1.54 s, 3 H (C(CH$_3$)$_2$); 1.53 s, 3 H (C(CH$_3$)$_2$); 1.10 s, 9 H, (C(CH$_3$)$_3$). ^{13}C NMR (100 MHz, CDCl$_3$): 150.5, 134.7, 125.7, 122.1, 119.3, 116.9, 99.5, 72.0, 60.9, 50.3, 50.2, 29.2, 24.9, 24.6.

Synthesis of (*S*)-4-(2-(*tert*-Butylamino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol ((*S*)-**9**)

To (*S*)-**8** (55.6 mg, 0.20 mmol) was added H$_2$O (4 ml) and then acetic acid (2 ml) and the reaction was heated to 50 °C. After 3 h it was cooled to room temperature and H$_2$O/acetic acid was evaporated under reduced pressure. The crude was taken up in 99% EtOH and after evaporation, the procedure was repeated twice. (*S*)-Salbutamol acetate ((*S*)-**9**) was obtained as a pale yellow oil in quantitative yield (60 mg, 0.2 mmol). Spectral data were in accordance with those reported in the literature[12b]. ^1H NMR (500 MHz, DMSO-*d*$_6$): 7.28 d, 1 H, *J* = 1.6 (Ar-H); 7.03 dd, 1 H, *J* = 6.6, 1.4 (Ar-H); 6.72 d, 1 H, *J* = 6.8 (Ar-H); 4.58 dd, 1 H, *J* = 7.6, 2.8 (CH**CH**$_2$), 4.47 s, 2 H (CH$_2$OH); 2.73 dd, 1 H, *J* = 9.4, 2.8 (CHC**H**$_2$); 2.65 app t, 1 H *J* = 8.4 (CHC**H**$_2$); 1.83 s, 3 H (COCH$_3$); 1.13 s, 9 H (C(CH$_3$)$_3$). ^{13}C NMR (125 MHz, DMSO-*d*$_6$): 173.6, 153.4, 133.5, 128.1, 125.1, 124.9, 114.2, 70.5, 58.3, 56.0, 52.2, 49.7, 27.1, 22.6, 18.6. [α]$_D^{20}$ +38.1 (*c* 0.8, MeOH); lit.[12b] [α]$_D$ –37.9 (*c* 0.5, MeOH) for (*R*)-**9**, 97% *ee*.

REFERENCES AND NOTES

1. McKeage K., Keam S. J.: *Drugs* **2009**, *69*, 1799.
2. Gupta M. K., Singh M.: *Indian J. Pediatr.* **2007**, *74*, 161.
3. Libretto S. E.: *Toxicology* **1994**, *8*, 213.
4. Breuer M., Ditrich K., Habicher T., Hauer B., Kesseler M., Stuermer R., Zelinski T.: *Angew. Chem. Int. Ed.* **2004**, *43*, 788.
5. Kamal A., Azhar M. A., Krishnaji T., Malik M. S., Azeeza S.: *Coord. Chem. Rev.* **2008**, *252*, 569.
6. Stecher H., Faber K.: *Synthesis* **1997**, 1.
7. For reviews on DKR see: a) Huerta F. F, Minidis A. B. E., Bäckvall J.-E.: *Chem. Soc. Rev.* **2001**, *30*, 321; b) Kim M.-J., Ahn Y., Park J.: *Curr. Opin. Biotechnol.* **2002**, *13*, 578; c) Pamies O., Bäckvall J.-E.: *Chem. Rev.* **2003**, *103*, 3247; d) Martín-Matute B., Bäckvall J.-E.: *Curr. Opin. Chem. Biol.* **2007**, *11*, 226; e) Ahn Y., Ko S.-B., Kim M.-J., Park J.: *Coord. Chem. Rev.* **2008**, *252*, 647; f) Lee J. H., Han K., Kim M.-J., Park J.: *Eur. J. Org. Chem.* **2010**, 999.

 8. a) Martín-Matute B., Edit M., Bogár K., Bäckvall J.-E.: *Angew. Chem. Int. Ed.* **2004**, *43*, 6535; b) Martín-Matute B., Edit M., Bogár K., Kaynak F. B., Bäckvall J.-E.: *J. Am. Chem. Soc.* **2005**, *127*, 8817.

 9. a) Hett R., Fang Q. K., Gao Y., Hong Y., Butler H. T., Nie X., Wald S. A.: *Tetrahedron Lett.* **1997**, *38*, 1125; b) Hett R., Senanayake C. H., Wald S. A.: *Tetrahderon Lett.* **1998**, *39*, 1705; c) Hett R., Stare R., Helqvist P.: *Tetrahedron Lett.* **1994**, *35*, 9375; d) Hong Y., Gao Y., Nie X., Zepp C. M.: *Tetrahedron Lett.* **1994**, *35*, 5551.

10. 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**, *12*, 3343.

11. Liu J., Zhou D., Jia X., Huang L., Li X., Chan A. S.: *Tetrahedron: Asymmetry* **2008**, *19*, 1824.

12. a) Hartley D., Middlemiss D.: *J. Med. Chem.* **1971**, *14*, 895; b) Caira M. R., Hunter R., Nassimbeni L. R., Stevens A. T.: *Tetrahedron: Asymmetry* **1999**, *10*, 2175.

13. Babad E., Carruthers N. I., Jaret R. S., Steinman M.: *Synthesis* **1988**, 966.

14. Gribble G. W.: *Chem. Soc. Rev.* **1998**, *27*, 395.

15. a) Träff A., Bogár K., Warner M., Bäckvall J.-E.: *Org. Lett.* **2008**, *10*, 4807; b) Johnston E., Bogár K., Bäckvall J.-E.: *J. Org. Chem.* **2010**, *75*, 4596.

16. $[\alpha]_D^{20}$ +38.1 (*c* 0.8, MeOH) compared to lit.[12b] $[\alpha]_D^{20}$ –37.9 (*c* 1, MeOH) for (*R*)-salbutamol 97% *ee*.