Preparation of perfluoroalkane-tagged chiral auxiliaries and their application to stereoselective synthesis of a β^2-amino acid building block

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Abstract

Both enantiomers of novel perfluoroalkane-tagged 5,5-diphenyl-2-oxazolidinone (DIOZ) auxiliaries have been prepared using a two-step one-pot synthesis, starting from commercially available *N*-(*tert*-butoxycarbonyl)-*L*-valine methyl ester. The key feature of this approach is the efficient generation of a suitably active perfluoroalkyl-aryllithium species. By use of this protocol, the perfluoroalkane-tagged DIOZ auxiliaries are obtained in high enantiomeric purity and on multigram scales with overall yields exceeding 50%. The perfluoroalkane-tagged auxiliaries enable the use of fluorous solid-phase extraction, allowing efficient purification of tagged intermediates from crude reaction mixtures. The new auxiliaries have been applied in an asymmetric synthesis of β^2-*N*-Fmoc-phenylalanine *via* a stereoselective conjugate addition.

Keywords: Fluorous phase, solution-phase synthesis, separation, β^2-amino acid

Introduction

In the field of stoichiometric asymmetric synthesis, fluorous solid-phase extraction (FSPE) techniques have been applied to many chemical transformations, offering a powerful alternative to standard separation and purification methods. Initially proposed as a method of separating catalysts from process streams, perfluoroalkane chains have been developed as general supports for organic reagents and auxiliaries. Perfluoroalkane-tagged chiral auxiliaries are soluble in typical organic reaction solvents, and the perfluoroalkane chains are impervious to most common reagents.

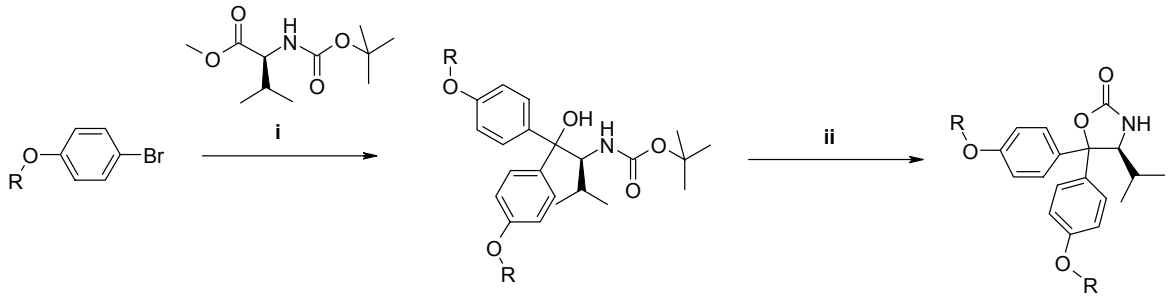
Generally, minor or no modifications to the classical reaction conditions are necessary. After a reaction is complete, selective recovery of the tagged material is easily accomplished by FSPE. Several research groups from academia and industry have demonstrated that fluorous synthesis

with chiral auxiliary methods is both viable and broadly applicable. For example, fluorous Evans-auxiliaries have been synthesized and applied successfully in aldol reactions and conjugate radical additions.[1-3] In this paper we report the short and efficient synthesis of perfluoroalkane tagged chiral DIOZ auxiliaries and their application to a novel synthesis of β^2-phenylalanine.[4-6]

Results and Discussion

Our initial approach to the synthesis was aimed at a late stage introduction of the perfluoroalkane tag to enable the use of a common intermediate in the preparation of a diverse range of auxiliaries in terms of the perfluoroalkane chain length and the manner of attachment of the tag (Scheme 1).

The oxazolidinone **3a** was synthesized using a modification of the procedure described by Seebach.[4] *para*-Bromophenol **1a** was protected with TIPS or TBDMS groups, *via* a standard protocol (silyl chloride, imidazole) to provide compounds **1b** and **1c** respectively, in nearly quantitative yields. The protected phenols were then converted into the corresponding Grignard reagents. The thus formed organo-magnesium halide species were immediately reacted with *N*-(*tert*-butoxycarbonyl)-*L*-valine methyl ester to deliver the tertiary alcohol intermediates **2b** and **2c** in good yields (87-95%). Treatment of these open-chain intermediates with potassium *tert*-butoxide in THF at room temperature gave the oxazolidinones **3b** and **3c** in 81% and 78% yields, respectively.



(i) Mg, THF, 17 h, 0 °C→RT, 87-95%. (ii) KO^{t}Bu, THF, 16 h, 0 °C-RT, 78-81%.

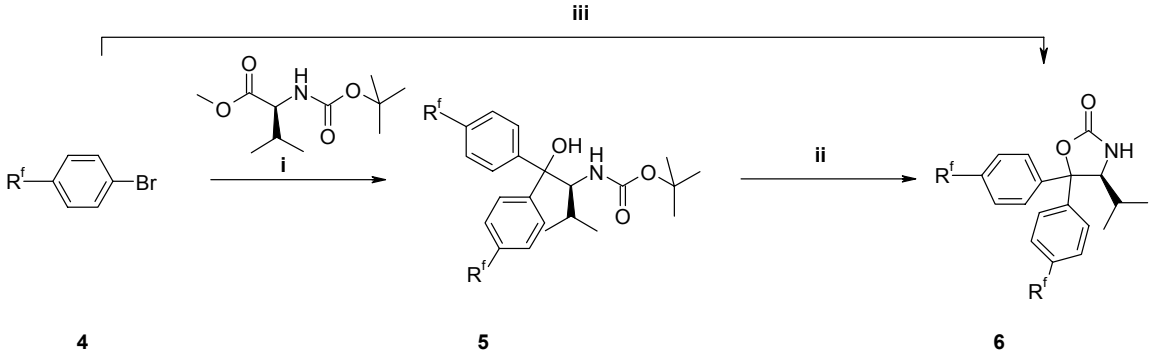
Scheme 1. Synthesis of Oxazolidinones.

Deprotection with HF•pyridine afforded the free *bis*-phenol **3a** (84-90%), which could be converted into the desired perfluoroalkane-tagged DIOZ auxiliaries either by re-protection with a freshly prepared perfluoroalkylsilyl chloride affording DIOZ **3d** (59%) or alkylation with hexadecafluoro-nonane triflate to provide perfluoro-ether DIOZ **3e** (43%).

Table 1. Derivatives of **1**,**2** and **3**

	R		R		R
1a	H			**3a**	H
1b	TIPS	**2b**	TIPS	**3b**	TIPS
1c	TBDMS	**2c**	TBDMS	**3c**	TBDMS
				3d	$Si(CH(CH_3)_2)_2CH_2CH_2C_8F_{17}$
				3e	$CH_2(CF_2)_7CF_2H$

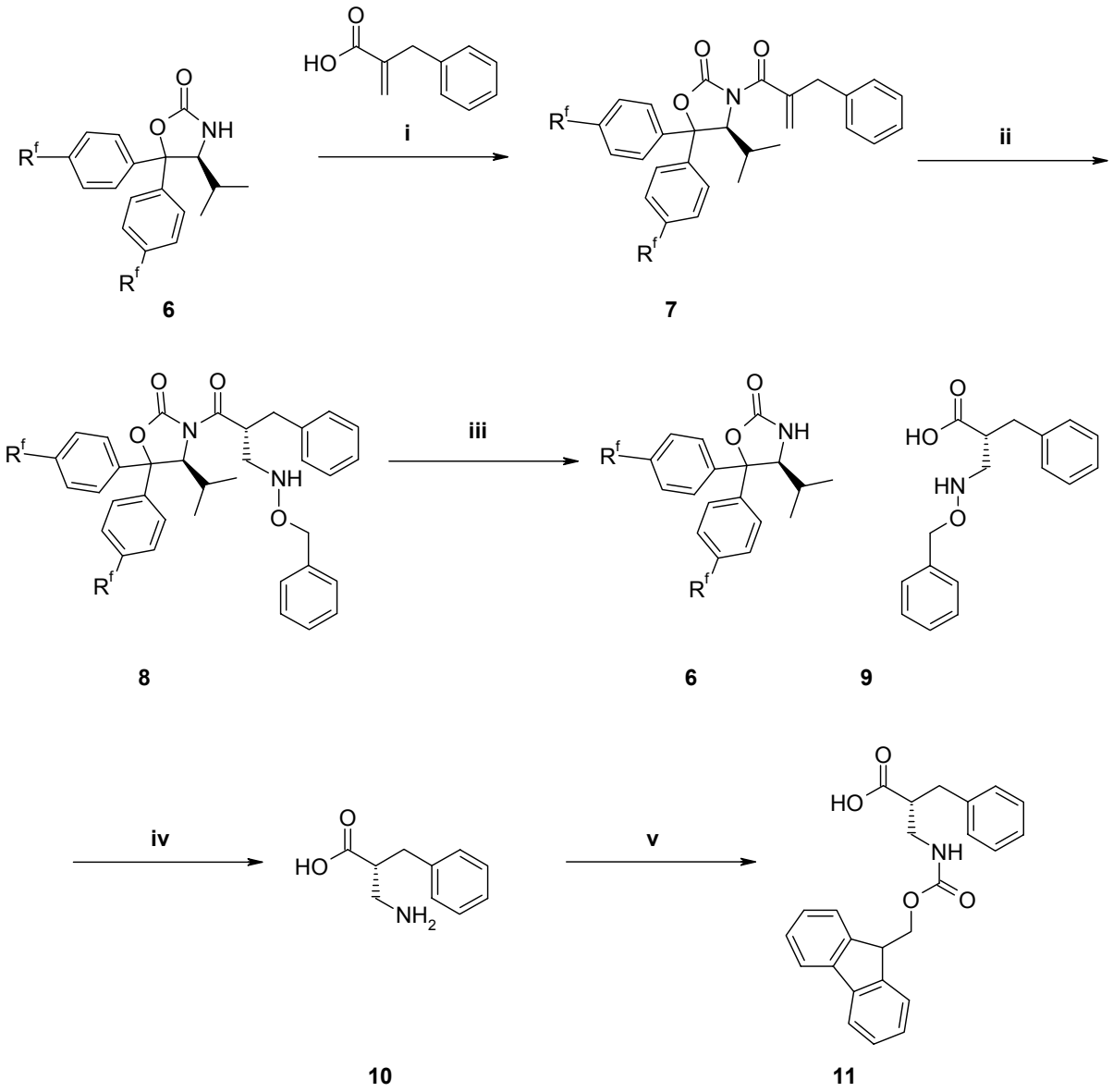
An alternative DIOZ auxiliary, where attachment of the perfluoroalkane tag to the phenyl rings is *via* a carbon-carbon bond, was synthesized from the commercially available perfluoroalkylaryl bromide **4** ($R^f = C_2H_4C_6F_{13}$, Scheme 2). Compound **4** was treated with *n*-BuLi at low temperature to afford the corresponding metallated species and immediately allowed to react with *N*-(*tert*-butoxycarbonyl)-*L*-valine methyl ester, providing the tertiary alcohol **5** (82%). Surprisingly, the application of the Grignard protocol resulted in absolutely no conversion, presumably as a result of failure to initiate formation of the Grignard reagent. Treatment of the perfluoroalkane-tagged open-chain intermediate **5** with potassium *tert*-butoxide in THF gave the DIOZ compound **6** in 57% yield. A more expeditious version of this route involved the synthesis of DIOZ auxiliary **6** from the commercially available aryl bromide **4** *via* metallation, addition and cyclisation in a one-pot process. The overall yield using this most convenient route was 50%. Using the same one-pot protocol but starting with *N*-(*tert*-butoxycarbonyl)-*D*-valine methyl ester, afforded the optical antipode of the auxiliary, namely DIOZ *ent*-**6**.



Scheme 2. Synthesis of perfluoroalkane tagged DIOZ auxiliary **6** ($R^f = C_2H_4C_6F_{13}$).
(i) *n*-BuLi, THF, -78 °C, 6 h, 82%. (ii) KO*t*-Bu, THF, 18 h, 0 °C-RT, 57%. (iii) *n*-BuLi, THF, -78 °C, 6h, then ↑ 18 ºC, 2 h, 50%.

The novel perfluoroalkane tagged chiral auxiliaries were then applied to stereoselective syntheses of a β^2-amino acid as depicted in Scheme 3.[6,7] A key aspect of this protocol was the application of FSPE purification techniques. As the fluorous tagged chiral auxiliaries **3d**, **3e** and **6** showed similar chromatographic behavior in several elution and separation experiments we choose **6** and *ent*-**6** as auxiliaries in an asymmetric synthesis on larger scale due to the ease of synthesis. Both enantiomers of the required α,β-unsaturated imide starting material, **7** and *ent*-**7**, were prepared using a standard acylation protocol (DMAP, DIPCD, 2 eq. 2-benzylacrylic acid) in good yield (78%). The imide intermediates **7** and *ent*-**7** were exposed to a twofold excess of *O*-benzyl hydroxylamine at 72 °C for 24 h in the key stereoselective conjugate addition reaction. Lower temperatures required significantly longer reaction times. The resultant aza-Michael adducts **8** and *ent*-**8** were purified using FSPE: A standard glass flash chromatography column was packed with commercially available Fluoroflash™ and pre-conditioned by passing through 80:20 MeOH-H_2O (v/v) under positive pressure. The residue was loaded on to the top of the column, using DMF as the loading solvent. The column was then eluted with MeOH/H_2O. The resulting crude products **8** and *ent*-**8** were a *ca*. 8.3:1 mixture of diastereomers, judged by HPLC, at the stereogenic centre introduced by the conjugate addition reaction. Formation of the tosylate salt of compound **8** and subsequent recrystallization thereof, improved the diastereomeric excess to 93% as determined by ^{1}H-NMR and HPLC. Removal of the auxiliary **6** and concomitant release of the β^2-aminoxy acid **9** was facilitated with LiOH/H_2O_2 in THF/H_2O (74%). The auxiliary was conveniently recovered (96%) using the same FSPE procedure. The previously reported β^2-aminoxy acid **9** was converted to the corresponding β^2-amino acid **10** *via* hydrogenation (H_2, Pd/C, MeOH, NH_3, H_2O) and Fmoc-protected using standard conditions (FmocOSu, $NaHCO_3$, THF) to afford compound **11** in 30% over the two steps.

This sample of the Fmoc-β^2-amino acid **11** was identical, as judged by ^{1}H-NMR and low resolution mass spectrometric analysis, to previously reported authentic material.[8,9] The depicted absolute stereochemistry is correlated to the chiral HPLC retention characteristics of the authentic material. The enantiomeric excess of the Fmoc-β^2-amino acid **11** resulting from both isomers of the auxiliary was analyzed *via* HPLC and found to exceed 95%.



(i) DMAP, DIPCD, DCM, 0 °C - RT 16 h 78%. (ii) *O*-benzyl hydroxylamine, THF, 72 °C, 24 h, 70%. (iii) H_2O_2, LiOH, THF, H_2O, 45 min, 74%. (iv) H_2, Pd/C(10%), MeOH, H_2O, NH_3 (v) Fmoc-OSu, $NaHCO_3$, THF, H_2O, 0 °C →RT, 2 h, 30% over two steps.

Scheme 3. Synthesis of Fmoc-β^2-phenylalanine using FSPE.

Conclusions

The experiments described in this publication have enabled production of perfluoroalkane-tagged DIOZ chiral auxiliaries from commercially available starting materials in a one-pot operation. Application of the perfluoroalkane-tagged DIOZ auxiliaries provided a short and efficient

synthesis of both enantiomeric forms of β^2-*N*-Fmoc-phenylalanine (described in the Experimental Section).[14,15] This route is distinguished by its succinctness and ease of recovery of the DIOZ auxiliary. Purification of products was achieved through silica and fluorous solid-phase extractions, with only one recrystallization being required. We have performed the complete sequence on various scales, up to the formation of 25 g of the target compound in a single batch and the process requires no equipment other than typical laboratory glassware. We believe that the reported perfluoroalkane-tagged DIOZ auxiliaries are truly powerful tools for drug discovery and high-throughput chemistry and are viable alternatives to conventional or solid supported auxiliaries.

Experimental Section

General Procedures. All reagents were obtained commercially and used as received unless otherwise noted. TLC was performed on Merck silica gel plates 60 F-254, Art. no. 5729.
Reverse-phase HPLC analyses were performed on an Agilent-1100 using a Macherey-Nagel CC 70/4 Nucleosil 100-3 C18 HD column, acetonitrile and water both containing 0.05% TFA, a column temperature of 35 °C, with a flow rate of 1.0 mL/min and measuring at 216 nm. The standard gradient used was 5–100% MeCN over 6 min, 100% MeCN for 1.5 min followed by 100–5% MeCN over 0.5 min.
NMR was performed using a 400 MHz Varian spectrometer, AS 400 Oxford. ^{1}H shifts were referenced to $CDCl_3$ at 7.25 ppm with tetramethylsilane as internal standard for ^{1}H NMR. MS was measured using VG Platform (Fisons Instruments), Spectraflow 783 Detector, HP 1100 Series HPLC. Melting points were measured using a Büchi, B-545 apparatus.

(4-Bromo-phenoxy)triisopropylsilane (1b). A solution of 4-bromophenol (**1a**, 43.96 g, 254 mmol) and TIPS-Cl (54.95 mL, 257 mmol) in DCM, was cooled, on an ice bath to 0 ºC whilst being stirred under nitrogen. The solution was treated with imidazole (43.3 g, 636 mmol) added gradually with caution, and then allowed to warm to RT, with stirring, over the course of 16 h. The resulting suspension was washed sequentially with HCl (2 x 200 mL of a 0.5 M aqueous solution), *sat. aq.* $NaHCO_3$ (200 mL) and brine (200 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was taken up into hexane (400 mL) and adsorbed onto silica gel (200 g) under reduced pressure. The resulting free-flowing solid was then added to the top of a short plug of silica (70 g) and eluted with hexane (3000 mL). Concentration of the appropriate fractions (R_f = 0.6-0.8) under reduced pressure afforded compound **1b** (81.7 g, 248 mmol, 98 %) as a colourless oil.
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31(2H, m), 6.76 (2H, m), 1.24 (3H, m), 1.09 (18H, d, J = 8.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.5, 132.5, 121.9, 113.4, 18.1, 12.8.
Mass Spectrum (ESI, -MS) *m/z* 327 (M-H), 249 (M-HBr).

(4-Bromo-phenoxy)-*tert*-butyldimethylsilane (1c). Compound **1c** was prepared in an analogous fashion to the preparation of compound **1b**, using 4-bromophenol (**1a**, 33.7 g, 194.8 mmol) as starting material. Purification via flash chromatography (R_f = 0.5-0.7, hexane elution) afforded compound **1c** (53.73 g, 187 mmol, 96 %) as a colourless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33 (2H, m), 6.73 (2H, m), 0.99 (9H, s), 0.20 (6H, s).

(-)-{(*S*)-1-[Hydroxy-*bis*-(4-triisopropylsilanyloxyphenyl)methyl]-2-methyl-propyl} carbamic acid *tert*-butyl ester (2b). The following protocol was adapted from a previously reported procedure.[4] A dry 250 mL round-bottomed flask fitted with a condenser, dropping funnel, thermometer and magnetic stirrer, was charged with Mg turnings (6.42 g, 264 mmol) and stirred, dry, under an atmosphere of nitrogen, overnight. A solution of compound **1b** (8.0 g, 24.3 mmol) in THF (20 mL) was added and stirring continued, until the reaction started spontaneously as evidenced by refluxing of the THF. At this stage, more of compound **1b** (74.82 g, 227.2 mmol) in THF (60 mL) was added, dropwise, at a rate sufficient to maintain reflux. The resultant mixture was heated at reflux, for 2 h, then cooled to below 6 ºC on an ice bath. A solution of *N*-(*tert*-butoxycarbonyl)-*L*-valine methyl ester (17.46 g, 75.5 mmol) in THF (20 mL) was added dropwise, at such a rate as to maintain the internal reaction temperature below 6 ºC, then the mixture was allowed to warm to RT, with stirring, over 18 h. The mixture was poured into ice-cold *sat. aq.* NH_4Cl (200), the aqueous phase was separated and extracted with EtOAc (2 x 150 mL). The combined organic phases were washed with brine (150 mL) and dried ($MgSO_4$), concentrated under reduced pressure and purified *via* flash chromatography. Concentration of the appropriate fractions (R_f = 0.3, 95:5 hexane / EtOAc) gave compound **2b** (44 g, 65.85 mmol, 87%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33-7.21 (4H, m), 6.80-6.75 (4H, m), 5.00 (1H d, J = 12 Hz), 4.45 (1H, m), 2.49 (1H, s), 1.78 (1H, complex m), 1.44 (1H, br. s), 1.36 (9H, s), 1.21 (6H, complex m), 1.06 (36H, d, J = 8.0 Hz), 0.86 (3H, d, J = 8.0 Hz), 0.81 (3H, d, J = 8.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.5, 154.8, 139.5, 138.6, 127.2, 126.8, 119.8, 119.6, 82.1, 79.1, 59.4, 28.9, 28.6, 22.9, 18.1, 17.6, 12.9, 12.8. Mass Spectrum (ESI, -MS) *m/z* 698 (M-H), 249 (TIPS-Phenol -H). Specific Rotation $[\alpha]_D^{22ºC}$ –39 (*c* 1.0, MeOH). HRMS (ESI^+) calcd for $C_{40}H_{69}NO_5Si_2Na$ $(M+Na)^+$: 722.4607, found: 722.4607; calcd for $C_{40}H_{69}NO_5Si_2K$ $(M+K)^+$: 738.4346, found: 738.4346.

(-)-{(*S*)-1-[Hydroxy-*bis*-(4-*tert*-butyldimethylsilanyloxyphenyl)methyl]-2-methyl-propyl}carbamic acid *tert*-butyl ester (2c). Compound **2c** was prepared in an analogous fashion to the preparation of compound **2b**, using compound **1c** (56.68 g, 197.3 mmol) and *N*-(*tert*-butoxycarbonyl)-*L*-valine methyl ester (13.05 g, 56.4 mmol) as starting materials. Purification *via* flash chromatography (R_f = 0.25, 95:5 hexane / EtOAc) afforded compound **2c** (33 g, 53.6 mmol, 95%), as an amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37-7.26 (4H, m), 6.78-6.73 (4H, m), 5.07 (1H, d, J = 12 Hz), 4.49 (1H, m), 2.74 (1H, s), 1.81 (1H, m), 1.45 (1H, br. s), 1.35 (9H, s), 0.98 (9H, s), 0.97 (9H, s), 0.89 (3H, d, J = 8 Hz), 0.85 (3H, d, J = 4 Hz), 0.19 (6H, s), 0.17 (6H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.8, 158.7, 158.6, 143.9, 143.0, 133.8, 131.5, 131.0, 125.7, 124.5, 124.0, 123.9, 86.3, 83.4, 63.7, 33.1, 32.8, 30.1, 27.1, 22.6, 21.9, 0.1. Mass Spectrum (ESI, -MS) *m/z* 614 (M-H), 542 (M-*tert*-butanol). Specific Rotation

$[\alpha]_D^{22°C}$ –31 (*c* 1.0, DCM). HRMS (ESI^+) calcd for $C_{34}H_{57}NO_5Si_2Na$ $(M+Na)^+$: 638.3668, found: 638.3668; calcd for $C_{34}H_{57}NO_5Si_2K$ $(M+K)^+$: 654.3407, found: 654.3407.

(-)-(*S*)-4-Isopropyl-5,5-*bis*-(4-triisopropylsilanyloxyphenyl)oxazolidin-2-one (3b). The following protocol was adapted from a previously reported procedure.[4] A solution of compound **2b** (44 g, 62.8 mmol) in THF (300 mL) magnetically stirred on an ice bath under an atmosphere of nitrogen, was treated with potassium *tert*-butoxide (8.9 g, 79.3 mmol) in one portion, and the reaction was allowed to warm slowly to RT over the course of 16 h. The resultant mixture was treated with NH_4Cl (300 mL of a 10% w/v aqueous solution) and stirred for 10 min. The aqueous phase was separated and extracted with Et_2O (2 x 200 mL) and the pooled organic phases were then dried ($MgSO_4$) and concentrated under reduced pressure. The resultant crude residue was purified *via* flash chromatography. Concentration of the appropriate fractions (R_f = 0.3, 4:1 hexane / EtOAc) afforded compound **3b** (33.5 g, 53.5 mmol, 81%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33-7.31 (2H, m), 7.15-7.13 (2H, m), 6.87 (1H, br. s), 6.84-6.78 (4H, m), 4.23 (1H, d, *J* = 4.0 Hz), 1.76-1.73 (1H, m), 1.27-1.17 (6H, m), 1.09-1.06 (36H, complex m), 0.83 (3H, d, *J* = 8.0 Hz), 0.69 (3H, d, *J* = 4.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.4, 156.1, 155.7, 136.5, 132.4, 128.2, 127.6, 119.8, 119.5, 89.6, 66.4, 29.9, 21.1, 18.1, 16.6, 12.9. Mass Spectrum (ESI, +MS) *m/z* 626 (M+H). Specific Rotation $[\alpha]_D^{22°C}$ –122 (*c* 1.0, MeOH). Anal. Calcd for $C_{36}H_{57}NO_4Si_2$: C, 69.07; H, 9.50; N, 2.24% Found: C, 68.96; H, 9.48; N, 2.16%

(-)-(*S*)-4-Isopropyl-5,5-*bis*-(4-*tert*-butyldimethylsilanyloxyphenyl)oxazolidin-2-one (3c). Compound **3c** was prepared in an analogous fashion to the preparation of compound **3b**, using compound **2c** (26.8 g, 43.5 mmol) as starting material. Purification *via* flash chromatography (R_f = 0.25, 9:1 hexane / EtOAc) afforded compound **3c** (18.4 g, 33.9 mmol, 78 %), as an amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36-7.33 (2H, m), 7.17-7.15 (2H, m), 6.81-6.74 (4H, m), 6.71 (1H, br. s), 4.23 (1H, d, J = 4.0 Hz), 1.80-1.73 (1H, m), 0.96 (18H, m), 0.83 (3H, d, J = 8.0 Hz), 0.70 (3H, d, J = 4.0 Hz), 0.18 (12H, m).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.5, 159.8, 159.5, 141.0, 136.6, 132.3, 131.7, 124.1, 123.8, 93.8, 70.6, 34.1, 30.0, 25.2, 22.6, 20.6, 0.01. Mass Spectrum (ESI, +MS) *m/z* 542 (M+H). Specific Rotation $[\alpha]_D^{22°C}$ –137 (*c* 1.0, MeOH). Anal. Calcd for $C_{30}H_{47}NO_4Si_2$: C, 66.50; H, 8.74; N, 2.58% Found: C, 66.21; H, 8.73; N, 2.52%

(-)-(*S*)-5,5-*Bis*-(4-hydroxyphenyl)-4-isopropyloxazolidin-2-one (3a). A dry polyethylene bottle flushed with nitrogen was charged with a magnetic stirrer and a solution of compound **3b** (17.5 g, 27.9 mmol) in THF (150 mL) and cooled in an ice bath with stirring, while HF·pyridine (35 mL of a 65-70% commercial solution) was added dropwise. The reaction was allowed to warm to RT over 16 h. The resultant mixture was diluted with diethyl ether (100 mL) and *sat. aq.* $NaHCO_3$ (500 mL). Solid $NaHCO_3$ was then added, in portions, until the reaction mixture was neutralised as evidenced by no more CO_2 being liberated. The organic layer was separated and the aqueous layer was extracted with 50:50 THF / diethyl ether (2 x 200 mL). The pooled organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified *via* flash chromatography. Concentration of the appropriate fractions (R_f = 0.45, 1:9 MeOH / DCM) afforded compound **3a** (7.36 g, 23.5 mmol, 84%). This protocol

was also used to prepare compound **3a**, in similar yield, *via* deprotection of compound **3c**. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.35-7.33 (2H, m), 7.16-7.13 (2H, m), 6.79-6.73 (4H, m), 4.96 (2H, br. s), 4.32 (1H, m), 1.85-1.73 (1H, m), 0.86 (3H, d, *J* = 8.0 Hz), 0.64 (3H, d, *J* = 8.0 Hz). ^{13}C-NMR (100 MHz, CD_3OD) δ 160.0, 157.1, 156.7, 135.7, 130.9, 127.6, 127.2, 114.9, 114.6, 89.9, 67.7, 65.7, 29.8, 25.4, 20.0, 15.0. Mass Spectrum (ESI, +MS) *m/z* 314 (M+H), 270 (M-CO_2). Specific Rotation $[\alpha]_D^{22^oC}$ –218 (*c* 1.0, MeOH). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47% Found: C, 67.80; H, 7.08; N, 3.95%

(-)-(*S*)-5,5-*Bis*-{4-[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)-diisopropylsilanyloxy]phenyl}-4-isopropyloxazolidin-2-one (3d). The following protocol was adapted from a previously reported procedure.[10] A 50 mL round-bottomed flask fitted with a septum and nitrogen entry and exit needles was charged with commercially available (1*H*,1*H*,2*H*,2*H*-perfluorodecyl)diisopropylsilane (4.84 g, 8.61 mmol) and then cooled to -10 ºC on a dry-ice / acetone bath. *Tert*-butyl hypochlorite (0.851 g, 7.84 mmol) was then added, dropwise, *via* syringe.[12] After 5 minutes, the reaction vessel was placed on a rotary evaporator and heated to 70 ºC under a reduced pressure of ~30 mBar to remove *tert*-butanol. To this vessel was then added a solution of compound **3a** (1.22 g, 3.89 mmol) in THF (10 mL) with stirring, at RT, under an atmosphere of nitrogen. Imidazole (1.06 g, 15.57 mmol) was then added, in a single portion, and stirring was continued at this temperature for 65 h. The mixture was diluted with diethyl ether (50 mL) and washed sequentially with HCl (2 x 20 mL of a 0.5 M aqueous solution), *sat. aq.* $NaHCO_3$ (20 mL) and H_2O (20 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. The resulting crude oil was purified *via* flash chromatography. Concentration of the appropriate fractions (R_f = 0.4, 1:4 EtOAc / hexane) gave compound **3d** (3.2 g, 2.28 mmol, 59%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35 (2H, m), 7.18 (2H, m), 6.79 (4H, m), 4.25 (1H, d, *J* = 4.0 Hz), 2.20-2.00 (4H, m), 1.78-1.68 (1H, m), 1.24-1.13 (4H, complex m), 1.09-1.02 (24H, m), 1.01-0.95 (4H, m), 0.84 (3H, d, *J* = 8.0 Hz), 0.70 (3H, d, *J* = 4.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.3, 155.3, 154.9, 137.1, 133.0, 131.1, 128.4, 127.8, 119.6, 119.2, 110.0, 89.4, 66.2, 29.9, 20.9, 17.51, 17.49, 17.46, 17.41, 17.39, 17.37, 16.3, 13.0. ^{19}F-NMR (376 MHz, $CDCl_3$) δ -81.35—-81.40 (6F, m), -117.06—-117.23 (4F, m), -122.32 (4F, s), -122.49 (8F, s), -123.29 (4F, s), -123.80 (4F, s), -126.71 (4F, s). Mass Spectrum (ESI, +MS) *m/z* 1435 (M+H). Specific Rotation $[\alpha]_D^{22^oC}$ –51 (*c* 1.0, MeOH).

(-)-(*S*)-5,5-*Bis*-[4-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-hexadecafluorononyloxy)-phenyl]-4-isopropyloxazolidin-2-one (3e). The following protocol was adapted from a previously reported procedure.[11] A mixture of compound **3a** (6.75 g, 21.56 mmol), 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-Hexadecafluoro-nonan-1-trifluoromethanesulfonate (29.58 g, 52.43 mmol) prepared as previously described[12] and Cs_2CO_3 (21.5 g, 65.9 mmol) in DMF (140 ml) was stirred, under a nitrogen atmosphere, at a temperature of 120 ºC, for 72 h. The resultant suspension was cooled to RT, then placed on an ice bath, and treated with HCl (250 mL of a 0.5 M aqueous solution). After stirring for 5 min, the mixture was diluted with diethyl ether (500 mL) and poured into a separation funnel. The aqueous phase was separated, and the organic phase was washed with HCl (2 x 250 mL of a 0.5 M aqueous solution), then dried ($MgSO_4$) and concentrated under

reduced pressure. The residue was purified *via* flash chromatography. Concentration of the appropriate fractions (R_f = 0.2, DCM elution) afforded compound **3e** (10.58 g, 9.27 mmol, 43%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47-7.45 (2H, m), 7.31-7.29 (2H, m), 6.93-6.88 (4H, m), 6.19-5.91 (2H, tt, *J* = 4.0 and 52.0 Hz), 6.10 (1H, br. s), 4.44 (4H, t, *J* = 12.0 Hz), 4.27 (1H, d, *J* = 4.0 Hz), 1.80-1.75 (1H, m), 0.87 (3H, d, *J* = 8.0 Hz), 0.70 (3H, d, *J* = 8.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.3, 157.4, 157.0, 138.2, 133.6, 128.1, 127.6, 155.0, 114.6, 107.7, 89.1, 66.1, 66.0, 65.6, 65.4, 65.3, 29.9, 20.9, 15.9. ^{19}F-NMR (376 MHz, $CDCl_3$) δ -120.1 (4F, s), -122.5 (12F, s), -123.7 (4F, s), -123.9 (4F, s), -130.0 (4F, s), -137.7 (4F, dt, *J* = 45.1 and 7.5 Hz). Mass Spectrum (ESI, +MS) *m/z* 1142 (M+H). Specific Rotation $[\alpha]_D^{22^oC}$ –62 (*c* 1.0, MeOH). HRMS (ESI^+) calcd for $C_{36}H_{24}F_{32}NO_4$ $(M+H)^+$: 1142.1189, found: 1142.1189; calcd for $C_{36}H_{23}F_{32}NO_4Na$ $(M+Na)^+$: 1164.1008, found: 1164.1015.

[(*S*)-1-{Hydroxy-*bis*-[4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phenyl]methyl}-2-methylpropyl]carbamic acid *tert*-butyl ester (5). A magnetically stirred solution of commercially available 1-bromo-4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)benzene (**4**, 5 g, 9.9 mmol) in THF (10 mL) maintained at -78 ºC under an atmosphere of nitrogen was treated, dropwise, with *n*-BuLi (6.2 mL of a 1.6 M solution in hexane, 9.92 mmol) and stirring was continued at this temperature for 20 minutes. The suspension was allowed to warm to -50 ºC for 10 minutes and then cooled again to -78 ºC, before being treated, dropwise, with *N*-(*tert*-butoxycarbonyl)-*L*-valine methyl ester (0.93 g, 4.0 mmol) in THF (5 mL). Stirring was continued at -78 ºC for 6 h before quenching, at this temperature, with *sat. aq.* NH_4Cl (25 mL). The resultant suspension was diluted with diethyl ether (50 mL). The aqueous phase was separated and the organic phase was washed sequentially with *sat. aq.* NH_4Cl (40 mL) and brine (40 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified *via* flash chromatography. Concentration of the appropriate fractions (R_f = 0.35, 9:1 hexane / EtOAc) yielded the desired compound **5** (3.4 g, 3.25 mmol, ~82%), albeit impure due to co-eluting *N*-(*tert*-butoxycarbonyl)-*L*-valine methyl ester starting material. This material was not characterised but rather was employed immediately in the next step.

(-)-(*S*)-4-Isopropyl-5,5-*bis*-[4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phenyl]-oxazolidin-2-one (6). The following protocol was adapted from a previously reported procedure.[4] A magnetically stirred solution of compound **5** (3.4 g, 3.25 mmol) maintained at 0 ºC under an atmosphere of nitrogen, was treated with potassium *tert*-butoxide (0.44 g, 3.9 mmol) in one portion, and the resultant mixture was allowed to slowly warm to RT over the course of 16 h. The suspension was treated with NH_4Cl (10 mL of a 10% aqueous solution). The aqueous phase was separated and washed with diethyl ether (2 x 20 mL). The pooled organic phases were then dried and concentrated under reduced pressure. The resultant crude material was then purified *via* flash chromatography. Concentration of the appropriate fractions (R_f = 0.3, 3:1 hexane / EtOAc) afforded compound **6** (1.8 g, 1.85 mmol, 57%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49 (2H, m), 7.34 (2H, m), 7.17 (4H, m), 7.15 (1H, br. s), 4.33 (1H, d, *J* = 4.0 Hz), 2.91-2.84 (4H, complex m), 2.41-2.25 (4H, complex m), 1.87-1.81 (1H, complex m), 0.92 (3H, d, *J* = 8.0 Hz), 0.70 (3H, d, *J* = 4.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.5, 142.8, 139.4, 138.8, 137.9,

128.7, 128.2, 126.8, 126.2, 89.3, 66.2, 53.6, 33.2, 33.1, 32.9, 32.8, 32.7, 32.6, 29.9, 26.1, 20.9, 15.7.

^{19}F-NMR (376 MHz, $CDCl_3$) δ -81.35 (6F, m), -115.20 (4F, m), -122.41 (4F, m), -123.41 (4F, s), -124.05 (4F, m), -126.70 (4F, m). Mass Spectrum (ESI, +MS) *m/z* 974 (M+H). Specific Rotation $[\alpha]_D^{22ºC}$ –79 (*c* 1.0, MeOH). HRMS (ESI^+) calcd for $C_{34}H_{26}F_{26}NO_2$ $(M+H)^+$: 974.1543, found: 974.1550; calcd for $C_{34}H_{29}F_{36}N_2O_2$ $(M+NH_4)^+$: 991.1808, found: 991.1813; $C_{34}H_{25}F_{36}NO_2Na$ $(M+Na)^+$: 996.1362, found: 996.1366; $C_{34}H_{25}F_{36}NO_2K$ $(M+K)^+$: 1012.1102, found: 1012.1102.

(-)-(*S*)-4-Isopropyl-5,5-*bis*-[4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phenyl]-oxazolidin-2-one (6): One-pot procedure

To a magnetically stirred solution of 1-bromo-4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-octyl)benzene (**4**, 40.83 g, 81.1 mmol) in THF (400 mL) maintained at -78 ºC under an atmosphere of nitrogen, was added *n*-BuLi (50.63 mL of a 1.6 M solution in hexane, 81.0 mmol) and stirring was continued at this temperature for 20 min. The resultant suspension was then treated, dropwise, with *N*-(*tert*-butoxycarbonyl)-*L*-valine methyl ester (7.5 g, 32.4 mmol) in THF (10 mL) and stirring was continued at -78 ºC for 6 h. After this time, the dry ice-actone bath was removed and the mixture was allowed to warm to RT with continued stirring for 16 h. The reaction was then quenched with *sat. aq.* NH_4Cl (200 mL) and diluted with diethyl ether (400 mL). The aqueous layer was separated and the organic layer was washed sequentially with *sat. aq.* NH_4Cl (200 mL) and brine (200 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified *via* flash chromatography. Concentration of the appropriate fractions (R_f = 0.3, 3:1 hexane / EtOAc) afforded compound **6** (15.3 g, 15.72 mmol, 50% over two steps). This material was identical, as judged by ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR and low resolution mass spectrometric analysis, as well as chromatographic behaviour (TLC and flash-column chromatography), with the material prepared *via* the two-step process reported above.

(+)-(*R*)-4-Isopropyl-5,5-*bis*-[4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phenyl]-oxazolidin-2-one (*ent*-6). Compound ***ent*-6** was prepared in an analogous fashion to the preparation of compound **6** (one-pot procedure), using compound *N*-(*tert*-butoxycarbonyl)-*D*-valine methyl ester (5.1 g, 22 mmol) as starting material. Purification *via* flash chromatography (R_f = 0.3, 3:1 hexane / EtOAc) afforded compound ***ent*-6** (10.04 g, 10.3 mmol, 47% over two steps). This material was identical, as judged by ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR and low resolution mass spectrometric analysis, as well as chromatographic behaviour (TLC and flash-column chromatography), with the optical antipode compound **6** reported above.

Specific Rotation $[\alpha]_D^{22ºC}$ +78 (*c* 1.0, MeOH).

(-)-(*S*)-3-(2-Benzylacryloyl)-4-isopropyl-5,5-*bis*-[4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phenyl]oxazolidin-2-one (7). The following protocol was adapted from a previously reported procedure.[1] A magnetically stirred suspension of compound **6** (3.88 g, 3.99 mmol), DMAP (0.098 g, 0.8 mmol) and 2-benzyl-acrylic acid (1.3 g, 8.0 mmol) in DCM (20 mL), maintained at 0 ºC under an atmosphere of nitrogen, was treated with DIPCD (1.24 mL,

1.01 g, 8.0 mmol). After 10 min, the reaction was allowed to warm to RT and stirring was continued for 16 h. The diisopropyl urea formed was filtered, and the precipitate washed with DCM (10 mL). The filtrate was washed with *sat. aq.* $NaHCO_3$ (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified *via* flash chromatography. Concentration of the appropriate fractions (R_f = 0.3, 95:5 hexane / EtOAc) gave compound **7** (3.5 g, 3.13 mmol, 78%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41 (2H, m), 7.36 (2H, m), 7.26-7.10 (9H, complex m), 5.35 (1H, d, *J* = 4.0 Hz), 5.20 (2H, s), 3.65 (2H, s), 2.92-2.85 (4H, complex m), 2.40-2.20 (4H, complex m), 2.00-1.90 (1H, m), 0.81 (3H, d, *J* = 4.0 Hz), 0.73 (3H, d, *J* = 8.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.2, 152.3, 143.2, 141.1, 139.8, 139.2, 137.3, 136.8, 129.5, 129.0, 128.6, 126.7, 126.5, 126.2, 120.5, 89.3, 68.2, 64.9, 39.5, 32.8, 30.2, 28.1, 26.2, 26.1, 25.8, 21.7, 16.2. ^{19}F-NMR (376 MHz, $CDCl_3$) δ -81.33 (6F, m), -115.19 (4F, m), -122.41 (4F, s), -123.39 (4F, s), -124.01 (4F, s), -126.69 (4F, s). Mass Spectrum (ESI, +MS) *m/z* 1118 (M+H). Specific Rotation $[\alpha]_D^{22^\circ C}$ –42 (*c* 1.0, MeOH).

(+)-(*R*)-3-(2-Benzyl-acryloyl)-4-isopropyl-5,5-*bis*-[4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phenyl]oxazolidin-2-one (*ent*-7). Compound ***ent*-7** was prepared in an analogous fashion to the preparation of compound **7**, using compound ***ent*-6** (6.94 g, 7.1 mmol) as starting material. Purification *via* flash chromatography (R_f = 0.3, 95:5 hexane / EtOAc) afforded compound ***ent*-7** (4.3 g, 3.85 mmol, 54%). This material was identical, as judged by ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR and low resolution mass spectrometric analysis, as well as chromatographic behaviour (TLC and flash-column chromatography), with the optical antipode compound **6** reported above. Specific Rotation $[\alpha]_D^{22^\circ C}$ +46 (*c* 1.0, MeOH).

(*S*)-3-[(*R*)-2-(Benzyloxyamino-methyl)-3-phenylpropionyl]-4-isopropyl-5,5-bis-[4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phenyl]oxazolidin-2-one (8). The following protocol was adapted from a previously reported procedure.[6] A dry round-bottomed flask was charged with a magnetic stirrer bead, compound **7** (3.11 g, 2.78 mmol), *O*-benzyl hydroxylamine (0.684 g, 5.55 mmol) and THF (10 mL). The resultant solution was heated, with stirring, to 72 ºC under an atmosphere of nitrogen. The reaction was allowed to proceed at this temperature for 24 h. The mixture was then cooled to RT, concentrated under reduced pressure and purified *via* FSPE. A standard glass flash chromatography column was packed with commercially available Fluoroflash™ (35 g) and pre-conditioned by passing through MeOH / H_2O (80 mL of an 80 : 20 v/v mixture) under positive pressure. The residue was loaded on to the top of the column, using DMF (4 mL) as the loading solvent. The column was then eluted with MeOH / H_2O (80 mL of an 80 : 20 v/v mixture). Concentration of this fraction under reduced pressure afforded *o*-benzyl hydroxylamine (0.27 g, 2.13 mmol). The column was then eluted successively with MeOH (100 mL), THF (120 mL) and acetone (120 mL). The three organic fractions were pooled and concentrated under reduced pressure to afford a clear colourless oil containing the desired compound **8** (3.24 g, 2.61 mmol, 94%). Subjection of this material to chiral HPLC analysis (Chiralpak™ AD-H 1196 analytical column, 2:98 v/v isopropanol-hexane elution, flowrate 1.0 mL/min) confirmed that it had been obtained in 80% *d.e*: R_t 12.85 (major diastereomer), 16.96 min (minor diastereomer). A magnetically stirred solution of compound **8**

(3.18 g, 2.56 mmol), in diethyl ether (250 mL) maintained at RT under an atmosphere of nitrogen, was treated with a solution of *p*-toluenesulfonic acid monohydrate (512 mg, 2.73 mmol) in diethyl ether (20 mL) and stirring was continued for 72 h. After this time, the resultant suspension was cooled to 0 ºC on an ice bath, and then filtered. The solid material was washed with ice cold diethyl ether (2 x 25 mL) and dried under reduced pressure to afford the toluene sulfonic acid salt of compound **8** (2.53 g, 1.79 mmol, 70%, 93% *d.e*. by ^{1}H-NMR). This material was suspended in EtOAc (20 mL) and treated with sodium carbonate (10 mL of a 1M aqueous solution), whilst being magnetically stirred at r.t. under an atmosphere of nitrogen. After 15 min, the aqueous layer was separated and discarded. The organic layer was washed with water (2 x 10 mL), then dried ($MgSO_4$), and concentrated under reduced pressure to afford compound **8** (2.06 g, 1.66 mmol, 93%). Subjection of this material to chiral HPLC analysis (Chiralpak™ AD-H 1196 analytical column, 2:98 v/v isopropanol-hexane elution, flow rate 1.0 mL/min) confirmed that it had been obtained in 93% *d.e*: R_t 12.85 (major diastereomer), 16.96 min (minor diastereomer). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35-6.94 (18H, complex m), 5.74 (1H, br. s), 5.35 (1H, d, *J* = 4.0 Hz), 4.66 (2H, m), 4.35-4.29 (1H, complex m), 3.31-3.26 (1H, complex m), 3.10-3.06 (1H, complex m), 2.92-2.83 (4H, complex m), 2.73-2.66 (1H, complex m), 2.56-2.51 (1H, complex m), 2.42-2.21 (4H, complex m), 1.97-1.90 (1H, complex m), 0.91 (3H, d, *J* = 8.0 Hz), 0.76 (3H, d, *J* = 8.0 Hz). Mass Spectrum (ESI, +MS) *m/z* 1241 (M+H). Anal. Calcd for $C_{58}H_{50}F_{26}N_2O_7S$: C, 49.30; H, 3.57; N, 1.98% Found: C, 49.14; H, 3.54; N, 1.94%

(*R*)-3-[(*S*)-2-(Benzyloxyaminomethyl)-3-phenylpropionyl]-4-isopropyl-5,5-bis-[4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phenyl]oxazolidin-2-one (*ent*-8). Compound ***ent*-8** was prepared using the same protocols as those described for the preparation of compound **8**, using compound ***ent*-7** (3.5 g, 3.13 mmol) as starting material. Purification *via* the same means (FSPE & precipitation of tosylate) afforded compound ***ent*-8** (2.25 g, 1.6 mmol, 51% over the two steps). This material was identical, as judged by ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR and low resolution mass spectrometric analysis, as well as chromatographic behaviour (TLC and flash-column chromatography), with the optical antipode compound **8** reported above.

(*R*)-2-(Benzyloxyaminomethyl)-3-phenylpropionic acid (9) and recovery of compound 6 *via* FSPE. A magnetically stirred solution of compound **8** (2.06 g, 1.66 mmol, 93% *d.e*), in THF (80 mL) and water (10 mL), maintained at 0 ºC under an atmosphere of nitrogen, was treated with H_2O_2 (40 mL of a 30% aqueous solution), followed by LiOH (160 mL of a 4.5% aqueous solution). The reaction mixture was stirred at this temperature for 45 min, before being quenched *via* addition of cold *sat. aq*. sodium sulfite (40 mL), and allowed to warm to RT over the course of 30 min. The resultant suspension was extracted with EtOAc (4 x 100 mL) and the organic extracts dried ($MgSO_4$), and concentrated under reduced pressure to give a residue which was subjected to FSPE. A commercially available Fluoroflash™ cartridge (20 g) was pre-conditioned by passing through MeOH / H_2O (60 mL of an 80 : 20 v/v mixture) under positive pressure. The residue was loaded on to the top of the column, using DMF (4 mL) as the loading solvent. The column was then eluted with MeOH / H_2O (60 mL of an 80 : 20 v/v mixture).

Concentration of this fraction under reduced pressure afforded non-fluorinated organic impurities. The column was then eluted successively with MeOH (80 mL), THF (100 mL) and acetone (100 mL). The three organic fractions were pooled and concentrated under reduced pressure to afford recovered compound **6** (1.56 g, 1.60 mmol, 96%) of high purity, as determined by ^{1}H-NMR and LCMS. The aqueous layer from the original solvent extraction was acidified with conc. HCl to a pH of 4-5, as determined using universal indicator strips, and then extracted with EtOAc (3 x 150 mL). The combined extracts were washed with water (2 x 50 mL) then dried ($MgSO_4$), and concentrated under reduced pressure to afford compound **9** (350 mg, 1.23 mmol, 74%). This crude sample was identical, as judged by ^{1}H-NMR and low resolution mass spectrometric analysis with previously reported authentic material. Due to the previously reported limited stability of this compound it was immediately subjected to the following hydrogenation step.[6]

(*R*)-2-Aminomethyl-3-phenylpropionic acid (10). The crude sample of compound **9** (350 mg, 1.23 mmol) from the previous step, was dissolved in MeOH, NH_3 and H_2O (3:1:1, 10 mL) and 10% Pd/C (100 mg) was added to the solution. The mixture was then stirred at RT under an atmosphere of hydrogen for 72 h (at which point TLC analysis indicated complete consumption of starting material), before being filtered through a plug of Celite, and concentrated under reduced pressure, to provide compound **10**. This crude sample was identical, as judged by ^{1}H-NMR with previously reported authentic material. [8,9]

(*R*)-2-[(9*H*-Fluoren-9-ylmethoxycarbonylamino)methyl]-3-phenylpropionic acid (11). The crude sample of compound **10** (350 mg) produced in the previous step was dissolved in THF and H_2O (10 mL of a 1:1 mixture) and cooled to 0 ºC, whilst being stirred under nitrogen. The solution was treated with Fmoc-OSu (0.420 g, 1.25 mmol) and $NaHCO_3$ (1.0 g, 11.88 mmol) and allowed to warm to RT over the course of 2 h. THF was removed under reduced pressure and the aqueous residue was washed with diethyl ether (2 x 10 mL). The organic layers were discarded and the aqueous layer was acidified with *sat. aq.* $KHSO_4$ and extracted with DCM (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified *via* flash chromatography. Concentration of the appropriate fractions (R_f = 0.3, 50:1 DCM / MeOH) afforded compound **11** (122 mg, 0.36 mmol, ~30% over two steps, >95% *e.e.* as determined by chiral HPLC). This sample of compound **11** was identical, as judged by ^{1}H-NMR, low resolution mass spectrometric analysis and chromatographic retention characteristics with previously reported authentic material.[8,9] Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.80; H, 5.77; N, 3.49% Found: C, 74.63; H, 5.77; N, 3.45%

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