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Resolution of albuterol acetonide

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Abstract

The (*R*)-enantiomer of albuterol has been isolated via resolution of albuterol acetonide with (2*S*,3*S*)-di-*O*-benzoyl- or (2*S*,3*S*)-di-*O*-toluoyltartaric acid. The absolute configuration of the resolved acetonide was assessed by ^{1}H NMR analysis of its (*R*)-Mosher's ester, and confirmed by an X-ray crystal structure determination of the (*R*)-phenylethylurea derivative of the (*S*)-enantiomer. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

Albuterol **1** is a β_2-adrenergic receptor agonist and is currently one of the most prescribed bronchodilators for the treatment of bronchial asthma.[1] The drug was developed in the late 1960s as a racemate in a process that has been reviewed.[2] The assignment of absolute configuration of the enantiomers of the drug was reported in 1971, based on circular dichroism studies.[3] More recently, the realisation that the inactive (*S*)-enantiomer may be associated with toxic side effects,[4–6] in addition to clinical trial data confirming the improved efficacy of the drug when administered as the (*R*)-enantiomer,[7] has spurred efforts towards single enantiomer production. In August 1997 Sepracor Inc. submitted an NDA (New Drug Application) for (*R*)-albuterol to the Food and Drug Administration (FDA) which received approval in March 1999.[8] This paper presents results on the successful resolution of albuterol using a resolution of its acetonide derivative, as well as reporting the first X-ray absolute configurational determination via single crystal analysis of the (*R*)-phenylethylurea derivative of the aforementioned ketal derivative.

2. Results and discussion

While (*R*)-albuterol has been successfully produced by asymmetric synthesis[9] using enantioselective reduction[9,10] with an oxazaborolidine catalyst as a key step, the use of resolution has met with far less

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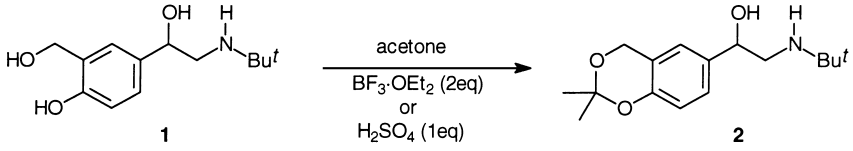
success. The best results to date have been obtained with (*S*)-naproxen,[1] which produced (*R*)-albuterol in 86% *ee* and 15% yield, and via salt formation with the metal complex (+)-Ba[CoEDTA]$_2$.[11] Various benzylated derivatives have been shown to be superior substrates for resolution[1,3,9,12] and a process based on one of these has been adopted by Sepracor Inc. to produce (*R*)-albuterol hydrochloride in multikilo quantities for clinical evaluation. In the light of these results we decided to study the resolution of a derivative and guided by the criteria used by ten Hoeve and Wynberg in the design of synthetic resolving agents,[13] we opted to introduce rigidity into the substrate by ring formation. Mindful that facile deprotection following resolution was an important criterion for the overall success of a scaled-up process, condensation of the racemic drug with acetone under acidic conditions to afford an oxazolidine or ketal was selected as our derivatisation method. In the event, reaction of albuterol with excess acetone and $BF_3 \cdot OEt_2$ (2 equiv.) at 0°C for 1 h furnished a 95% yield of the acetonide **2** after column chromatography. Upon scale-up, direct crystallisation of the crude material from acetone or acetonitrile afforded high quality material in high yield (>80%) and pure as judged by ^{1}H NMR. Optimisation studies revealed that conc. H_2SO_4 (1 equiv.) under the same experimental conditions gave the same result (Scheme 1).



Scheme 1.

^{1}H and ^{13}C NMR spectroscopy were used to assign the structure of **2** as an acetonide as opposed to the oxazolidine alternative. Of note were the appearance of resonances at 1.505 and 1.510 ppm in the ^{1}H NMR spectrum (400 MHz) for the diastereotopic methyl resonances as well as a ^{13}C signal for the ketal quaternary carbon at 99.5 ppm which is in good agreement with the reported value for 2,2-dimethyl-1,3-dioxanes (99 ppm) and significantly downfield to the analogous value for 2,2-dimethyl-1,3-oxazolidines (81 ppm).[14] Subsequently, single crystal X-ray analysis on resolved **2** proved this assignment to be correct.

*2.1. Resolution of **2***

In order to determine whether (*rac*)-**2** crystallised as a conglomerate which could be resolved by direct crystallisation,[15] a series of X-ray photographs were taken in an attempt to determine the space group. These indicated two possible space groups, Cmma or Cm2a. Both space groups contain mirror planes which necessitate the presence of both enantiomers of a chiral molecule in the crystal. Crystalline (*rac*)-**2** was thus assigned as a true racemate and resolution employing diastereomer formation was the necessary approach.

Owing to the well-documented lack of predictability in identifying a successful resolving agent for classical resolution, a crystallisation array strategy as advocated by Wilen et al.[16] was adopted. An alternative combinatorial approach has since been proposed by Vries et al.[17] and further discussed by Collet.[18] The following components were included in the study:

(i) resolution substrates (bases): albuterol **1** and albuterol acetonide **2**;
(ii) resolving agents (acids): (1*R*)-(−)-camphor-10-sulfonic acid; (2*R*,3*R*)-(−)-di-*O*-benzoyltartaric acid monohydrate (DOBT); (2*R*,3*R*)-(−)-di-*O*-toluoyltartaric acid (DOTT); (*S*)-(−)-malic acid; (2*R*,3*R*)-(+)-tartaric acid; (*S*)-(+)-mandelic acid; (*S*)-(+)-1,1′-binaphthylphosphoric acid;
(iii) solvents: methanol, ethanol, acetone and ethyl acetate.

Table 1
Specific rotations of material from salt formation experiments

Resolving Agent	Precipitate $[\alpha]_D$	Mother Liquor $[\alpha]_D$	Resolving Agent $[\alpha]_D$
(-)-DOBT	-30	-60	-116
(-)-DOTT	-39	-73	-138

Experiments with **1** as substrate failed to produce any solid material, thereby confirming literature reports on the problematic nature of this compound in classical resolution. Albuterol acetonide **2** proved to be slightly more accommodating and gave fine crystals with DOBT and DOTT using methanol or ethanol as solvent. The ^{1}H NMR spectrum of the filtered salt indicated a stoichiometry of acid:base, 1:2 which was confirmed by microanalysis and is advantageous industrially since only 0.5 equiv. of resolving agent is required for the process. The infra-red spectra of both the DOBT and DOTT salts revealed a broad band at 2700 cm^{-1} and a strong band at 1640 cm^{-1} assigned to ammonium N–H and carboxylate anion stretching frequencies, respectively. These data present strong evidence in favour of the compounds being salts rather than complexes. Moreover, a recent study[19] on the diastereomers formed between pipecolic acid anilides and DOBT showed that salts were formed with an acid:base ratio of 1:2 whereas the ratio for complexes was 1:1.

From the optical rotations of the precipitates, mother liquors and resolving agents shown in Table 1, it was concluded that some enrichment had taken place and that the *n*-salts, i.e. (+)-**2**/(−)-acid were being formed.

The enriched acetonides were extracted from the salts using a standard acid/base extraction and a specific rotation of +16 determined for each sample. Since the specific rotation of **2** was unknown, various methods for evaluating the optical purity of **2** were used. Hydrolysis of the resolved acetonide (+)-**2** (see below) gave rise to (*S*)-albuterol acetate based on the sign of the optical rotation. Since the (*R*)-enantiomer was desired ultimately, further work was undertaken using (2*S*,3*S*)-(+)-DOBT and (2*S*,3*S*)-(+)-DOTT. Although the (2*S*,3*S*)-resolving agents are derivatives of unnatural tartaric acid and hence more expensive, a recent resolution of DOBT by preferential crystallisation of its calcium salt–methoxyethanol complex promises a cheaper source of this material.[20]

2.2. Determination of enantiomeric purity of **2**

(*R*)- or (*S*)-*O*-Acetylmandelic acid (OAM) is well documented to form soluble diastereomeric salts with a range of chiral amines and amino alcohols,[21] thus permitting a direct measure of their enantiomeric composition by ^{1}H NMR spectroscopy. The spectra for (−)-**2** isolated from both the DOBT and DOTT resolutions with (*R*)-OAM were recorded. The integrals for the *t*-butyl singlets of the diastereomeric salts (δ=1.14, 1.27 ppm/0°C; 1.15, 1.24 ppm/25°C), were used to calculate the enantiomeric excess of each sample which were determined to be 90% in both cases.

More accurate *ee* values were obtained by HPLC on a Pirkle-type chiral stationary phase (Phenomenex Chirex 3022). Separation of the enantiomers of albuterol on this stationary phase has been reported[22] and satisfactory separation of the enantiomers of **2** was obtained by reducing the polarity of the mobile phase. Subsequently, separation of the enantiomers of albuterol and its acetonide under the same conditions was demonstrated on a Chirobiotic Teicoplanin HPLC column. The (−)-**2** obtained from resolution experiments gave *ee* values of 89.5% (DOBT) and 92.1% (DOTT) which were in good agreement with the ^{1}H NMR results. Recrystallisation of (−)-**2** from acetone produced a substantial increase in optical purity as recorded in Table 2.

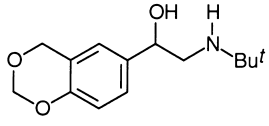
Table 2
Comparison of DOBT and DOTT resolutions of **2**

Resolution Stage		DOBT	DOTT
First precipitation	Yield (%)[a]	70	90
	ee (%)	89.5	92.1
Recrystallised salt	Yield (%)[a]	63	80
	ee (%)	>99.5	95.5

a) 100% = complete recovery of a single diastereomer

2.3. Hydrolysis studies

In a recent publication describing an attempted synthesis of (*R*)-albuterol from optically active cyanohydrins,[23] hydrolysis (aq. HCl/Δ) of acetals **3** and **4** resulted in racemisation and partial decomposition of the product.



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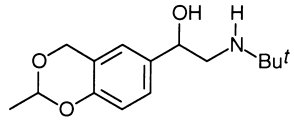

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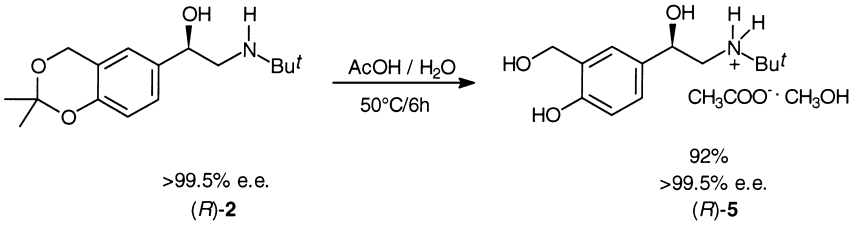
We were able to achieve complete hydrolysis of the isopropylidine ketal by heating it in aqueous acetic acid (1:1) at 50°C for 6 h. Vacuum distillation at 40°C allowed removal of the reagents without promoting any albuterol decomposition. The resultant oil was taken up in methanol, and albuterol acetate monomethanolate **5** precipitated in 92% yield by the addition of ethyl acetate without any loss of enantiomeric purity as judged by HPLC (Scheme 2). Further investigation of the hydrolysis conditions revealed that refluxing in the same reagents for 2 h did cause a reduction in *ee* to 97.7%.



>99.5% e.e.
(*R*)-**2**

92%
>99.5% e.e.
(*R*)-**5**

Scheme 2.

Characterisation of (*R*)-**5** was not straightforward owing to its crystallisation as a methanol solvate. Inconsistent microanalytical results were obtained due to partial desolvation on drying. Thermogravimetric analysis of a sample freshly removed from the mother liquor showed a mass loss of approximately 10% over the range 80–140°C which is as expected for the inclusion of one molecule of methanol per salt formula unit (theoretical mass loss=9.7%). This is followed by mass loss due to decomposition of the salt after melting of the desolvated crystal at 144°C. The trace produced by differential scanning calorimetry over the same temperature range showed two endotherms confirming these two events (desolvation and melting). ^{1}H NMR of the same sample revealed a peak at δ=3.17 ppm integrating for three protons and corresponding to that expected for the methyl protons on methanol, thus confirming the presence of a 1:1 methanol solvate. Microanalysis was performed on a sample dried at 120°C overnight and gave the correct analysis for the desolvated salt. Specific rotation determinations were also carried out on the dried salt.

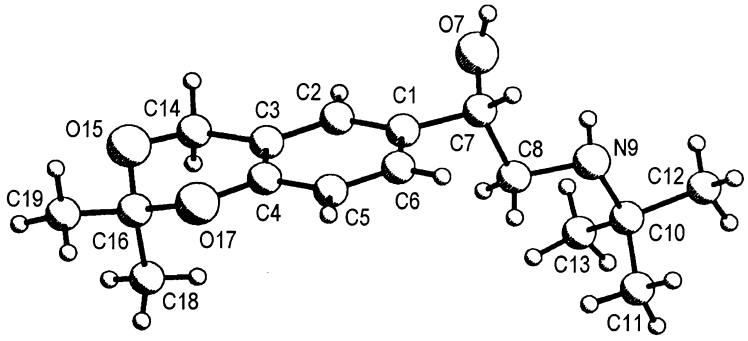


Figure 1. Molecular structure of (+)-**2**

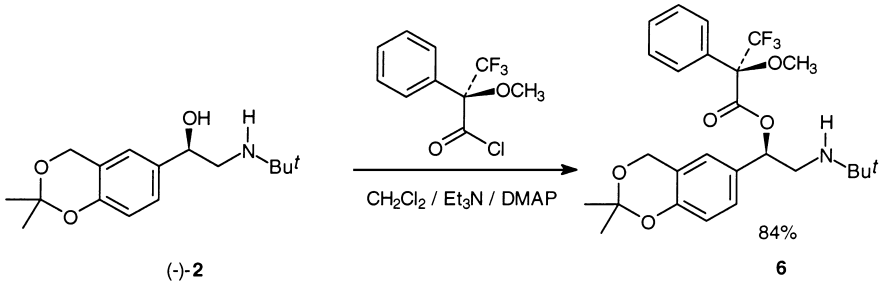
Treatment of (*R*)-**2** with 1 equiv. of sulfuric acid in methanol at ambient temperatures also led to complete hydrolysis without any racemisation. Neutralisation of the reaction mixture with 1 equiv. of chilled methanolic sodium hydroxide and subsequent filtration to remove the resulting salts allowed the recovery of (*R*)-albuterol as a free base. However, yields were vastly inferior to those achieved with the acetic acid hydrolysis. The use of sulfuric acid at elevated temperatures to effect racemisation, and thus facilitate recycling of the unwanted enantiomer, was also demonstrated in our studies and is applicable to an industrial scale-up.

2.4. Absolute configuration studies

The absolute configuration of albuterol was assigned by Hartley and Middlemiss in 1971[3] on the basis of a negative Cotton effect in the circular dichroism spectrum of the (−)-enantiomer. This effect coincided with that of (*R*)-octopamine, and (−)-albuterol was thus assigned as having the (*R*)-configuration. A search of the Cambridge Structural Database[24] revealed that no crystallographic studies on homochiral albuterol or derivatives thereof had been reported and we thus decided to apply these techniques in order to make an unambiguous assignment of the absolute configuration. Although the DOBT and DOTT salts of albuterol acetonide were crystalline, no suitable crystals for structural determination could be obtained. We thus decided to carry out the structural determination of resolved (+)-albuterol acetonide in order to evaluate the Flack absolute structure parameter.[25] Although the refined value of the Flack parameter was not decisive in indicating the absolute configuration, even with a low temperature data-collection (223 K), the presence of the isopropylidine ketal, as was inferred from ^{13}C NMR data, was confirmed, as shown in Fig. 1.

We then decided to pursue the preparation of a covalent diastereomer of (−)-**2**, by reaction with a homochiral reagent of known absolute stereochemistry, for structural determination. After several failed derivatisations with some standard reagents including (*S*)-mandelic acid/DCC/HOBt[26] and (1*R*)-camphor-10-sulfonyl chloride/pyridine/DMF,[27,28] (−)-**2** was successfully chemoselectively *O*-acylated by (*S*)-Mosher's acid chloride[29,30] to give the ester **6** (Scheme 3).

Assignment of **6** as a Mosher ester, as opposed to an amide, was based on the appearance of a C=O stretching frequency at 1748 cm^{-1} in the infra-red spectrum, as well as a downfield shift in the benzylic methine proton in the ^{1}H NMR spectrum (δ=4.8 to 5.9 ppm), and the benzylic carbon (72 to 79 ppm) in the ^{13}C spectrum. Although **6** was an oil, thus preventing single crystal X-ray analysis, it did present an opportunity to undertake a Mosher analysis[31] for the configurational assignment. The analogous derivatisation of (*rac*)-**2** was carried out and the ^{1}H NMR resonances of the two diastereomers **6** and **7** (from (+)-**2**) were identified, as shown in Table 3.



Scheme 3.

Table 3
^{1}H chemical shift data for the (*R*)-Mosher esters of (+)- and (−)-**2**

Proton	**7** (ppm)	**6** (ppm)	**7** - **6** (ppm)
t-Bu	0.98	1.06	-0.08
2x2'-CH_3	1.52	1.53	-0.01
2-H_A	2.75	2.83	-0.08
2-H_B	2.99	3.00	-0.01
2''-OCH_3	3.43	3.54	-0.11
4'-H_A	4.78	4.72	+0.06
4'-H_B	4.84	4.79	+0.05
1-H	5.92	5.87	+0.05
8'-H	6.79	6.75	+0.04
5'-H	6.99	6.83	+0.16
7'-H	7.18	7.07	+0.11
other Ar-H	7.2-7.5	7.2-7.5	-

Inspection of these data revealed the shielding of the phenyl protons of **6** and deshielding of its C-2 and *t*-butyl protons relative to those on **7**. Applying this outcome to the minimum energy conformation[32] for the Mosher ester resulted in the (*R*)-configuration being assigned to the (−)-acetonide, (−)-**2**, as illustrated in Fig. 2.

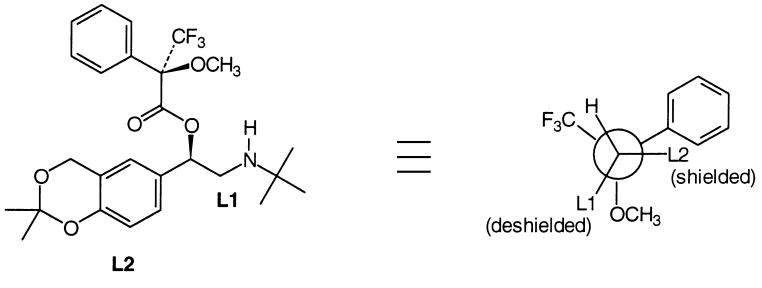
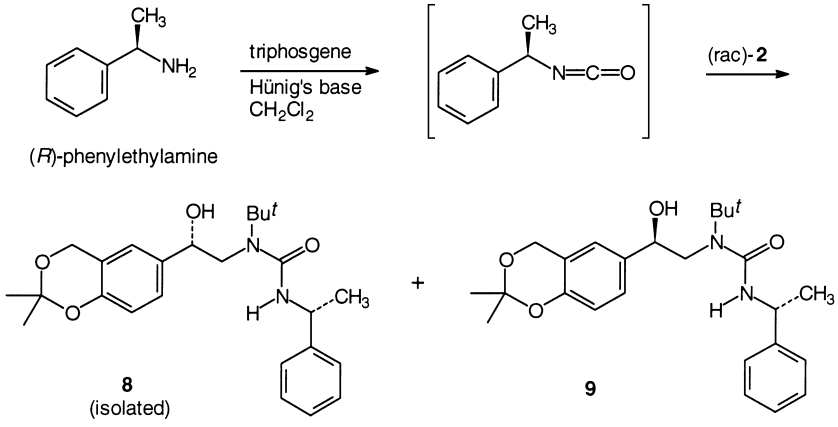


Figure 2.

In the light of uncertainty cast on this analysis by the identification of three low energy conformations,[33] we decided to pursue the derivatisation to a crystalline diastereomer. We were eventually gratified to discover a suitable urea derivative. Reaction of (*rac*)-**2** with (*R*)-phenylethylisocyanate prepared in situ from (*R*)-phenylethylamine[34] and triphosgene[35] gave a high

yield of the diastereomeric urea derivatives **8** and **9** which were separated. The same reaction with (−)-**2** produced diastereomer **9**. The assignment of these products as ureas was made on the basis of NMR and infra-red spectra, and later corroborated by X-ray crystal structure determination. The observed chemoselectivity, which is in contrast to that of the Mosher adduct, is probably due to the greater 'softness' of the isocyanate carbon compared to that of Mosher's acid chloride (Scheme 4).



Scheme 4.

The urea arising from (+)-**2**, i.e. **8**, produced material suitable for X-ray crystal structure determination. The molecular structure, clearly showing the relative stereochemistry at the stereogenic centres is shown in Fig. 3. Since the configuration of the phenylethylamine was known to be (*R*), that of the (+)-albuterol acetonide moeity, which upon hydrolysis gave rise to (+)-albuterol acetate, was unambiguously assigned as (*S*). This was in agreement with the original assignment made on the basis of circular dichroism studies.[3]

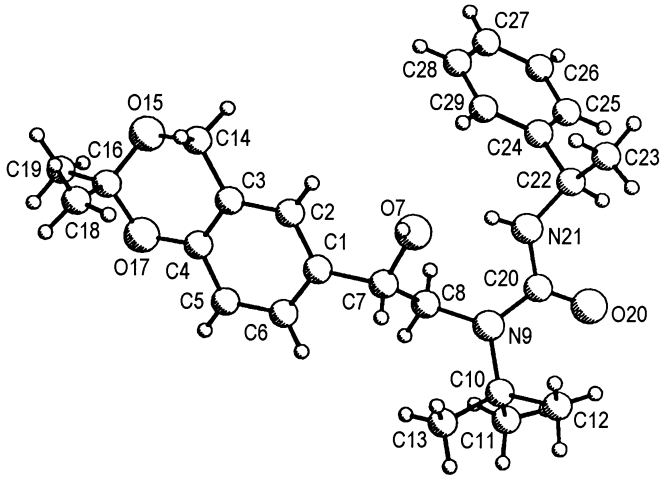


Figure 3. Molecular structure of **8**

3. Conclusion

A novel route to obtaining large quantities of (*R*)-albuterol has been devised by performing a low cost, high yielding protection of (*rac*)-albuterol and resolving the resulting acetonide via diastereomeric

salt formation with (2*S*,3*S*)-di-*O*-benzoyltartaric acid and (2*S*,3*S*)-di-*O*-toluoyltartaric acid. (*R*)-Albuterol was obtained as its acetate salt in high yield and optical purity by acid hydrolysis of the resolved acetonide derivative. The efficiency of the resolution step as well as the simplicity of the protection and deprotection steps make this an attractive industrial alternative to the present resolution methods. The successful structure elucidation of the (*R*)-phenylethylurea derivative of (*S*)-albuterol acetonide is the first structural evidence available for confirmation of the assignment of the absolute configuration of the enantiomers of albuterol.

4. Experimental

4.1. General

Melting points were measured using a Reichert–Jung Thermovar hot-stage microscope and are uncorrected. Optical rotations were measured on a Perkin–Elmer 141 polarimeter at 24°C. Infra-red spectra were recorded using a Perkin–Elmer Paragon 1000 FT-IR spectrometer over the range 4000–600 cm^{-1}. Microanalyses were determined using a Fisons EA 1108 CHNS-O instrument. Mass spectra were recorded on a VG micromass 16F spectrometer operating at 70 eV with an accelerating voltage of 4 kV. Accurate masses were determined on a VG-70E spectrometer. ^{1}H NMR spectra were recorded on a Varian VXR-200 (200 MHz) or a Varian Unity spectrometer (400 MHz). ^{13}C NMR spectra were recorded on the same instruments at 50 or 100 MHz. The relevant solvent peak ($CHCl_3$ or DMSO) was used as an internal standard in each case. Thermal gravimetric analysis and differential scanning calorimetry were performed on a Perkin–Elmer PC7 series thermal analysis system. High performance liquid chromatography was performed on a Hewlett–Packard 1090 system with a diode array detection and a Hewlett–Packard 3393A integrator. Thin layer chromatography was performed on aluminium backed silica gel 60 F_{254} plates. The plates were visualised under ultraviolet light and by spraying with ceric ammonium sulfate in 8 mol dm^{-3} sulfuric acid and baking at 200°C. Column chromatography was conducted with Merck Kieselgel 60, 70–230 mesh. Acetone was distilled from Drierite (anhydrous $CaSO_4$) and stored over 4 Å molecular sieves. Dichloromethane was freshly distilled from P_2O_5 prior to use. Solvents used for HPLC were BDH HiperSolv grade. Albuterol was supplied by South African Druggists, Port Elizabeth, South Africa. The resolving agents were purchased from the Aldrich Chemical Company.

4.2. 2-(N-tert-Butylamino)-1-(2,2-dimethyl-1,3-benzodioxin-6-yl)ethanol **2**

4.2.1. $BF_3 \cdot OEt_2$ procedure

Freshly distilled $BF_3 \cdot OEt_2$ (2.7 cm^3, 3.1 g, 22.0 mmol) was added dropwise to a stirred mixture of albuterol (2.39 g, 10.0 mmol) in dry acetone (50 cm^3) under nitrogen at 0°C. The solution was stirred at 0°C for 60 min after which it was slowly poured into 50 cm^3 of cold aqueous Na_2CO_3. The excess acetone was removed under reduced pressure and the mixture extracted into ethyl acetate. The combined organic phases were dried ($MgSO_4$) and the solvent removed in vacuo to give a crystalline crude product (2.70 g). Column chromatography on silica gel with ethyl acetate:petroleum ether:triethylamine (50:45:5) afforded **2** as a colourless crystalline product (2.67 g, 9.6 mmol, 96%), mp 91–92°C (acetone); found C, 68.9; H, 9.3; N, 5.0; $C_{16}H_{25}NO_3$ requires C, 68.8, H, 9.0; N, 5.0%; ν_{max} ($CHCl_3$)/cm^{-1} 3402 (O–H), 2969 (-CH_2-), 1501 (aromatic C–C), 1118 (C–O); δ_H (400 MHz, $CDCl_3$) 1.07 (9H, s, *t*-Bu), 1.505 (3H, s, 2′-CH_3), 1.510 (3H, s, 2′-CH_3), 2.56 (1H, dd, *J* 11.7 and 9.0 Hz, 2-H_A), 2.75 (2H, br s, OH/NH), 2.80

(1H, dd, *J* 11.7 and 3.5 Hz, 2-H_B), 4.50 (1H, dd, *J* 9.0 and 3.5 Hz, 1-H), 4.81 (2H, s, 4′-H_2), 6.76 (1H, d, *J* 8.3 Hz, 8′-H), 6.99 (1H, d, *J* 1.6 Hz, 5′-H), 7.11 (1H, dd, *J* 8.3 and 1.6 Hz, 7′-H); δ_C (100 MHz, $CDCl_3$) 24.6 and 24.8 (2′-CH_3), 29.1 (*t*-Bu -*C*H_3), 50.3 (C-2), 50.3 (*t*-Bu -*C*$(CH_3)_3$), 61.0 (C-4′), 72.0 (C-1), 99.5 (C-2′), 116.8 (C-8′), 119.2 (C-4′a), 122.0 (C-5′), 125.7 (C-7′), 134.9 (C-6′), 150.5 (C-8′a), (found M^+, 279, $C_{16}H_{25}NO_3$ requires M, 279).

4.2.2. $CuSO_4/H_2SO_4$ procedure

Acetone (50 cm^3) was added to a flask containing albuterol (2.39 g, 10.0 mmol) and anhydrous copper sulfate (1.65 g, 10.0 mmol) and the resulting mixture was cooled to 0°C under nitrogen. Concentrated sulfuric acid (1.3 cm^3, 22.0 mmol) was added dropwise and the solution was stirred for 60 min at 0°C. The work-up procedure as used above resulted in 2.70 g crude material which was purified in an identical manner to yield crystalline **2** (2.65 g, 9.5 mmol, 95%).

4.3. Diastereomeric salt formation

4.3.1. General procedure for pilot study

The relevant acid and base (0.2 mmol of each) were weighed into a glass vial. The required solvent (1 cm^3) was added and the solution heated sufficiently to allow dissolution of all solids (not achieved in all cases). The vials were stoppered and left to stand at room temperature. Where no precipitate was observed after 24 h, the lids were removed to allow slow evaporation. In each case either an oil, paste or crystalline material was obtained. Where solid crystalline material was obtained, the melting point was compared to that of the parent acid and base to indicate formation of a new species.

4.4. (2S,3S)-Di-O-benzoyl tartrate salt of (R)-2

To a refluxing solution of (*rac*)-**2** (1.90 g, 6.8 mmol) in methanol (15 cm^3) was added a hot solution of (2*S*,3*S*)-di-*O*-benzoyltartaric acid monohydrate (1.32 g, 3.5 mmol) in methanol (10 cm^3). Heating was discontinued and the solution stirred until a solid cake of precipitate formed. A further 20 cm^3 methanol was added and the solution refluxed for a further 10 min whereafter it was stirred at room temperature for 2 h. The resulting precipitate was isolated by filtration, washed with ethyl acetate and dried under vacuum to yield the diastereomeric salt (1.10 g, 1.20 mmol, 71% yield as a single enantiomer, 93.9% *de*[†]). A portion of this salt (0.80 g, 0.87 mmol) was further purified by redissolving it in boiling methanol (70 cm^3) followed by stirring at 0°C overnight. The salt was isolated and dried as above (0.50 g, 0.55 mmol, 63% for this step, 45% overall yield as a single enantiomer, >99.5% *de*[†]), mp 188–190°C (methanol); $[\alpha]_D$ +24.6 (*c* 0.19 methanol); found C, 65.5; H, 7.1; N, 3.0; $C_{50}H_{64}N_2O_{14}$ requires C, 65.5; H, 7.0; N, 3.1%; ν_{max} (KBr)/cm^{-1} 3411 (O–H), 2900–2400 (N^+–H), 1723 (C=O ester), 1641 (C=O carboxylate (s)), 1504 (C=O carboxylate (as)), 1118 (2° C–O); δ_H (400 MHz, DMSO-d_6) 1.13 (9H, s, *t*-Bu), 1.44 (6H, s, 2×2′-CH_3), 2.68 (1H, dd, *J* 11.9 and 10.3 Hz, 2-H_A), 2.90 (1H, dd, *J* 11.9 and 2.4 Hz, 2-H_B), 3.36 (2H, br s, NH), 4.72 (1H, dd, *J* 10.3 and 2.4 Hz, 1-H), 4.76 (2H, s, 4′-H_2), 5.66 (1H, s, DOBT 2-H), 6.71 (1H, d, *J* 8.4 Hz, 8′-H), 7.00 (1H, d, *J* 1.9 Hz, 5′-H), 7.10 (1H, dd, *J* 8.4 and 1.9 Hz, 7′-H), 7.50 (1H, m, DOBT 3′′-H and 5′′-H), 7.63 (1H, m, DOBT 4′′-H), 8.00 (1H, dd, *J* 7.8 and 1.4 Hz, DOBT 2′′-H and 6′′-H); δ_C (100 MHz, DMSO-d_6) 24.4 and 24.5 (2′-CH_3), 25.1 (*t*-Bu -*C*H_3), 48.1 (C-2), 54.7 (*t*-Bu -*C*$(CH_3)_3$), 60.0 (C-4′), 68.2 (C-1), 74.9 (DOBT C-2), 99.1 (C-2′), 116.0 (C-8′), 119.0 (C-4′a),

[†] Note: diastereomeric excesses of the above salts were determined by liberation of **2** from the salt as outlined below and subsequent chiral HPLC determination.

122.4 (C-5′), 125.5 (C-7′), 128.3 (DOBT C-3′′ and C-5′′), 129.1 (DOBT C-2′′ and C-6′′), 130.6 (DOBT C-1′′), 132.8 (DOBT C-4′′), 134.1 (C-6′), 149.9 (C-8′a), 165.1 (DOBT C-1′), 170.2 (DOBT C-1).

4.5. (2S,3S)-Di-O-toluoyl tartrate salt of (R)-2

(*rac*)-**2** (7.50 g, 26.9 mmol) was dissolved in methanol (60 cm^3) and heated to reflux. A hot solution of (2*S*,3*S*)-di-*O*-toluoyltartaric acid (5.30 g, 13.7 mmol) in methanol (40 cm^3) was slowly added to the refluxing solution. Precipitation started during the addition and a solid cake formed on complete addition of the resolving agent. A further 100 cm^3 methanol was added and the resulting slurry refluxed for 10 min followed by stirring at room temperature for 2 h. The precipitate was filtered off, washed with ethyl acetate and dried under vacuum to yield the salt (5.75 g, 6.1 mmol, 91% as a single enantiomer, 90.0% *de*†). This salt (5.25 g, 5.6 mmol) was added to boiling methanol (450 cm^3) and stirred at 0°C overnight. The solid material was again isolated by filtration, washed with ethyl acetate and vacuum dried (4.19 g, 4.4 mmol; 80% for this step, 73% overall yield as a single enantiomer, 95.2% *de*†), mp 191–192°C (methanol); $[\alpha]_D$ +38.5 (*c* 0.15 methanol); found C, 65.8; H, 7.3; N, 2.9; $C_{52}H_{68}N_2O_{14}$ requires C, 66.1; H, 7.2; N, 3.0%; ν_{max} (KBr)/cm^{-1} 3409 (O–H), 2900–2400 (N^+–H), 1721 (C=O ester), 1641 (C=O carboxylate (s)), 1503 (C=O carboxylate (as)), 1123 (2° C–O); δ_H (400 MHz, DMSO-d_6) 1.14 (9H, s, *t*-Bu), 1.45 (6H, s, 2×2′-CH_3), 2.37 (3H, s, DOTT 4′′-CH_3), 2.67 (1H, dd, *J* 12.0 and 10.4 Hz, 2-H_A), 2.89 (1H, dd, *J* 12.0 and 2.2 Hz, 2-H_B), 3.35 (2H, br s, NH), 4.71 (1H, dd, *J* 10.4 and 2.2 Hz, 1-H), 4.76 (2H, s, 4′-H_2), 5.61 (1H, s, DOTT 2-H), 6.71 (1H, d, *J* 8.4 Hz, 8′-H), 6.99 (1H, d, *J* 2.0 Hz, 5′-H), 7.09 (1H, dd, *J* 8.4 and 2.0 Hz, 7′-H); 7.29 (1H, d, *J* 8.2 Hz, DOTT 3′′-H and 5′′-H), 7.87 (1H, d, *J* 8.2 Hz, DOTT 2′′-H and 6′′-H); δ_C (100 MHz, DMSO-d_6) 21.1 (DOTT 4′′-CH_3), 24.4 and 24.5 (2′-CH_3), 25.0 (*t*-Bu -CH_3), 48.1 (C-2), 54.7 (*t*-Bu -*C*(CH_3)$_3$), 60.0 (C-4′), 68.2 (C-1), 74.8 (DOTT C-2), 99.1 (C-2′), 116.0 (C-8′), 118.9 (C-4′a), 122.4 (C-5′), 125.5 (C-7′), 128.0 (DOTT C-1′′), 128.8 (DOTT C-3′′ and C-5′′), 129.2 (DOTT C-2′′ and C-6′′), 134.1 (C-6′), 142.9 (DOTT C-4′′), 149.9 (C-8′a), 165.2 (DOTT C-1′), 170.6 (DOTT C-1).

4.6. (R)-2-(N-tert-Butylamino)-1-(2,2-dimethyl-1,3-benzodioxin-6-yl)ethanol (R)-2

To a vigorously stirring mixture of ethyl acetate (200 cm^3) and aqueous Na_2CO_3 (200 cm^3) was added the DOTT salt (4.19 g, 4.4 mmol). Stirring was continued until no solid material remained. The organic layer was removed and the aqueous phase extracted twice with equal volumes of ethyl acetate. The combined organic phases were dried ($MgSO_4$) and the solvent removed under reduced pressure to yield a colourless crystalline solid (2.43 g, 8.7 mmol, 98%). Recrystallisation from acetone was used to improve the optical purity as follows (by chiral HPLC): crude extract 95.2% *ee*; recrystallisation 1 gave 99.5% *ee*; recrystallisation 2 gave >99.5% *ee* and recrystallisation 3 gave 100% *ee*, mp 102–103°C (acetone); $[\alpha]_D$ −18.9 (*c* 1.5 methanol); found C, 68.5; H, 9.6; N, 5.1; $C_{16}H_{25}NO_3$ requires C, 68.8; H, 9.0; N, 5.0%; δ_H (400 MHz, $CDCl_3$) 1.11 (9H, s, *t*-Bu), 1.53 (3H, s, 2′-CH_3), 1.54 (3H, s, 2′-CH_3), 2.56 (1H, dd, *J* 11.7 and 9.1 Hz, 2-H_A), 2.12 (2H, br s, OH/NH), 2.87 (1H, dd, *J* 11.7 and 3.5 Hz, 2-H_B), 4.51 (1H, dd, *J* 9.0 and 3.5 Hz, 1-H), 4.84 (2H, s, 4′-H_2), 6.79 (1H, d, *J* 8.4 Hz, 8′-H), 7.01 (1H, d, *J* 1.5 Hz, 5′-H), 7.13 (1H, dd, *J* 8.4 and 1.5 Hz, 7′-H).

Liberation of (*R*)-**2** from the analogous DOBT salt was performed in an identical fashion and the same % yield was achieved.

4.7. (R)-Albuterol acetate monomethanolate (R)-5

Glacial acetic acid (0.4 cm^3, 7.2 mmol) was added to a mixture of (*R*)-**2** (90 mg, 0.32 mmol, 95.5% *ee*‡) in H_2O (0.4 cm^3, 0.4 g, 22 mmol). The resulting solution was stirred at 60°C for 5 h. The solvents were removed by vacuum distillation to leave a colourless tacky oil which was taken up in methanol and chilled. Ethyl acetate was added to this solution resulting in the precipitation of (*R*)-**5** (98 mg, 0.30 mmol, 92%, 97.0% *ee*‡), mp 143–144°C (methanol/ethyl acetate) (lit. 144.3°C); δ_H (400 MHz, DMSO) 1.15 (9H, s, *t*-Bu), 1.82 (3H, s, C*H*$_3$COO$^-$), 2.66 (1H, dd, *J* 11.7 and 9.6 Hz, 2-H_A), 2.75 (1H, dd, *J* 11.7 and 3.4 Hz, 2-H_B), 3.17 (3H, s, C*H*$_3$OH), 4.48 (2H, s, 3′-C*H*$_2$OH), 4.60 (1H, dd, *J* 9.6 and 3.4 Hz, 1-H), 5.22 (3H, br s, OH/NH), 6.73 (1H, d, *J* 8.1 Hz, 5′-H), 7.03 (1H, dd, *J* 8.1 and 1.9 Hz, 6′-H), 7.27 (1H, d, *J* 1.9 Hz, 2′-H), δ_C (200 MHz, DMSO) 23.5 (*C*H$_3$COO$^-$), 27.6 (*t*-Bu -CH_3), 49.2 (*C*H$_3$OH), 50.2 (C-2), 53.1 ((*t*-Bu -*C*(CH$_3$)$_3$), 59.0 (3′-*C*H$_2$OH), 71.1 (C-1), 114.8 (C-5′), 125.5 (C-6′), 125.7 (C-2′), 128.7 (C-3′), 134.1 (C-1′), 154.1 (C-4′), 174.5 (CH$_3$*C*OO$^-$). Since desolvation of the salt occurred on drying at room temperature, the following analyses were performed on the fully desolvated material: $[\alpha]_D$ −37.9 (*c* 0.5 methanol); found C, 60.4; H, 8.6; N, 4.7; $C_{15}H_{25}NO_5$ requires C, 60.2; H, 8.4; N, 4.7%.

4.8. Racemisation of (R)-2

A solution of (*R*)-**2** (4.18 g, 15.00 mmol, 68% *ee*‡) in 0.50 M aqueous sulfuric acid (150 cm^3) was stirred for 7 h while the temperature was maintained in the range 57–67°C. The solution was cooled and a cold aqueous solution of sodium hydroxide added. The resulting solution was then re-acidified to pH 3 with 0.5 M sulfuric acid and the solvent removed by azeotropic distillation with toluene under reduced pressure at 50°C. The resulting slurry was stirred in methanol (70 cm^3) whilst the pH was adjusted to 9.7 with methanolic sodium hydroxide. The solid material was removed by filtration and the solvent removed from the filtrate to yield an orange oil. Redissolution of the oil in acetone followed by removal of the solvent under reduced pressure afforded crude, racemised albuterol (3.07 g, 12.85 mmol, 86%, 10% *ee*‡).

4.9. (1R,2″R)-2-(N-tert-Butylamino)-1-(2,2-dimethyl-1,3-benzodioxin-6-yl)ethyl-(2-methoxy-2-trifluoromethyl)phenylacetate 6

To a solution of (*R*)-**2** (280 mg, 1.0 mmol) in dichloromethane (5 cm^3) at room temperature and under nitrogen was added *N*,*N*-dimethylaminopyridine (127 mg, 1.0 mmol), triethylamine (0.7 cm^3, 511 mg, 5.0 mmol), and (*R*)-(2-methoxy-2-trifluoromethyl) phenylacetyl chloride (0.23 cm^3, 311 mg, 1.2 mmol). The resulting yellow solution was stirred for 90 min followed by quenching with aqueous Na_2CO_3. The mixture was extracted into dichloromethane and the combined organic phases dried ($MgSO_4$) and the solvent removed under reduced pressure giving an oil (500 mg) which was adsorbed onto silica and chromatographed using ethyl acetate:petroleum ether (20:80) as eluent to give the product **33** as an oil (416 mg, 0.8 mmol, 84%), $[\alpha]_D$ 1.7 (*c* 1.5 methanol); ν_{max} ($CHCl_3$)/cm^{-1} 1748 (C=O ester), δ_H (400 MHz, $CDCl_3$) 1.06 (9H, s, *t*-Bu), 1.53 (6H, s, 2×2′-CH_3), 2.83 (1H, dd, *J* 12.3 and 4.1 Hz, 2-H_A), 3.01 (1H, dd, *J* 12.3 and 9.3 Hz, 2-H_B), 3.55 (3H, s, 2″-OCH_3), 4.72 (1H, d, *J* 15.0 Hz, 4′-H_A), 4.79 (1H, d, *J* 15.0 Hz, 4′-H_B), 5.87 (1H, dd, *J* 9.3 and 4.1 Hz, 1-H), 6.75 (1H, d, *J* 8.5 Hz, 8′-H), 6.83 (1H, d, *J* 2.2 Hz, 5′-H), 7.07 (1H, dd, *J* 8.5 and 2.2 Hz, 7′-H), 7.2–7.4 (3H, m, 3‴-H, 4‴-H, 5‴-H), 7.46 (2H, d, *J* 7.4 Hz, 2‴-H, 6‴-H); δ_C (100 MHz, $CDCl_3$) 24.6 and 24.7 (2′-CH_3), 28.8 (*t*-Bu -CH_3), 47.8 (C-2), 50.3

‡ Note: enantiomeric excesses determined by HPLC.

(*t*-Bu -*C*(CH_3)$_3$), 55.5 (2′′-OCH_3), 60.7 (C-4′), 79.0 (C-1), 84.6 (q, 2′′-CF_3), 99.6 (C-2′), 117.0 (C-8′), 119.2 (C-4′a), 123.3 (C-5′), 126.6 (C-7′), 127.5 (C-2′′′, C-6′′′), 128.2 (C-3′′′, C-5′′′), 129.4 (C-4′′′), 129.6 (C-1′′′), 132.3 (C-6′), 151.3 (C-8′a), 165.7 (C-1′′); (HRMS: found M^+ 495.2226, $C_{26}H_{32}NO_5F_3$ requires M, 495.2231).

*4.10. (1*R,*2′′*R*)-2-(*N-tert-*Butylamino-1-(2,2-dimethyl-1,3-benzodioxin-6-yl)ethyl-(2-methoxy-2-trifluoromethyl)phenylacetate **6** and its (1*S,*2′′*R*)-diastereomer **7***

Reaction of (*rac*)-**2** under the conditions described above resulted in an inseparable mixture of diastereomers. These were purified as above and analysed by ^{1}H NMR (Table 4).

Table 4
^{1}H-NMR shift data for the diastereomeric (*R*)-Mosher esters **6** and **7**

6		**7**		Multiplicity	Assignment
δ (ppm)	*J* (Hz)	δ (ppm)	*J* (Hz)		
1.06	-	0.98	-	s	*t*-Bu
1.53	-	1.52	-	s	2x2'-CH_3
2.83	12.3 and 4.1	2.75	12.3 and 3.9	dd	2-H_A
3.00	12.3 and 9.5	2.99	12.3 and 9.3	dd	2-H_B
3.54	-	3.43	-	s	2"-OCH_3
4.72	15.2	4.78	15.0	d	4'-H_A
4.79	15.2	4.84	15.0	d	4'-H_B
5.87	9.5 and 4.1	5.92	9.3 and 3.9	dd	1-H
6.75	8.6	6.79	8.4	d	8'-H
6.83	2.2	6.99	2.1	d	5'-H
7.07	8.6 and 2.2	7.18	8.4 and 2.1	dd	7'-H
7.2-7.5	-	7.2-7.5	-	m	other Ar-H

*4.11. (1*S,*1′′*R*)-2-[*N-tert-*Butyl*-N-*(1-phenethylamido)amino]-1-(2,2-dimethyl-1,3-benzodioxin-6-yl)-ethanol **8***

A solution of triphosgene (220 mg, 0.7 mmol) in dichloromethane (4 cm^3) was stirred at room temperature under nitrogen while a solution of (*R*)-phenylethylamine (0.26 cm^3, 247 mg, 2.0 mmol) and *N*,*N*-diisopropylethylamine (0.40 cm^3, 296 mg, 2.3 mmol) in dichloromethane (3.5 cm^3) was added over 45 min. The resulting solution was stirred for a further 10 min followed by the addition of a solution of (*rac*)-**16** (558 mg, 2.0 mmol) in dichloromethane (4 cm^3). After 10 min of stirring the solution was evaporated to dryness under reduced pressure and the residue taken up in ethyl acetate (100 cm^3), washed with equal volumes of 10% $NaHCO_3$ and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to produce 768 mg crude material (largely comprising two major products and starting material). The material was adsorbed onto silica and chromatographed using a mixture of ethyl acetate and petroleum ether (10:90 followed by 20:80) as eluent. Only the more polar of the products could be isolated cleanly to give **8** (156 mg, 0.4 mmol, 37% as a single diastereomer), mp 149–150°C (ethyl acetate/hexane); $[\alpha]_D$ −3.5 (*c* 1.1 methanol); found C, 70.1; H, 8.6; N, 6.7; $C_{25}H_{34}N_2O_4$ requires C, 70.4;

H, 8.0; N, 6.6%; ν_{max} ($CHCl_3$)/cm^{-1} 1652 (C=O urea); δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s, *t*-Bu), 1.47 (3H, d, *J* 6.8 Hz, 2′′-H), 1.54 (6H, s, 2×2′-CH_3), 3.23 (1H, dd, *J* 16.3 and 2.3 Hz, 2-H_A), 3.44 (1H, dd, *J* 16.3 and 9.6 Hz, 2-H_B), 4.76 (1H, dd, *J* 9.6 and 2.3 Hz, 1-H), 4.82 (2H, s, 4′-H_2), 4.94 (1H, m, 1′′-H), 6.60 (1H, d, *J* 7.4 Hz, 1′′-NH), 6.80 (1H, d, *J* 8.4 Hz, 8′-H), 6.93 (1H, d, *J* 1.9 Hz, 5′-H), 7.09 (1H, dd, *J* 8.4 and 1.9 Hz, 7′-H), 7.2–7.4 (5H, m, 2′′′-6′′′-H); δ_C (100 MHz, $CDCl_3$) 23.3 (C-2′′), 24.7 and 24.8 (2′-CH_3), 29.1 (*t*-Bu -*C*H_3), 49.9 (C-1′′), 54.4 (C-2), 55.9 (*t*-Bu -*C*$(CH_3)_3$), 60.9 (C-4′), 76.7 (C-1), 99.7 (C-2′), 117.3 (C-8′), 119.7 (C-4′a), 121.9 (C-5′), 125.5 (C-7′), 126.0, 126.7 and 128.5 (C-2′′′-C-6′′′), 134.1 (C-6′), 145.3 (C-1′′′), 151.1 (C-8′a), 160.7 (C=O); (HRMS: found M^+ 426.2507, $C_{25}H_{34}N_2O_4$ requires M 426.2518).

4.12. Analyses

4.12.1. NMR determination of optical purity of (R)-albuterol acetonide, (R)-2

Typically, **2** (5 mg) and (*R*)- or (*S*)-*O*-acetylmandelic acid (6 mg) were dissolved in $CDCl_3$ (1 cm^3) and the ^1H NMR spectra recorded (400 MHz). Several of the protons in **2** gave well distinguished peaks for each diastereomer formed in solution and integration of these pairs (usually the *t*-Bu peaks) allowed determination of the enantiomeric excess.

4.12.2. Chiral high performance liquid chromatography on (R)-2 and (R)-5

The conditions used for the chromatographic determinations are shown in Table 5.

Table 5
Chiral high performance liquid chromatography on (*R*)-**2** and (*R*)-**5**

	(*R*)-**2**	(*R*)-**5**	(*R*)-**2** and (*R*)-**5**
Column:	Phenomenex Chirex 3022	Phenomenex Chirex 3022	Chirobiotic Teicoplanin
Mobile Phase:	hexane/1,2-dichloroethane /methanol/trifluoroacetic acid (240/140/7.5/1)	hexane/1,2-dichloroethane /methanol/trifluoroacetic acid (240/140/20/1)	acetonitrile/methanol/ acetic acid/triethylamine (700/300/5/2)
Temperature:	ambient	ambient	ambient
Flow rate:	1.0 $cm^3.min^{-1}$	1.2 $cm^3.min^{-1}$	1.8 $cm^3.min^{-1}$
Detection λ:	254 nm	280 nm	230 nm
Injection volume:	25 μl	25 μl	10 μl
Sample concentration	10 $mg.cm^{-3}$	5 $mg.cm^{-3}$	5-10 $mg.cm^{-3}$

4.13. Crystal structure determinations

For both (+)-**2** and **8**, preliminary unit cell and space group data were determined from X-ray precession photographs using Ni-filtered CuKα-radiation (λ=1.5418 Å). Intensity data were collected using graphite-monochromated MoKα-radiation (λ=0.7107 Å) and corrected for Lorentz-polarisation effects. The structures were solved using program SHELXS-86[36] and refined on F^2 with SHELXL-93[37] with H atoms in idealised positions and treated isotropically while non-H atoms were refined anisotropically. Details for the individual crystals follow.

(+)-**2**: MW=297.38, $C_{16}H_{25}NO_3$, crystal size 0.2×0.4×0.3 mm, orthorhombic, $P2_12_12_1$ (No. 19), a=5.958(1), b=8.716(2), c=30.481(3) Å, V=1582.9(4) Å^3, Z=4, D_{calc}=1.172 g cm^{-3}. Intensity data in the range 1°<θ<30° were measured on an Enraf–Nonius CAD4 diffractometer with the crystal cooled to −50±1°C. A total of 4612 reflection intensities were measured of which 3950 were unique (R_{int}=0.029) and 2507 had $I>2\sigma(I)$. Final R indices were R_1=0.0488 and wR_2=0.3352 for 185 parameters.

8: MW=426.56, $C_{25}H_{34}N_2O_4$, crystal size 0.3×0.4×0.4 mm, orthorhombic, $P2_12_12_1$ (No. 19), a=6.749(1), b=13.860(2), c=25.628(3) Å, V=2397.3(4) Å^3, Z=4, D_{calc}=1.182 g cm^{-3}. Intensity data in the range 3°<θ<28° were measured at 20±1°C on a Nonius Kappa CCD diffractometer using the following strategy: 200 frames, 40 s per frame, χ=0°, 1° rotation in φ per frame; 37 frames, 40 s per frame, χ=−90°, 1° rotation in ω per frame. Data were processed with the DENZO-SMN package.[38] Of the 5919 reflections measured, 5750 were unique (R_{int}=0.024) and 4765 had $I>2\sigma(I)$. Final refinement involved two restraints and 290 parameters, yielding R_1=0.0396 and wR_2=0.1173.

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