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Potassium trimethylsilanolate induced cleavage of 1,3-oxazolidin-2- and 5-ones, and application to the synthesis of (*R*)-salmeterol

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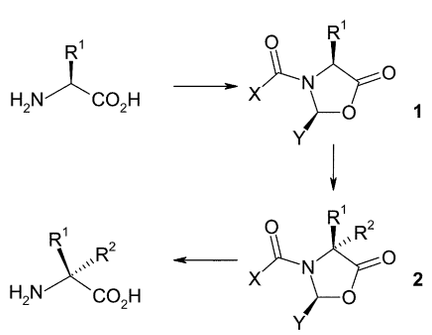
A convenient and efficient method for the cleavage of 1,3-oxazolidin-5-ones and 1,3-oxazolidin-2-ones utilising potassium trimethylsilanolate in tetrahydrofuran is described. The benzyloxycarbonyl-protecting group is readily removed under the reaction conditions, whereas the *N*-benzoyl group is stable. A synthesis of (*R*)-salmeterol exploiting the 2-oxazolidinone ring as a protecting group for the ethanolamine moiety is also described.

Introduction

Methods for the asymmetric synthesis of homochiral α-substituted aminoacids include Schöllkopf's bis-lactim ether,[1] Seebach's oxazolidinones,[2] Williams's diphenyloxazinones,[3] and Corey's[4] and Lygo's[5] asymmetric alkylation of glycine Schiff's bases. The most commonly used method is probably Seebach's oxazolidinone methodology or one of its variants (Scheme 1). The variants differ in the nature of groups X and Y, in the ratio of *cis* : *trans* isomers of oxazolidinones **1**, and the cleavage conditions of oxazolidinones **2**. The Seebach[2] oxazolidinones (X = Ph; Y = *tert*-Bu) are hydrolysed under strongly acidic conditions (6 M hydrochloric acid for 3 h at reflux). The Karady[6] oxazolidinones (X = $PhCH_2O$; Y = Ph) are cleaved by a two-step process involving hydrolysis with excess sodium hydroxide in methanol, followed by hydrogenolysis over 10% palladium on carbon and at 40 psi of hydrogen. The Smith[7] oxazolidinones (X = allyloxy; Y = *tert*-Bu) are also cleaved by a two stage procedure involving first hydrolysis using sodium hydroxide in methanol at reflux for 16 h, followed by removal of the allyloxycarbonyl group using tetrakis(triphenylphosphine)-palladium (0) and dimedone. The Davies[8] oxazolidinones (X = *tert*-Bu; Y = ferrocene) being the more labile of this group are cleaved by Amberlyst-15 ion exchange resin in aqueous acetone over 12 h. Finally, the Mutter[9] oxazolidinones (X = Y = Ph) being the more stable are hydrolysed in concentrated hydrochloric acid at reflux.



Scheme 1

Lithium, sodium and potassium trimethylsilanolates are commercially available and are recognized as hydroxide anion equivalents soluble in organic solvents. Despite this unique property there are only a few reports describing their use. The most frequently encountered application of potassium trimethylsilanolate is in the preparation of anhydrous carboxylate salts from esters and acid chlorides introduced by Laganis and Chenard.[10] Two more reports describe the use of sodium trimethylsilanolate as a base to promote elimination of methanol from β-methoxyketones,[11] and the deprotonation of propyne iminium salts.[12] Another report describes the use of sodium trimethylsilanolate in the displacement of fluoride from activated aromatic rings to produce phenols by aromatic nucleophilic substitution,[13] and finally Merchant reported the conversion of nitriles to primary amides using potassium trimethylsilanolate.[14]

Discussion

As part of a medicinal chemistry project both enantiomers of 3-iodo-α-methylphenylalanine were required for conversion to the corresponding hydantoins and for further elaboration.[15] It was decided to use the oxazolidinone chemistry, because of its simplicity and the fact that Kapadia has recently described an improved procedure for the preparation of one of the required starting materials benzyl (2*S*,4*S*)-4-methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate **3** from CBZ-L-alanine, benzaldehyde dimethyl acetal, thionyl chloride and anhydrous zinc chloride.[16] The oxazolidinone **3** was alkylated in tetrahydrofuran with 3-iodobenzyl bromide by adding the substrate and electrophile at the same time to lithium bis(trimethylsilyl)amide at −30 °C in order to minimize the decomposition of the resulting enolate. In this way alkylated oxazolidinone **4** was obtained in 72% yield. ^{1}H NMR indicated that the compound existed as two rotamers, which collapsed to one on heating a DMSO NMR solution to 100 °C. In our experience oxazolidinones **2** bearing a carbamate protecting group (X = $PhCH_2O$-) and bulky α-substituents are difficult to hydrolyse with hydroxide in alcohol and we therefore sought an alternative cleavage procedure. We envisaged that potassium trimethylsilanolate would cleave **4** to (*R*)-3-iodo-α-methylphenylalanine **5** in one step rather than the usual two-step process involving hydrolysis and hydrogenolysis. Treatment of **4** with 3 equiv. of potassium trimethylsilanolate in tetrahydrofuran for 2.5 h at 75 °C indeed not only cleaved the oxazolidinone ring, but also removed the nitrogen protecting group in 95% yield (Scheme 2). The whole process shown in Scheme 2 was repeated starting from CBZ-D-alanine to give (*S*)-3-iodo-α-methylphenylalanine (ent **5**) in similar yields.

Having established a single step method for the cleavage of 1,3-oxazolidin-5-ones containing a CBZ protecting group, the cleavage of the Seebach oxazolidinones containing the more robust *N*-benzoyl group was investigated. (*R*)-Phenylalanine was converted to oxazolidinone **6** (64%) using the Seebach protocol, and alkylated with iodomethane to give **7** (Scheme 3). LCMS of the crude reaction mixture indicated the presence of

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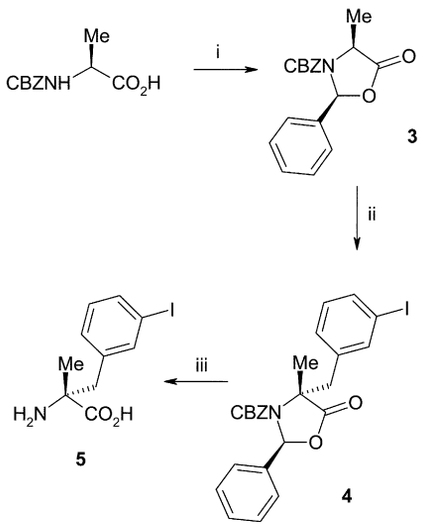
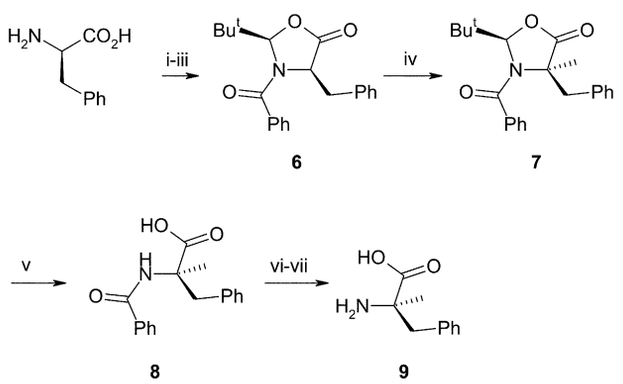


Scheme 2 *Reagents and conditions*: i) $(MeO)_2CHPh$, $ZnCl_2$, $SOCl_2$, THF, 0 °C; ii) $LiN(TMS)_2$, THF, 3-I-$C_6H_4CH_2Br$, −30 °C; iii) $KOSiMe_3$, THF, 75 °C.

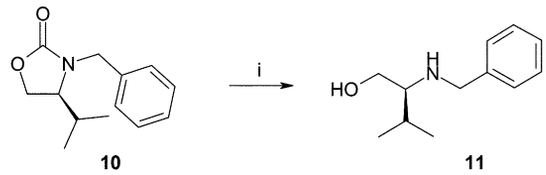


Scheme 3 *Reagents and conditions*: i) NaOH, H_2O; ii) t-BuCHO, petroleum ether; iii) PhCOCl, CH_2Cl_2; iv) $LiN(TMS)_2$, THF, MeI, −30 °C; v) $KOSiMe_3$, THF, 60 °C; vi) 6 M HCl, 110 °C; vii) SCX-2 ion exchange resin.

small quantities of another diastereoisomer (4%). Treatment of **7** with 2 equivalents of potassium trimethylsilanolate in tetrahydrofuran at 60 °C gave ring cleavage product **8**, whilst retaining the *N*-benzoyl group (100%), allowing thus for further manipulation of the free carboxylic acid group. Even prolonged heating (24 h) with 5 equivalents of potassium trimethylsilanolate did not cleave the benzoyl group. However, heating **8** to reflux in 6 M hydrochloric acid gave (*R*)-α-methylphenylalanine **9** (100%). The enantiomeric excess of **9** was determined using chiral HPLC and found to be >96%.

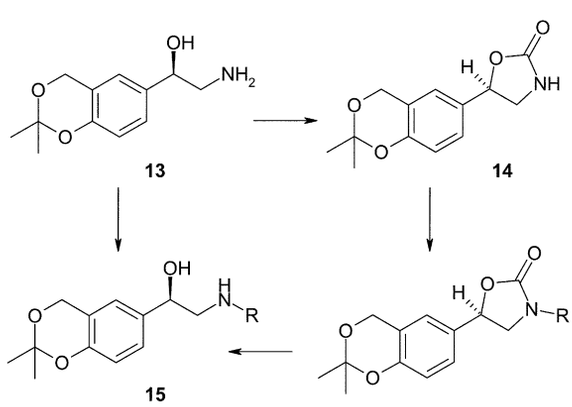
1,3-Oxazolidin-2-ones are useful intermediates in the synthesis of a variety of 1,2-amino alcohols.[17–22] Typical cleavage conditions involve the use of an excess hydroxide in an aqueous organic solvent and at elevated temperatures.[17–22] Recently Bergmeier reported two new methods for the hydrolysis of 1,3-oxazolidin-2-ones the first involving the use of polymer-supported hydroxide (Dowex 1 × 8–100) and the second involving the use of polymer-supported ethylenediamine [*N*-(2-aminoethyl)aminomethyl polystyrene].[23] Following on from the successful application of potassium trimethylsilanolate in the cleavage of 1,3-oxazolidin-5-ones it was of interest to apply this methodology to the cleavage of 1,3-oxazolidin-2-ones. Thus, treatment of **10**[24] with excess potassium trimethylsilanolate in refluxing tetrahydrofuran for 2 h gave the amino alcohol **11** in 83% yield (Scheme 4).

This result encouraged us to apply oxazolidinone chemistry in the synthesis of salmeterol (**12**). Salmeterol is a potent, long acting β_2 adrenoceptor agonist used as a bronchodilator for the

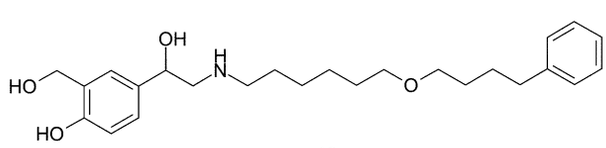


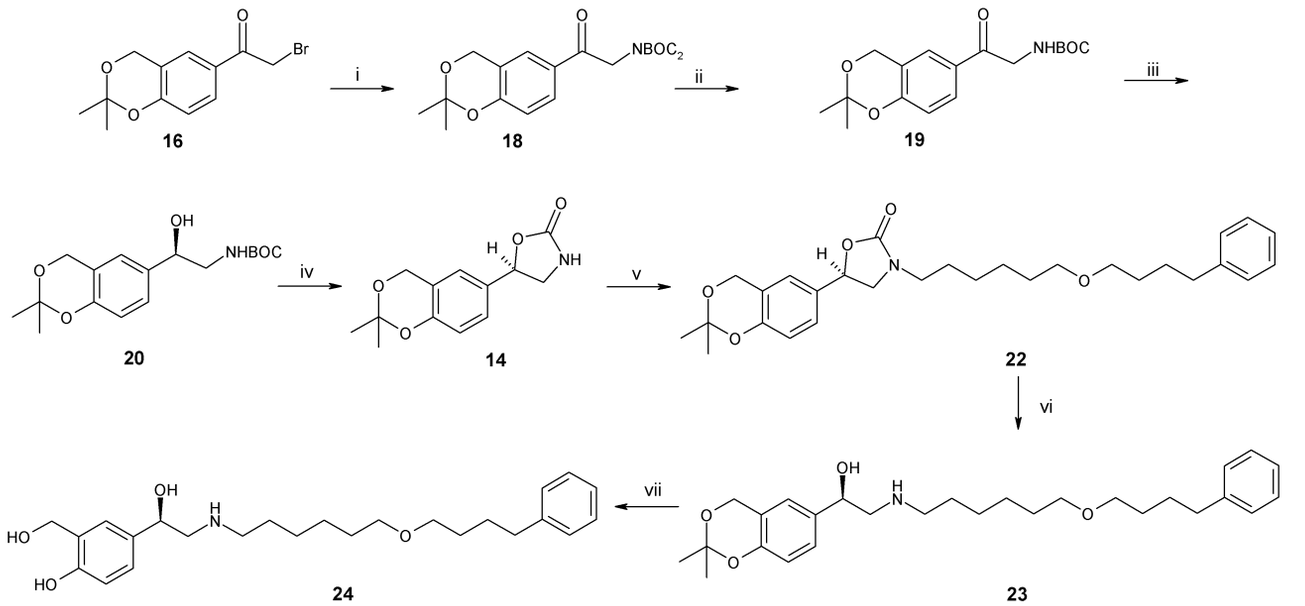
Scheme 4

prevention of bronchospasm in patients with asthma or chronic obstructive pulmonary disease. Recently we described the synthesis of (*S*)-salmeterol utilizing an enantioselective reduction of an azidoketone using *Pichia angusta*.[25] More recently we have published the synthesis of (*R*)-salmeterol utilizing a novel diastereoselective reduction of a phenacyl phenylglycinol derivative with calcium chloride–sodium borohydride.[26] Herein we report a versatile route to (*R*)-salmeterol which was used to prepare a variety of homochiral analogues for biological screening. It was envisaged that conversion of the amino alcohol **13** to oxazolidinone **14** be used as a protecting group for the amino and hydroxy groups in order to block further reaction (dialkylation on nitrogen) and concurrently moderate the reactivity of the amine nitrogen towards any reactive functional groups that might be present in the electrophiles (Scheme 5). Previously we had used an excess of amino alcohol **13** for the direct alkylation to **15** in order to minimize the formation of dialkylated products, however, this is not efficient in terms of the expensive chiral reagent **13**.[25] The synthesis (Scheme 6) commenced by condensing the bromoketone **16**[27] with di-*tert*-butyl iminodicarboxylate **17**[28] in the presence of caesium carbonate in acetonitrile to give **18** in 53% yield. One of the butoxycarbonyl groups was removed selectively using trifluoroacetic acid in dichloromethane (84%) and the resulting ketone **19** was reduced to the protected amino alcohol **20** using the chiral CBS-oxazaborolidine protocol[29] (99%) and in 98 : 2 diastereoisomeric ratio. Treatment of **20** with sodium hydride in dimethylformamide gave the oxazolidinone **14** (70%) and in 99 : 1 diastereoisomeric ratio. This intermediate proved extremely useful as it was a stable crystalline solid which could be alkylated very cleanly under mild conditions with a variety of electrophiles. Thus, deprotonation of **14** and alkylation with bromide **21**[30] gave **22** in 77% yield. Treatment of **22** with two equivalents of potassium trimethysilanolate in refluxing tetrahydrofuran gave amino alcohol **23** (96%), which was deprotected in methanolic acetic acid at 20 °C to give (*R*)-salmeterol **24** in 80% yield and >98% ee.



Scheme 5





Scheme 6 *Reagents and conditions*: i) di-*tert*-butyl iminodicarboxylate (**17**), Cs_2CO_3, CH_3CN; ii) CF_3CO_2H, CH_2Cl_2; iii) (*R*)-tetrahydro-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole, BH_3.THF, PhMe; iv) NaH, DMF; v) NaH, THF, $Br(CH_2)_6O(CH_2)_4Ph$ (**21**); vi) $KOSiMe_3$, THF; vii) AcOH, MeOH.

In conclusion a convenient and efficient method for the cleavage of 1,3-oxazolidin-5-ones and 1,3-oxazolidin-2-ones utilising potassium trimethylsilanolate in tetrahydrofuran is described. The *N*-benzoyl group is stable under the reaction conditions, however, the benzyloxycarbonyl group is readily removed. A synthesis of (*R*)-salmeterol is also described which exploits the 2-oxazolidinone moiety as a protecting group for the ethanolamine functionality, and is cleaved by potassium trimethylsilanolate. The oxazolidinone route has successfully been applied to the synthesis of a variety of homochiral salmeterol analogues.[31]

Experimental

Organic solutions were dried over anhydrous $MgSO_4$. TLC was performed on Merck 0.25 mm Kieselgel 60 F_{254} plates. Products were visualised under UV light and/or by staining with aqueous $KMnO_4$ solution. LCMS analysis was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm × 4.6 mm) eluting with 0.1% formic acid and 0.01 M ammonium acetate in water (solvent A), and 0.05% formic acid and 5% water in acetonitrile (solvent B), using the following elution gradient 0–0.7 min 0% B, 0.7–4.2 min 100% B, 4.2–5.3 min 0% B, 5.3–5.5 min 0% B at a flow rate of 3 ml min^{-1}. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES+ve and ES−ve). Analytical HPLC was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm × 4.6 mm) eluting with 0.1% formic acid and 0.01 M ammonium acetate in water (solvent A), and 0.05% formic acid and 5% water in acetonitrile (solvent B), using the following elution gradient for the 15 min run: 0–1.00 min 0% B, 1.00–10.00 min 100% B, 10.00–13.00 min 100% B, 13.00–15.00 min 0% B or for the 30 min run: 0–2.00 min 0% B, 2.00–22.00 min 100% B, 22.00–27.00 min 100% B, 27.00–29.00 min 0% B, 29.00–30.00 min 0% B, at a flow rate of 1 ml min^{-1}, injecting 5 μl of solution and detecting between 215 to 330 nm. Column chromatography was performed on Merck Kieselgel 60 (art. 9385), or Biotage pre-packed silica gel cartridges containing KP-Sil run on a flash 12i chromatography module. Optical rotations were measured with an Optical Activity AA100 digital Polarimeter at 20 °C and are given in units of 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR spectra were recorded at 400 MHz unless otherwise stated and ^{13}C NMR at 100 MHz. The chemical shifts are expressed in ppm relative to tetramethylsilane. Potassium trimethylsilanolate (technical grade, 90% pure) was purchased from Aldrich and used without any further purification.

Benzyl (2*S*,4*R*)-4-(3-iodobenzyl)-4-methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate (4)

A solution of benzyl (2*S*,4*S*)-4-methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate (**3**) (1.205 g, 3.87 mmol) and 3-iodobenzyl bromide (1.15 g, 3.87 mmol) in tetrahydrofuran (8 ml) was added dropwise at −30 °C to a solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1 M, 4.1 ml) diluted in tetrahydrofuran (32 ml). The mixture was stirred at this temperature for 1 h and then allowed to warm to 20 °C and stirred for 3 h. Aqueous sodium bicarbonate solution was then added and the mixture was extracted with diethyl ether. The organic phase was separated and dried, filtered and evaporated under reduced pressure. The residue was purified by chromatography on a Biotage cartridge (40 g) eluting with diethyl ether–petroleum ether (1 : 9, 1 : 4) to give **4** (1.48 g, 72%) as a yellow wax: Analytical HPLC (15 min) 9.20 min, 2%; 9.33 min, 98%; LCMS t_R 4.02 min, 100%; ES+ve *m*/*z* 528 $(M+H)^+$; δ_H ($CDCl_3$) two rotamers (4 : 1) 7.63 (1H, d, *J* 8 Hz), 7.60 (0.8H, s), 7.50–7.09 (10H, m), 6.98 (1H, t, *J* 8 Hz), 6.86 (1.6H, d, *J* 8 Hz), 5.37 (0.2H, d, *J* 12 Hz), 5.34 (1H, s), 5.12 (0.2H, d, *J* 12 Hz), 5.07 (0.8H, d, *J* 12 Hz), 4.99 (0.8H, d, *J* 12 Hz), 3.70 (0.8H, d, *J* 13 Hz), 3.32 (0.2H, d, *J* 14 Hz), 3.07 (0.8H, d, *J* 13 Hz), 1.94 (2.4H, s) and 1.86 (0.6H, s); δ_H (250 MHz; DMSO-d_6) (two rotamers collapse to one on heating to 100 °C) 7.67 (1H, br d, *J* 8 Hz), 7.45 (1H, s), 7.4–7.2 (8H, m), 7.2–6.95 (4H, m), 5.57 (1H, s), 5.08 (2H, AB q, *J* 10 Hz), 3.53 (1H, d, *J* 14 Hz), 3.02 (1H, d, *J* 14 Hz), and 1.83 (3H, s).

Benzyl (2*R*,4*S*)-4-(3-iodobenzyl)-4-methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate (*ent*-4)

Was obtained by the method described for its enantiomer above (4.1 g, 75%) as a yellow solid: LCMS t_R 3.98 min; ES+ve *m*/*z* 528 $(M+H)^+$. NMR spectrum identical to the one reported above.

(*R*)-3-Iodo-α-methylphenylalanine (5)

A mixture of **4** (1.47 g, 2.79 mmol) and potassium trimethylsilanolate (90% pure; 1.2 g, 8.4 mmol) was suspended in tetrahydrofuran (50 ml) and heated to 75 °C for 2.5 h. Methanol

(10 ml) was added and the solvents were removed under reduced pressure. The residue was re-dissolved in methanol and applied to two 10 g SCX-2 ion exchange cartridges eluting with methanol and then with 0.2 M ammonia in methanol. The ammoniacal solutions were evaporated to dryness to give **5** (810 mg, 95%) as a white solid: LCMS t_R 1.93 min, 100%; ES+ve *m*/*z* 306 $(M + H)^+$; ES−ve *m*/*z* 304 $(M - H)^-$; δ_H (CD_3OD) 7.66 (1H, t, *J* 2 Hz), 7.53 (1H, br d, *J* 8 Hz), 7.27 (1H, br d, *J* 8 Hz), 7.01(1H, t, *J* 8 Hz), 3.12 (1H, d, *J* 13 Hz), 2.61 (1H, d, *J* 13 Hz), and 1.31 (3H, s) (Found: C, 37.3; H, 4.3; N, 4.4. $C_{10}H_{12}INO_2.H_2O$ requires C, 37.2; H, 4.4; N, 4.3%).

(*S*)-3-Iodo-α-methylphenylalanine (*ent*-5)

White solid: LCMS t_R 2.00 min, 98%; ES+ve *m*/*z* 306 $(M + H)^+$; ES−ve *m*/*z* 304 $(M - H)^-$. NMR spectrum identical to the one reported above.

(2*R*, 4*R*)-3-Benzoyl-4-benzyl-2-(*tert*-butyl)-1,3-oxazolidin-5-one (6)

Sodium hydroxide (4.117 g, 103 mmol) in water was added to (*R*)-phenylalanine (17 g, 103 mmol), and the mixture was strirred until homogeneous. The water was removed under reduced pressure and the residue was treated with pivalaldehyde (16 g, 186 mmol) and petroleum ether (40–60 °C) (300 ml). The mixture was heated to reflux with azeotropic removal of water using a Dean and Stark apparatus for 6 h. The solvent was removed under reduced pressure and the residue was dried overnight under vacuum. Dichloromethane (200 ml) was added, the mixture was cooled to −50 °C and treated with a solution of benzoyl chloride (17.37 g, 124 mmol) in dichloromethane (30 ml). The reaction mixture was kept at −50 °C for 8 h, allowed to warm to 20 °C over 2 h and then stirred for 60 h. Water (50 ml) was added and the organic solution separated, washed with sodium bicarbonate solution, dilute citric acid solution, water and dried. The solution was filtered and evaporated under reduced pressure, the residue was recrystallised twice from diethyl ether–petroleum ether to give **6** (22.24 g, 64%) as white needles: $[a]_D^{20}$ + 29 (*c* 1.565 in $CHCl_3$); LCMS t_R 3.54 min, 100%; ES+ve *m*/*z* 338 $(M+H)^+$; δ_H ($CDCl_3$) 7.56–7.45 (3H, m), 7.43–7.40 (2H, m), 7.20–7.15 (3H, m), 6.75–6.70 (2H, m), 6.11 (1H, s), 4.27 (1H, dd, *J* 5, 8 Hz), 3.2–3.1 (2H, m) and 1.12 (9H, s); δ_C ($CDCl_3$) 173.7, 171.4, 135.8, 135.7, 130.5, 129.1, 129.0, 128.5, 127.1, 126.4, 95.2, 59.3, 40.8, 37.0 and 25.3 (Found: C, 74.5; H, 6.9; N, 4.2 $C_{21}H_{23}NO_3$ requires C, 74.75; H, 6.9; N, 4.15%).

(2*R*, 4*R*)-3-Benzoyl-4-benzyl-2-(*tert*-butyl)-4-methyl-1,3-oxazolidin-5-one (7)

A solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (0.5 M, 6 ml) was cooled to −30 °C under nitrogen. A solution of **6** (530 mg, 1.57 mmol) and iodomethane (0.35 ml, 5.62 mmol) in tetrahydrofuran (10 ml) was added at −30 °C. The colour of the reaction mixture turned dark orange. The mixture was stirred at this temperature for 1 h and then allowed to warm to 20 °C and stirred for a further 2 h. The dark orange colour was discharged after 1 h of stirring. Aqueous sodium bicarbonate solution was added and the mixture was extracted with diethyl ether. The organic phase was separated, washed with aqueous sodium bicarbonate, brine and dried. The solution was filtered and the filtrate evaporated to dryness to give **7** (553 mg, 100%) as a colourless gum: Analytical HPLC (30 min) t_R 14.45 min, 1.5%; t_R 14.98 min, 4.3%; t_R 15.25 min, 94%; LCMS t_R 3.92 min, 100%; ES+ve *m*/*z* 352 $(M+H)^+$; δ_H ($CDCl_3$) 7.62–7.50 (5H, m), 7.30–7.12 (5H, m), 6.18 (1H, br s), 3.43 (2H, br s), 1.39 (3H, br s) and 0.90 (9H, br s); δ_C ($CDCl_3$) 174.0, 137.2, 135.2, 131.2, 130.8, 128.5, 128.3, 128.2, 128.0, 127.9, 127.2, 125.6, 94.1, 63.4, 53.4, 44.8, 37.8, 35.7, 31.0, 30.3, 25.2 and 25.1; HRMS (ES+ve) *m*/*z* 352.1910 $[(M + H)^+$ calcd. for $C_{22}H_{26}NO_3$ 352.1913].

N-Benzoyl-(*R*)-α-methylphenylalanine (8)

A solution of **7** (550 mg, 1.56 mmol) in tetrahydrofuran (5 ml) was treated with potassium trimethylsilanolate (90% pure; 445 mg, 3.12 mmol) and the mixture was heated to 60 °C for 1 h by which time all starting material was consumed. The mixture was diluted with ethyl acetate and poured into 2 M hydrochloric acid. The organic phase was washed with brine, dried, filtered and concentrated under reduced pressure. The residue was dissolved in methanol and applied to an isolute NH2 cartridge (5 g) eluting with methanol, followed by 2 M hydrochloric acid in methanol (1 : 9). The acidic fractions were concentrated under reduced pressure to give **8** (440 mg, 100%) as a white foam:[32] $[a]_D^{20}$ −32 (*c* 0.839 in $CHCl_3$); LCMS t_R 3.02 min, 100%; ES+ve *m*/*z* 284 $(M + H)^+$; δ_H ($CDCl_3$) 9.5–9.05 (1H, br), 7.73 (2H, br d, *J* 8 Hz), 7.56 (1H, t, *J* 8 Hz), 7.46 (2H, br t, *J* 8 Hz), 7.29 (1H, under $CHCl_3$), 7.24–7.18 (2H, m), 6.88 (1H, s), 3.70 (1H, d, *J* 13 Hz) and 1.88 (3H, s); δ_C ($CDCl_3$) 178.0, 167.8, 136.0, 134.4, 131.8, 130.0, 128.7, 128.4, 127.1, 127.0, 61.4, 40.9 and 23.3 (Found: C, 68.5; H, 5.95; N, 4.5 $C_{17}H_{17}NO_3.0.75H_2O$ requires C, 68.8; H, 6.3; N, 4.7%).

(*R*)-α-Methylphenylalanine (9)

A suspension of **8** (60 mg, 0.21 mmol) in 6 M hydrochloric acid was heated to reflux for 1.5 h. The mixture was concentrated under reduced pressure and the residue was dissolved in ethanol and applied to an SCX-2 ion exchange cartridge (5 g) eluting with ethanol, followed by 10% aqueous ammonia in ethanol. The ammoniacal fractions were concentrated under reduced pressure to give **9**[2,6,8] (37 mg, 100%) as a white solid: LCMS t_R 0.74 min, 100%; ES+ve *m*/*z* 180 $(M + H)^+$; ES−ve *m*/*z* 178 $(M - H)^-$; δ_H (CD_3OD) 7.36–7.26 (5H, m), 3.29 (1H, d, *J* 14 Hz), 2.97 (1H, d, *J* 14 Hz) and 1.54 (3H, s). Chiral HPLC on a Chirobiotic V column (25 cm × 0.46 cm) eluting with ethanol–methanol (1 : 1) containing 0.1% trifluoroacetic acid and 0.025% triethylamine at a flow rate of 1 ml min^{-1} and detecting at 215 nm: t_R 7.39 min, 1.6%; t_R 8.47 min, 98.4% (racemate: t_R 7.23 min and 8.62 min).

(2*S*)-2-(Benzylamino)-3-methylbutan-1-ol (11)

Potassium trimethylsilanolate (90% pure; 1.23 g, 8.6 mmol) was added to a stirred solution of (4*S*)-3-benzyl-4-isopropyl-1,3-oxazolidinone[24] (**10**) (0.4 g, 1.82 mmol) in anhydrous tetrahydrofuran (7.5 ml). The resultant mixture was heated at reflux for 2 h then cooled to room temperature and methanol (1 ml) was added. The resultant solution was applied to an SCX-2 ion-exchange cartridge (10 g) and eluted with methanol (2 × 30 ml) and then methanolic ammonia (0.67 M, 2 × 30 ml). The fractions were combined and evaporated under reduced pressure to give **11**[33] (0.29 g, 83%) as a yellow oil: δ_H ($CDCl_3$) 7.40–7.24 (5H, m), 3.84 (1H, d, *J* 13 Hz), 3.77 (1H, d, *J* 13 Hz), 3.66 (1H, dd, *J* 11, 4), 3.38 (1H, dd, *J* 11, 7), 2.49 (1H, m), 1.89 (1H, m), 0.99 (3H, d, *J* 7 Hz) and 0.93 (3H, d, *J* 7 Hz); ES +ve *m*/*z* 194 $(M + H)^+$.

Di-(*tert*-butyl) 2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxoethylimidodicarbonate (18)

Caesium carbonate (66.54 g, 204 mmol) was added to a stirred suspension of 2-bromo-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanone[27] (**16**) (58.4 g, 205 mmol) and di-*tert*-butyl iminodicarboxylate (**17**) (44.56 g, 205 mmol) in acetonitrile (600 ml) under nitrogen. After vigorous stirring at 21 °C for 24 h the mixture was diluted with water (1 L) and the product was extracted with diethyl ether (1 L). The organic layer was washed with brine (500 ml), dried and evaporated. The resultant yellow solid was re-crystallised from diethyl ether to give

18 (24.4 g, 28%) as a white crystalline solid: LCMS t_R 3.72 min, 100%; ES+ve *m*/*z* 366 $(MH - C_4H_9)^+$; δ_H ($CDCl_3$) 7.78 (1H, dd, *J* 8, 2 Hz), 7.65 (1H, br s), 6.87(1H, d, *J* 8 Hz), 4.97 (2H, s), 4.88 (2H, s), 1.56 (6H, s) and 1.48 (18 H, s); δ_C ($CDCl_3$) 192.0, 155.9, 152.3, 128.4, 127.7, 125.3, 119.4, 117.3, 100.6, 82.8, 60.7, 51.7, 28.0 and 24.8 (Found: C, 62.3, H, 7.6, N, 3.4. $C_{22}H_{21}NO_7$ requires C, 62.7, H, 7.4, N, 3.3%). Further concentration of the mother liquors gave additional product (17.32 g, 20%). A third crop (4.34 g, 5%) was obtained after purifying the mother liquors by chromatography on silica gel eluting with heptane–ethyl acetate (5 : 1), evaporating the appropriate fractions and re-crystallising from diethyl ether.

tert-Butyl 2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxoethylcarbamate (19)

Trifluoroacetic acid (10.2 ml, 132 mmol) was added to a stirred solution of **18** (46.37 g, 110 mmol) in dichloromethane (500 ml) at 20 °C and the reaction was stirred for 4 h. Aqueous sodium hydroxide solution (0.5 M; 400 ml) was added and the phases were separated. The organic layer was washed with water (500 ml), dried, evaporated and the residue crystallised from diethyl ether to give **19** (15.15 g, 43%): LCMS t_R 3.24 min, 100%; ES+ve *m*/*z* 322 $(M + H)^+$; δ_H ($CDCl_3$) 7.78 (1H, d, *J* 8 Hz), 7.65 (1H, s), 6.87(1H, d, *J* 8Hz), 5.56 (1H, br s), 4.87 (2H, s), 4.58 (2H, d, *J* 4 Hz), 1.56 (6H, s) and 1.47 (9H, s); δ_C ($CDCl_3$) 192.9, 155.6, 155.8, 128.4, 127.2, 125.4, 119.5, 117.5, 100.8, 79.8, 60.6, 47.1, 28.4 and 24.8. (Found: C, 63.85, H, 7.0; N, 4.15. $C_{17}H_{23}NO_5$ requires C, 63.5, H, 7.2, N, 4.4%). Further product (14.60 g, 41%) was obtained from the mother liquors after evaporation and chromatography on silica gel eluting with cyclohexane–ethyl acetate (5 : 1).

tert-Butyl (2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethylcarbamate (20)

A solution of borane–tetrahydrofuran complex in tetrahydrofuran (1 M; 47 ml) was added slowly to a solution of (*R*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]-[1,3,2]oxazaborole in toluene (1 M; 4.7 ml) at 5 °C under nitrogen. After 0.25 h a solution of **19** (15.08 g, 46.92 mmol) in tetrahydrofuran (500 ml) was added slowly. The reaction was allowed to warm to room temperature and stirred for 2 h. After cooling to 5 °C the reaction mixture was quenched by the dropwise addition of 2 M hydrochloric acid. The mixture was partitioned between ethyl acetate (1 L) and water (1 L) and the organic layer was washed with brine and dried. The solvent was removed by evaporation to give **20** (15.1 g, 99%) as a white solid: $[\alpha]_D^{20}$ −36 (*c* 1.315 in $CHCl_3$); LCMS t_R 2.96 min, 100%; ES+ve *m*/*z* 647 $(2M + H)^+$, 306 $(MH - H_2O)^+$; δ_H ($CDCl_3$) 7.13 (1H, br d, *J* 8 Hz), 6.98 (1H, br s), 6.89 (1H, d, *J* 8Hz), 4.99 (1H, br s), 4.82 (2H, s), 4.72 (1H, br s), 3.40 (1H, m), 3.32 (2H, m), 1.53 (6H, s) and 1.44 (9H, s); δ_C ($CDCl_3$) 156.9, 150.8, 133.8, 125.7, 122.2, 119.4, 117.1, 99.6, 79.8, 73.6, 60.9, 48.4, 28.4, 24.8 and 24.6 (Found: C, 63.2, H, 7.75, N, 4.2. $C_{17}H_{25}NO_5$ requires C, 63.1, H, 7.8, N, 4.3%). Chiral HPLC on a chiralpak AD column (25 cm × 0.46 cm) eluting with ethanol–heptane (1 : 9) at a flow rate of 1 ml min^{-1} and detecting at 215 nm: t_R 13.13 min, 98%; t_R 15.16 min, 2% (racemate: t_R 13.20 min and 15.18 min).

(5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (14)

A solution of **20** (16.40 g, 50.71 mmol) in dimethylformamide (150 ml) was added dropwise to a stirred suspension of sodium hydride (60% oil dispersion; 2.65 g, 66.2 mmol) in dimethylformamide (50 ml) at 5 °C under nitrogen. The mixture was stirred at 20 °C for 3 h. The mixture was re-cooled to 0 °C and quenched by the addition of 2 M hydrochloric acid. The mixture was partitioned between ethyl acetate (1000 ml) and water (1000 ml). The organic phase was washed with brine (250 ml), dried and evaporated. The solid was triturated with diethyl ether to give **14** (8.84 g, 70%) as a white crystalline solid: $[\alpha]_D^{20}$ −20 (*c* 1.379 in $CHCl_3$); LCMS t_R 2.49 min, 100%; ES+ve *m*/*z* 250 $(M + H)^+$, 267 $(M + NH_4)^+$, 516 $(2M + NH_4)^+$; ES−ve *m*/*z* 294 $(M + HCO_2)^-$; δ_H ($CDCl_3$) 7.16 (1H, dd, *J* 9 and 2 Hz), 7.03 (1H, d, *J* 2 Hz), 6.84 (1H, d, *J* 9 Hz), 6.28 (1H, br s), 5.53 (1H, t, *J* 8 Hz), 4.85 (2H, s), 3.93 (1H, t, *J* 8 Hz), 3.53 (1H, t, *J* 8 Hz) and 1.54 (6H, s); δ_C ($CDCl_3$) 160.0, 151.8, 130.1, 126.0, 122.6, 119.8, 117.6, 99.9, 77.9, 60.8, 48.3, 24.8, and 24.7 (Found: C, 62.7; H, 6.1; N, 5.75. $C_{13}H_{15}NO_4$ requires C, 62.6; H, 6.1; N, 5.6%). Chiral HPLC on a Whelk-O 1 column (25 cm × 0.46 cm) eluting with ethanol–heptane (35 : 65) at a flow rate of 1 ml min^{-1} and detecting at 215 nm: t_R 8.11 min, 0.9%; t_R 10.38 min, 99.1% (racemate: t_R 7.99 min and 10.50 min).

(5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-[6-(4-phenylbutoxy)hexyl]-1,3-oxazolidin-2-one (22)

A solution of **14** (504 mg, 2.02 mmol) in dimethylformamide (10 ml) was added dropwise to a stirred suspension of sodium hydride (60% dispersion in oil, 90 mg, 2.25 mmol) in dimethylformamide (5 ml) at 5 °C under an atmosphere of nitrogen. After 5 min a solution of 6-bromohexyl 4-phenylbutyl ether[30] (**21**) (0.97 g, 3.10 mmol) in dimethylformamide (5 ml) was added dropwise. The reaction mixture was stirred at 5 °C for 1 h then at 20 °C for 3 h. After re-cooling to 5 °C the reaction was quenched with 2 M hydrochloric acid, the mixture was partitioned between ethyl acetate (100 ml) and water (100 ml). The organic phase was separated, washed with brine (50 ml), dried and concentrated. The residue was purified by chromatography on a silica Bond Elut cartridge (10 g) eluting with cyclohexane, dichloromethane and diethyl ether to give **22** (745 mg, 77%) as a colourless gum: LCMS t_R 3.91 min, 100%; ES +ve *m*/*z* 499 $(M + NH_4)^+$, 980 $(2M + NH_4)^+$; ES−ve *m*/*z* 526 $(M + HCO_2)^-$; δ_H ($CDCl_3$) 7.31–7.24 (3H, m), 7.19–7.14 (2H, m), 7.12 (1H, dd, *J* 8 and 2 Hz), 7.00 (1H, d, *J* 2 Hz), 6.84 (1H, d, *J* 8Hz), 5.39 (1H, t, *J* 8 Hz), 4.84 (2H, s), 3.84, (1H, t, *J* 8 Hz), 3.42 (2H, t, *J* 7Hz), 3.38 (2H, t, *J* 7 Hz), 3.37–3.20 (2H, m), 2.63 (2H, t, *J* 7 Hz), 1.72–1.52 (14H, m) and 1.42–1.30 (4H, m); δ_C ($CDCl_3$) 157.9, 151.7, 142.5, 130.5, 128.4, 128.3, 125.7, 122.3, 119.8, 117.5, 99.8, 74.2, 70.7, 60.8, 52.1, 44.1, 35.7, 29.6, 29.4, 28.1, 27.3, 26.5, 25.9, 24.8 and 24.7; HRMS (ES +ve) *m*/*z* 482.2897 [$(M + H)^+$ calcd. for $C_{29}H_{40}NO_5$ 482.2906].

(1*R*)-1-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-{[6-(4-phenylbutoxy)hexyl]amino}ethanol (23)

Potassium trimethylsilanolate (90% pure; 285 mg, 2.00 mmol) was added to a stirred solution of **22** (519 mg, 1.08 mmol) in tetrahydrofuran (10ml). The resultant mixture was heated at reflux for 1 h then cooled to room temperature. The mixture was partitioned between ethyl acetate (100 ml) and water (75 ml). The organic phase was washed with brine (50 ml), dried and concentrated to give **23**[25] (472 mg, 96%). LCMS t_R 3.20 min, 100%; ES+ve *m*/*z* 456 $(M + H)^+$; ES−ve *m*/*z* 500 $(M + HCO_2)^-$; δ_H ($CDCl_3$) 7.30–7.24 (3H, m), 7.19–7.15 (2H, m), 7.12 (1H, dd, *J* 8 and 2 Hz), 7.00 (1H, d, *J* 2 Hz), 6.79 (1H, d, *J* 8Hz), 4.84 (2H, s), 4.60 (1H, dd, *J* 3 and 9 Hz), 3.41 (2H, t, *J* 7Hz), 3.38 (2H, t, *J* 7 Hz), 2.86 (1H, dd, J 4 and 12 Hz), 2.71–2.58 (5H, m), 1.71–1.45 (14H, m) and 1.40–1.30 (4H, m).

2-(Hydroxymethyl)-4-((1*R*)-1-hydroxy-2-{[6-(4-phenylbutoxy)-hexyl]amino}ethyl)phenol (24)

A solution of **23** (20 mg, 0.04 mmol) in methanol (0.25 ml) and acetic acid (0.25 ml) was stirred at 20 °C for 3 days. The reaction mixture was partitioned between ethyl acetate and aqueous sodium bicarbonate solution. The organic phase was separated and washed with brine, dried, filtered and evaporated under reduced pressure to give **24** (13 mg, 80%) as a colourless gum.

LCMS t_R 3.55 min, 100%; ES+ve *m/z* 416 $(M + H)^+$; ES−ve *m/z* 414 $(M - H)^-$; δ_H ($CDCl_3$) 7.30–7.24 (4H, m), 7.20–7.13 (2H, m), 7.11 (1H, dd, *J* 8 and 2 Hz), 7.06 (1H, d, *J* 2 Hz), 6.80 (1H, d, *J* 8Hz), 4.75 (2H, s), 4.52 (1H, dd, *J* 9 and 4 Hz), 2.75 (1H, dd, *J* 4 and 12 Hz), 2.70–2.50 (5H, m), 1.70–1.40 (8H, m) and 1.38–1.25 (4H, m). Chiral HPLC on a chiralcel OJ column (25 cm × 0.46 cm) eluting with ethanol–heptane (1 : 4) at 0 °C, at a flow rate of 1 ml min^{-1} and detecting at 215 nm: t_R 8.86 min, >98% (racemate: t_R 9.08 min and 11.29 min).

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