Tetrahedron 64 (2008) 11876–11883

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An asymmetric, SmI_2-mediated approach to γ-butyrolactones using a new, fluorous-tagged auxiliary

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ARTICLE INFO

Article history:
Received 29 July 2008
Accepted 12 August 2008
Available online 20 September 2008

Keywords:
Samarium
Radicals
Asymmetric
Fluorous
Lactones

ABSTRACT

A new, fluorous-tagged chiral auxiliary has been developed for the asymmetric, SmI_2-mediated coupling of aldehydes and α,β-unsaturated esters. γ-Butyrolactones are obtained in moderate to good isolated yield and in high enantiomeric excess. The fluorous tag allows the auxiliary to be conveniently recovered by fluorous solid-phase extraction (FSPE) and reused.

1. Introduction

Samarium(II) iodide (SmI_2) continues to be used widely in organic synthesis.[1] This mild, single-electron reductant has been used to mediate a broad range of radical and anionic transformations ranging from functional group interconversions to complex carbon–carbon bond-forming sequences.[1] The reductive coupling of carbonyl compounds with olefins represents one of the most important classes of SmI_2 carbon–carbon bond-forming reaction. In 1986, Fukuzawa[2] and Inanaga[3] described the SmI_2-mediated, intermolecular coupling of aldehydes and ketones with α,β-unsaturated esters to give substituted γ-butyrolactones. In 1997, Fukuzawa reported a useful, asymmetric variant in which acrylates and crotonates derived from ephedrine are coupled with aldehydes and ketones.[4] We have applied Fukuzawa's approach in a short asymmetric synthesis of an antifungal, γ-butyrolactone natural product.[5] We have also adapted Fukuzawa's methodology in the development of a solid-phase asymmetric catch and release approach to γ-butyrolactones using acrylates and crotonates linked to resin through an ephedrine chiral linker.[6] Lin[7] and Dai[8] have also reported the use of new chiral auxiliaries in asymmetric, SmI_2-mediated approaches to γ-butyrolactones (Fig. 1).

Here, we describe the design and synthesis of a new, fluorous-tagged[9] auxiliary for the asymmetric, SmI_2-mediated coupling of aldehydes and α,β-unsaturated esters to give γ-butyrolactones in high enantiomeric excess. The fluorous tag allows the auxiliary to be conveniently recovered by fluorous solid-phase extraction (FSPE)[10] and reused.

2. Results and discussion

Our auxiliary design is inspired by Braun's (*R*)-2-hydroxy-1,2,2-triphenyl-1,2-diol (HYTRA) auxiliary that has found application in a number of asymmetric reactions.[11] To our knowledge the use of

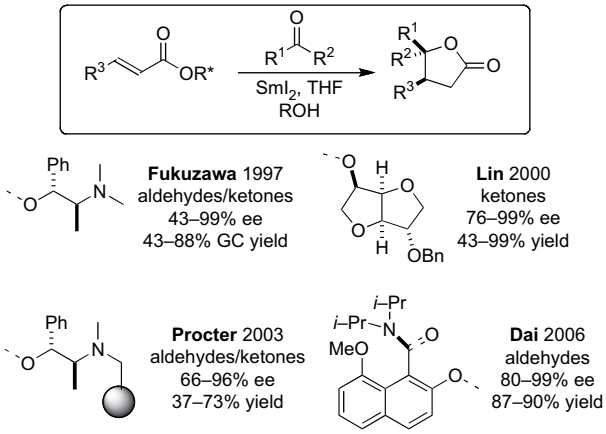

Figure 1. Asymmetric, SmI_2-mediated approaches to γ-butyrolactones.

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doi:10.1016/j.tet.2008.08.110

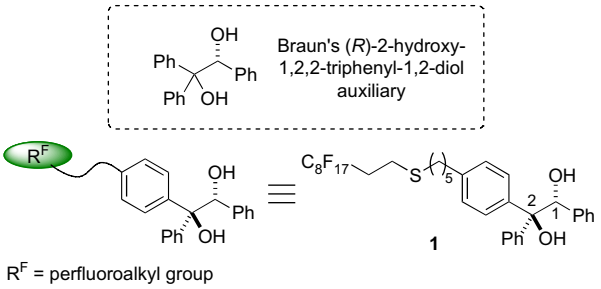
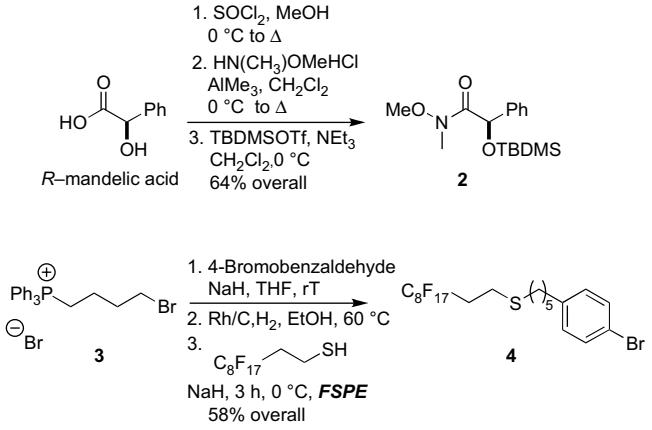


Figure 2. Design of a new, fluorous-tagged auxiliary.

the 1,2,2-triphenyl-1,2-diol auxiliary in radical reactions has not been reported. We chose to attach the fluorous tag using a spacer unit located at the 4-position of a 2-phenyl ring thus minimizing the effect of the linker and tag on the proposed asymmetric transformations. Our initial goal, therefore, was the diastereoselective synthesis of tagged auxiliary **1** (Fig. 2).

The synthesis of the fluorous-tagged auxiliary **1** began with the preparation of Weinreb amide **2** from (*R*)-mandelic acid (inexpensive in either enantiomeric form) in three steps (Scheme 1).[12]



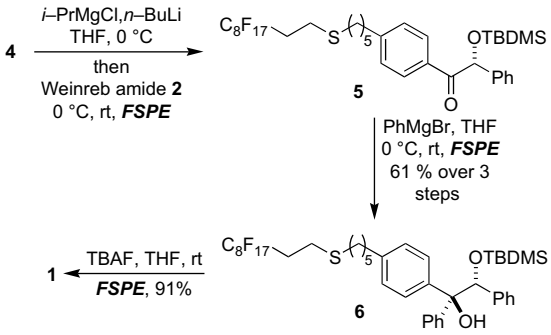
Scheme 1. *En route* to the fluorous-tagged auxiliary **1**.

To form the spacer and the phase tag unit, 4-bromobenzaldehyde was reacted with phosphonium bromide **3** to give almost exclusively the *cis*-alkene. Rhodium on carbon-mediated hydrogenation of the double bond and reaction with commercially available 1H,1H,2H,2H-perfluorodecane thiol and NaH gave the tagged thioether **4** in good overall yield after rapid purification by FSPE. For the remainder of the synthesis, FSPE was used to conveniently purify all intermediates. The fluorous tag therefore has an additional role in that it facilitates the synthesis of the auxiliary by allowing purification of intermediates without recourse to conventional chromatography.

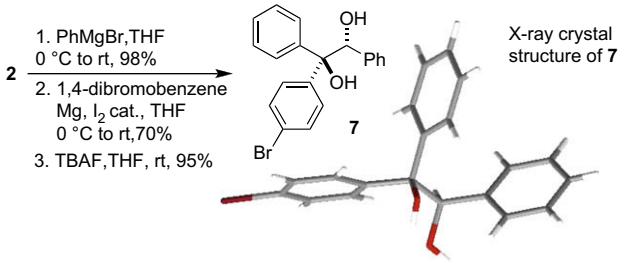
Lithium magnesiate exchange[13] reaction of **4** and subsequent coupling with Weinreb amide **2** gave phenylketone **5**. Addition of PhMgBr then gave protected auxiliary **6** as a single diastereoisomer in 61% overall yield for three steps. Finally, deprotection of **6** gave the new, fluorous-tagged auxiliary **1** in excellent yield (Scheme 2).

The stereochemistry of **1** was confirmed indirectly by the sequential addition of phenylmagnesium bromide and 4-bromophenylmagnesium bromide to **2**, followed by TBAF deprotection of the resultant secondary alcohol to give **7**. X-ray crystallographic analysis was used to confirm the stereochemical configuration of **7** and, by analogy, the configuration of **1** (Scheme 3).

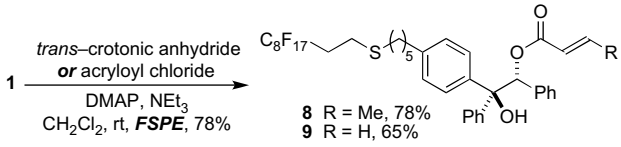
We next investigated the use of the fluorous-tagged diol auxiliary in the asymmetric synthesis of γ-butyrolactones via the SmI_2-mediated coupling of aldehydes and α,β-unsaturated esters. Tagged



Scheme 2. Synthesis of the fluorous-tagged auxiliary **1**.



Scheme 3. Indirect confirmation of the stereochemistry in **1**.



Scheme 4. Loading of auxiliary **1**.

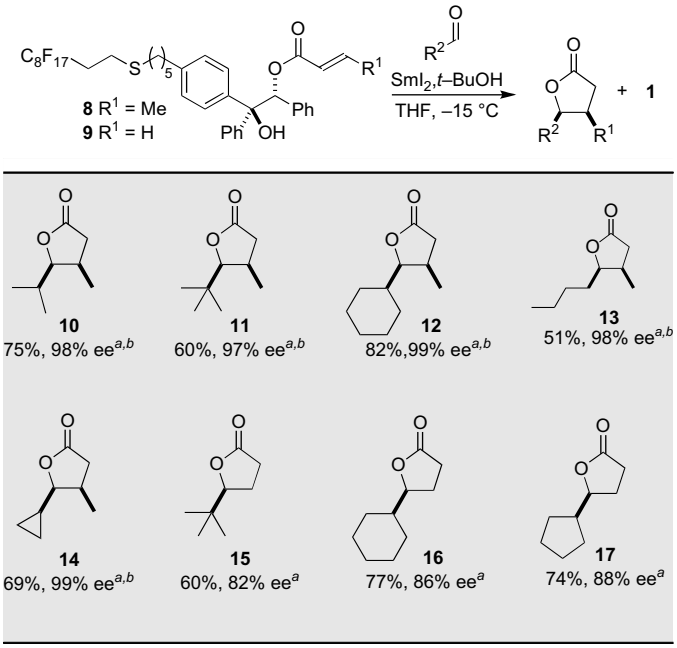
auxiliary **1** was first converted to the crotonate and acrylate esters, **8** and **9**, respectively (Scheme 4).

The SmI_2-mediated coupling of **8** and **9** with a range of aldehydes was then studied (Table 1). Couplings of crotonate **8** with a range of aldehydes proceeded in moderate to good yield and with excellent diastereo- and enantioselectivity (97–99% ee) to give *cis*-lactones **10**–**14**. Reductive couplings of acrylate **9** also proceeded to give lactones **15**–**17** in good yield but with slightly lower enantioselectivity (82–88% ee). The tagged auxiliary **1** was recovered from the crude product mixtures by FSPE (approx. 70%) and reused. We have previously observed that lower enantioselectivities are often obtained with acrylate substrates bearing an ephedrine auxiliary[6] (Table 1).

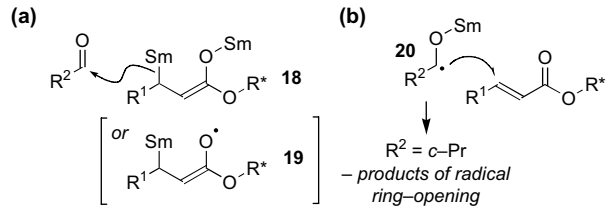
Interestingly, the successful use of cyclopropane carboxaldehyde in the reductive coupling to give **14** appears to confirm that the reaction proceeds by reduction of the α,β-unsaturated ester to give either a dianionic intermediate **18** or a radical-anionic intermediate **19** that adds to the aldehyde.[2] For cyclopropane carboxaldehyde, the alternative mechanism involving reduction of the aldehyde to give a ketyl-radical anion **20** would be expected to lead to fragmentation of the cyclopropane ring (Scheme 5).[14]

Couplings of ketones and nitrones using the tagged auxiliary **1** were less successful. For example, in preliminary experiments coupling of acetophenone with acrylate **9** gave lactone **21** in excellent yield but in only 46% ee. Similarly, coupling of nitrone **22** with **8**, adapting the conditions of Vallée[15] and Skrydstrup,[16] gave γ-lactam **23** in 73% yield and 45% ee (Scheme 6).

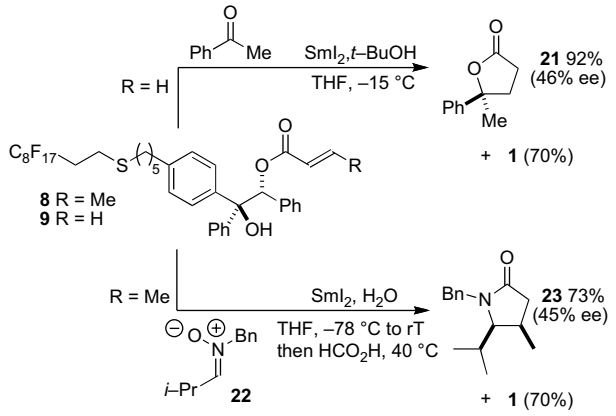
Table 1
SmI_2-mediated couplings using auxiliary **1**



[a] Enantiomeric excesses were determined by chiral GC.
[b] No other diastereoisomers were observed in the crude ^{1}H NMR.



Scheme 5. Two possible mechanisms (R* = tagged chiral auxiliary).



Scheme 6. Preliminary couplings of a ketone and a nitrone.

The low enantioselectivities obtained in preliminary studies using ketone and nitrone substrates and tagged auxiliary **1** suggest that these reactions may proceed via a different mechanism to those involving aldehydes. Our current understanding is that auxiliary **1** gives high diastereocontrol in couplings that proceed via mechanisms of type (a), but currently gives low diastereocontrol in couplings of type (b) (Scheme 5).

3. Conclusions

We have developed a new, fluorous-tagged chiral auxiliary for the asymmetric, SmI_2-mediated coupling of aldehydes and α,β-unsaturated esters. γ-Butyrolactones are obtained in moderate to good isolated yield and in high enantiomeric excess. For couplings using crotonate substrates, near perfect diastereocontrol is achieved. The fluorous tag allows the auxiliary to be conveniently recovered by fluorous solid-phase extraction (FSPE) and reused.

4. Experimental

4.1. General

All solvents were dried and distilled prior to use if not stated otherwise. All glasswares were dried before use either by heating with a heat gun under vacuum or by drying in an oven at 110 °C. Thin layer chromatography (TLC) was carried out using silica plates and mixtures of petroleum ether (40–60 °C) and ethyl acetate. TLC plates were visualised using UV or by staining with 0.5% potassium permanganate in 2.5% aqueous sodium hydrogen carbonate and drying with a heat gun. ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ on a Fourier transform spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C spectra. The results are quoted in parts per million downfield from the Me_4Si standard and given in the following format for ^{1}H NMR: (i) number of equivalent nuclei (by integration); (ii) multiplicity (s, d, t, q, quintet, sextet, etc.); (iii) coupling constants quoted in hertz; (iv) assignment. For ^{13}C NMR the chemical shift in parts per million and the assignment are quoted. Proton spectra are referenced to residual $CHCl_3$ at 7.27 ppm and carbon spectra to $CDCl_3$ at 77.4 ppm. Mass spectra were recorded at the University of Manchester. Infrared spectra were obtained using a Fourier transform spectrometer. Optical rotations were measured in chloroform ($CHCl_3$) and the values quoted in 10^{-1} deg cm^2 g^{-1}. In a typical fluorous solid-phase extraction (FSPE), a crude product mixture containing tagged and non-tagged organic compounds was loaded onto the fluorous silica by using a minimum amount of organic solvent (less than 20% of silica gel volume). Elution with fluorophobic solvent mix, such as 80% MeCN/H_2O or MeOH/H_2O, removes non-fluorinated compounds from the column. The column was then eluted with a fluorophilic solvent such as MeCN or methanol, which removes tagged compounds from the column. The fluorous silica gel could often be reused. R^F=C_8F_{17}.

4.1.1. (R)-(−)-Methyl mandelate[12]

(*R*)-(−)-Mandelic acid (10.0 g, 0.066 mol) was dissolved in methanol (80 ml) in a dry two-necked round-bottomed flask fitted with a condenser under N_2 atmosphere. The mixture was cooled to 0 °C using an ice bath. Thionyl chloride (1.16 g, 0.014 mol) was then added to the reaction mixture once it had cooled to the desired temperature. Subsequently the reaction was heated under reflux. After 80 min, the reaction was quenched by adding water (80 ml). The layers were separated and the aqueous layer was washed with diethyl ether (4×100 ml). The combined organic layers were then washed with saturated aqueous sodium hydrogen carbonate solution. Subsequently the organic layer was dried (Na_2SO_4) and concentrated in vacuo. The resultant crude mixture was then purified by chromatography (80:20 ethyl acetate to petroleum ether as eluent) to give (*R*)-(−)-methyl mandelate (9.39 g, 0.057 mol, 86%) as a white crystalline solid. Data was in agreement with that in the literature. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.58 (1H, br s, OH), 3.78 (3H, s, OC*H*$_3$), 5.20 (1H, s, PhC*H*(OH)CO_2CH_3), 7.3–7.5 (5H, m, 5×Ar*H*).

4.1.2. (2R)-N-methoxy-N-methyl-(2-hydroxy-2-phenyl)-acetamide[12]

HN(CH_3)OMe hydrochloride (11.0 g, 0.113 mol) was dissolved in CH_2Cl_2 (120 ml) in a dry three-necked round-bottomed flask fitted

with a condenser under a nitrogen atmosphere and cooled to 0 °C using an ice bath. Trimethylaluminium (56.5 ml, 2 M in hexane, 0.113 mol) was then slowly added using a syringe pump (flow rate: 70 ml/20 min). Once the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for 2 h. Subsequently, (*R*)-(−)-methyl mandelate (9.39 g, 0.057 mol) dissolved in CH_2Cl_2 (80 ml) was added dropwise by syringe pump (flow rate: 70 ml/20 min). Following the addition, the solution was heated under reflux overnight. The reaction mixture was then poured into a 1:1 mixture of ice (125 ml) and aqueous hydrochloric acid (125 ml, 1 M). The resultant yellow solid was dissolved using concentrated hydrochloric acid (37%) and the aqueous layer was washed with CH_2Cl_2 (2×200 ml). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. Chromatography using an eluent system of 10:90 ethyl acetate to petroleum ether gave (2*R*)-*N*-methoxy-*N*-methyl-(2-hydroxy-2-phenyl)acetamide (8.36 g, 0.043 mol, 76%) as a white, crystalline solid. Data was in agreement with that in the literature. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.23 (6H, s, NCH_3 and OCH_3), 4.30 (1H, br s, OH), 5.37 (1H, s, PhC*H*(OH)), 7.30–7.50 (5H, m, 5×Ar*H*).

4.1.3. (2R)-tert-Butyldimethylsilanyloxy-N-methoxy-N-methyl-2-phenylacetamide (**2**)[12]

(2*R*)-*N*-methoxy-*N*-methyl-(2-hydroxy-2-phenyl)acetamide (0.681 g, 3.50 mmol) and NEt_3 (0.580 ml, 4.20 mmol) in CH_2Cl_2 (10 ml) were cooled to 0 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.88 ml, 3.85 mmol) was then added and the mixture was left to stir for 1 h. The reaction was quenched using aqueous, saturated $NaHCO_3$ (10 ml) and the aqueous layer was washed with CH_2Cl_2 (3×10 ml). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified using column chromatography (10:90 ethyl acetate and petroleum ether as the eluent) to give **2** (0.996 g, 3.22 mmol, 92%) as a colourless oil. Data was in agreement with that in the literature. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.01 (3H, s, SiCH_3), 0.02 (3H, s, SiCH_3), 0.81 (9H, s, 3×SiC(CH_3)), 3.03 (3H, s, NCH_3), 3.39 (3H, br s, OCH_3), 5.49 (1H, s, PhC*H*(OH)), 7.18–7.35 (5H, m, 5×Ar*H*).

4.1.4. (Z)-1-Bromo-4-(5-bromopentyl-1-enyl)benzene

4-Bromobutyltriphenylphosphonium bromide **3** (10.9 g, 0.023 mol) was suspended in THF (50 ml) under nitrogen atmosphere. NaH (0.547 g, 0.023 mol) was added to the mixture and the reaction was stirred for 30 min. 4-Bromobenzaldehyde (3.50 g, 0.108 mol, 1 equiv) in THF (20 ml) was then added and the reaction mixture stirred overnight. The mixture was quenched with water (70 ml) and the aqueous layer washed with petroleum ether (3×70 ml). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (10:90 ethyl acetate and petroleum ether as the eluent) gave (*Z*)-1-bromo-4-(5-bromopentyl-1-enyl)benzene (4.39 g, 0.014 mol, 76%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05 (2H, pentet, *J*=7 Hz, CH=CHCH_2CH_2CH$_2$Br), 2.45 (2H, m, CH=CHCH_2CH$_2$CH$_2$Br), 3.40 (2H, t, *J*=6.7 Hz, CH_2Br), 5.69 (1H, dt, *J*=11.4 Hz, 7.4 Hz, ArCH=C*H*), 6.44 (1H, d, *J*=11.4 Hz, ArC*H*=CH), 7.17 (2H, d, *J*=8.6 Hz, 2×Ar*H*), 7.5 (2H, d, *J*=8.6 Hz, 2×Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.1 (*C*H$_2$CH$_2$Br), 32.8 (CH=CH*C*H$_2$), 33.1 (*C*H$_2$Br), 120.6 (PhCH=*C*H), 127.1 (Ph*C*H=CH), 129.4 (Ar*C*–Br), 130.2 (2×Ar*C*H), 131.0 (Ar*C*–CH=CH), 136.1 (2×Ar*C*H); *m*/*z* (EI$^+$ mode) 304 (M^{+2} 100%), 224 (10%), 197 (10%), 116 (23%); found: (M), 301.9303. $C_{11}H_{12}Br_2$ requires *M*, 301.9300; ν_{max} (ATR) 3010 (=C–H), 2947 (C–H), 1484 cm^{-1} (C=C).

4.1.5. 1-Bromo-4-(5-bromopentyl)benzene

(*Z*)-1-Bromo-4-(5-bromopentyl-1-enyl)benzene (9.45 g, 0.031 mol) was suspended in ethanol (100 ml) and rhodium on carbon (0.472 g, 5% w/w) was added. The reaction mixture was then heated under an atmosphere of hydrogen gas at 40 °C overnight. Filtration through silica gel and concentration in vacuo gave 1-bromo-4-(5-bromopentyl)benzene (9.45 g, 0.031 mol, 99%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (2H, m, ArCH$_2$CH$_2$CH_2), 1.47 (2H, pentet, *J*=7.8 Hz, CH_2CH$_2$Br), 1.73 (2H, pentet, *J*=7 Hz, ArCH$_2$CH_2), 2.43 (2H, t, *J*=7.8 Hz, CH_2Br), 3.25 (2H, t, *J*=7 Hz, ArCH_2), 6.90 (2H, d, *J*=8.2 Hz, 2×Ar*H*), 7.24 (2H, d, *J*=8.2 Hz, 2×Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.8 (ArCH$_2$CH$_2$CH$_2$), 30.5 (CH$_2$CH$_2$Br), 32.7 (ArCH$_2$*C*H$_2$), 33.8 (*C*H$_2$Br), 35.2 (Ar–CH$_2$), 119.5 (Ar*C*–Br), 130.3 (2×Ar*C*H), 131.4 (2×Ar*C*H), 141.3 (Ar*C*); *m*/*z* (Cl$^+$ mode) 306 (M^{+2}, 19%), 186 (100%), 171 (72%), 108 (20%), 89 (23%); found: (M), 303.9468. $C_{11}H_{14}Br_2$ requires *M*, 303.9457; ν_{max} (ATR) 2924 (=C–H), 2855 (C–H), 1712 cm^{-1} (C=C).

4.1.6. 1-Bromo-4-[5-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)pentyl]benzene (**4**)

NaH (0.45 g, 11.2 mmol) was suspended in THF (13 ml) and the suspension cooled to 0 °C. 1H,1H,2H,2H-Perfluorodecane-1-thiol (2.98 ml, 10.2 mmol) in THF (13 ml) was then added slowly with vigorous stirring. The reaction was left to stir for 1 h, followed by the addition of 1-bromo-4-(5-bromopentyl)benzene (4.00 g, 12.2 mmol) in THF (14 ml). The reaction mixture was then allowed to warm to room temperature and left for 2 h before quenching with water (40 ml). The aqueous layer was washed with Et_2O (3×40 ml) and the combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The crude product was then purified using fluorous solid-phase extraction (FSPE) to give **4** (7.67 g, 10.9 mmol, 89%) as a white, waxy solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (2H, m, ArCH$_2$CH$_2$CH_2CH$_2$CH$_2$S), 1.58 (4H, m, ArCH$_2$CH_2CH$_2$CH_2CH$_2$S), 2.25 (2H, m, SCH_2CH$_2$R$_F$), 2.48 (4H, two overlapping t, *J*=7.8, 7.3 Hz, CH_2S and ArCH_2), 2.64 (2H, m, SCH$_2$CH_2R$_F$), 6.97 (2H, d, *J*=8.3 Hz, 2×Ar*H*), 7.32 (2H, d, *J*=8.6 Hz, 2×Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6 (CH$_2$), 28.3 (ArCH$_2$CH$_2$*C*H$_2$), 29.7 (CH$_2$CH$_2$S), 30.9 (ArCH$_2$*C*H$_2$), 31.9 (SCH_2CH$_2$R$_F$), 32.1 (SCH_2CH$_2$R$_F$ and *C*H$_2$), 35.2 (ArCH$_2$), 118.2 (Ar*C*–Br), 130.1 (2×Ar*C*H), 131.3 (2×Ar*C*H), 141.3 (Ar*C*–CH$_2$S); *m*/*z* (EI$^+$ mode) 704 (MH$_2^+$, 60%), 535 (90%), 224 (97%), 169 (100%), 145.1 (100%); found: (M), 704.0033. $C_{21}H_{18}BrF_{17}S$ requires *M*, 704.0036; ν_{max} (IR, neat) 2933 (C–H), 2858 (C–H), 1213 (strong, C–F) cm^{-1}.

4.1.7. (1R)-{4-[5-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluoro)decylsulfanylpentylphenyl]}-2-(tert-butyldimethylsilanyloxy)-2-phenylethanone (**5**)

n-BuLi (12.7 ml, 1.99 M in hexane, 26.0 mmol) in THF (39 ml) was added slowly to a solution of *i*-PrMgCl (6.53 ml, 13.0 mmol) in THF (39 ml) at 0 °C. The mixture was allowed to stir for 15 min at 0 °C. Bromide **4** (7.67 g, 10.9 mmol) in THF (39 ml) was then added to the reaction mixture and the solution was stirred for 30 min, followed by dropwise addition of **2** (4.04 g, 13 mmol) in THF (39 ml). The reaction mixture was then allowed to warm to room temperature and was stirred for 2 h. The reaction was quenched with aqueous, saturated NH_4Cl (156 ml) and the aqueous layer washed with Et_2O (3×75 ml), dried (Na_2SO_4) and concentrated in vacuo. The crude product was thus purified using FSPE to give **5** as a clear oil that was used without further purification. $[\alpha]_D$=+8.2° (*c*=0.018, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.00 (3H, s, SiCH_3), 0.08 (3H, s, SiCH_3), 0.89 (9H, s, 3×SiC(CH_3)), 1.37 (2H, m, ArCH$_2$CH$_2$CH_2), 1.57–1.65 (4H, m, ArCH$_2$CH_2CH$_2$CH_2CH$_2$S), 2.35 (2H, m, SCH_2CH$_2$R$_F$), 2.52 (2H, t, *J*=7.6 Hz, CH_2S), 2.61 (2H, t, *J*=7.5 Hz, ArCH_2), 2.71 (2H, m, SCH$_2$CH_2R$_F$), 5.72 (1H, s, PhC*H*(OTBDMS)), 7.13 (2H, d, *J*=8.2 Hz, 2×Ar*H*), 7.23 (1H, m, Ar*H*), 7.33 (2H, m, 2×Ar*H*), 7.50 (2H, d, *J*=8.2 Hz, 2×Ar*H*), 7.93 (2H, d, *J*=8.2 Hz, 2×Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.1 (SiCH_3), −4.9 (SiCH_3), 18.4 (SiC(CH$_3$)), 22.6 (SCH$_2$CH$_2$R$_F$), 25.8 (3×SiC(*C*H$_3$)), 25.7 (ArCH$_2$CH$_2$CH$_2$), 28.3 (CH$_2$CH$_2$S), 29.1 (ArCH$_2$*C*H$_2$), 30.5 (*C*H$_2$S), 31.9 (SCH_2CH$_2$R$_F$), 35.8 (ArCH$_2$), 80.5 (PhCH(OTBDMS)), 125.7 (2×Ar*C*H), 127.6 (Ar*C*H), 128.1 (2×Ar*C*H), 128.5 (2×Ar*C*H), 130.2 (2×Ar*C*H), 132.1 (Ar*C*), 139.1

(ArC), 148.0 (ArC–C=O), 198.6 (C=O); *m/z* (ES$^+$ mode) 897 (MNa$^+$, 90%); found: (MNa$^+$), 897.2056. $C_{35}H_{39}O_2F_{17}NaSSi$ requires *M*, 897.2061; ν_{max} (neat) 2858 (C–H), 1676 (C=O), 1678 (C=O), 1212 cm^{-1}.

4.1.8. (1R,2S)-{4-[5-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluoro)decylsulfanyl pentyl]-phenyl}-2-(tert-butyldimethylsilanyloxy)-1,2-diphenylethanol (**6**)

Magnesium turnings (0.283 g, 11.8 mmol) and a small crystal of iodine were suspended in THF (10 ml). The suspension was cooled to 0 °C and bromobenzene (1.11 ml, 10.5 mmol) was added slowly with vigorous stirring. The reaction was allowed to warm to room temperature. In a separate, dry round-bottomed flask, crude **5** (5.41 g, 6.20 mmol) in THF (55 ml) was cooled to 0 °C and the freshly prepared solution of phenylmagnesium Grignard added. The solution was allowed to warm to room temperature and stirred for 2 h. The reaction was then quenched with aqueous, saturated NH_4Cl (50 ml) and the aqueous layer was washed with Et_2O (3×50 ml). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified using FSPE to give **6** (4.89 g, 5.13 mmol, 62% over two steps) as a clear, viscous oil. $[\alpha]_D$=+9.6° (*c*=0.018, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.02 (3H, s, SiC*H*$_3$), 0.00 (3H, s, SiC*H*$_3$), 0.78 (9H, s, 3×SiC(C*H*$_3$)), 1.40–1.45 (2H, m, ArCH$_2$CH$_2$C*H*), 1.57–1.70 (4H, m, ArCH$_2$C*H*$_2$CH$_2$C*H*$_2$CH$_2$S), 2.46 (2H, m, SC*H*$_2$CH$_2$R$_F$), 2.56 (2H, t, *J*=7.6 Hz, C*H*$_2$S), 2.62 (2H, t, *J*=7.3 Hz, ArC*H*$_2$), 2.83 (2H, t, *J*=8.5 Hz, SC*H*$_2$CH$_2$R$_F$), 5.55 (1H, s, PhC*H*(OTBDMS)), 6.96 (2H, d, *J*=7.9 Hz, Ar*H*), 7.17–7.23 (8H, m, 8×Ar*H*), 7.46 (2H, m, Ar*H*), 7.81 (2H, d, *J*=7.9 Hz, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.4 (SiCH$_3$), −4.3 (SiCH$_3$), 17.9 (SiC(CH$_3$)), 22.6 (SCH$_2$*C*H$_2$R$_F$), 25.6 (3×SiC(*C*H$_3$)), 28.3 (ArCH$_2$CH$_2$*C*H$_2$), 29.2 (*C*H$_2$CH$_2$S), 30.8 (ArCH$_2$*C*H$_2$), 31.9 (SCH$_2$*C*H$_2$R$_F$), 32.3 (*C*H$_2$S), 35.1 (Ar*C*H$_2$), 80.1 (Ph*C*H(OTBDMS)), 80.9 (*C*OH), 126.3–128.7 (15×Ar*C*H, Ar*C*), 139.7 (Ar*C*), 140.2 (Ar*C*), 145.9 (Ar*C*); *m/z* (ES$^-$ mode) 953 (M$^+$, 24%); found: (MNa$^+$), 975.2539. $C_{41}H_{45}O_2F_{17}NaSSi$ requires *M*, 975.2530; ν_{max} (neat) 3546 (O–H), 2931 (=C–H), 2857 (C–H), 1213, 1067 cm^{-1}.

4.1.9. (1R,2S)-[4-(5-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluoro)decyl sulfanylpentyl)-phenyl]-1,2-diphenylethane-1,2-diol (**1**)

Silyl ether **6** was dissolved in THF (49 ml) and *tert*-butylammonium fluoride (7.64 ml, 2 M in THF) was added. After 5 min the reaction was quenched with water (50 ml) and the aqueous phase washed with Et_2O (3×50 ml). The combined organic layers were washed with brine (3×50 ml), dried (Na_2SO_4) and concentrated in vacuo. The crude product was then purified using FSPE to give **1** (4.16 g, 46.7 mmol, 91%) as a viscous oil. $[\alpha]_D$=+23.1° (*c*=0.018, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25–1.27 (2H, m, ArCH$_2$CH$_2$C*H*$_2$), 1.48 (4H, m, ArCH$_2$C*H*$_2$CH$_2$C*H*$_2$CH$_2$S), 2.27 (2H, m, SC*H*$_2$CH$_2$R$_F$), 2.40–2.43 (4H, m, ArC*H*$_2$CH$_2$CH$_2$CH$_2$C*H*$_2$S), 2.62 (2H, t, *J*=8.2 Hz, SCH$_2$C*H*$_2$R$_F$), 5.49 (1H, s, PhC*H*(OH)), 6.82 (2H, d, *J*=8.2 Hz, Ar*H*), 6.95 (4H, m, 4×Ar*H*), 7.09 (2H, m, Ar*H*), 7.21 (2H, m, Ar*H*), 7.30 (2H, m, Ar*H*), 7.58 (2H, d, *J*=7.9 Hz, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6 (SCH$_2$*C*H$_2$R$_F$), 28.5 (ArCH$_2$*C*H$_2$CH$_2$), 29.3 (*C*H$_2$CH$_2$S), 30.9 (ArCH$_2$*C*H$_2$), 31.9 (SCH$_2$*C*H$_2$R$_F$), 35.2 (*C*H$_2$S), 35.4 (Ar*C*H$_2$), 78.0 (Ph*C*H(OH)), 80.7 (*C*OH), 126.2 (2×Ar*C*H), 127.1 (2×Ar*C*H), 127.3 (Ar*C*H), 127.4 (2×Ar*C*H), 127.6 (Ar*C*H), 127.7 (2×Ar*C*H), 128.2 (2×Ar*C*H), 128.4 (2×Ar*C*H), 139.0 (Ar*C*), 140.8 (Ar*C*), 140.9 (Ar*C*), 145.2 (Ar*C*); MS *m/z* (ES$^-$ mode) 837 (M$^-$, 80%), 731 (22%), 439 (23%), 269 (100%); found: (MNa$^+$), 861.1680. $C_{35}H_{31}O_2F_{17}NaS$ requires *M*, 861.1666; ν_{max} (neat) 3367 (br, O–H), 2923 (=C–H), 2853 (C–H), 1460, 1041 cm^{-1}.

4.1.10. (2R)-tert-Butyldimethylsilyloxy-1,2-diphenylethanone

Magnesium turnings (0.518 g, 0.0216 mol) and a small crystal of iodine were suspended in THF (20 ml) and cooled to 0 °C. Bromobenzene (2.01 ml, 0.019 mol) was added slowly with vigorous stirring. The reaction was allowed to warm to room temperature and stirred for 2 h. An aliquot of the phenyl Grignard solution (9.74 ml, 0.95 M in THF, 9.26 mmol) was then added dropwise to a solution of **2** (1.91 g, 6.17 mmol) in THF (57 ml) at 0 °C. The solution was left to stir for 1.5 h and then quenched with aqueous, saturated NH_4Cl (60 ml). The aqueous layer was washed with ethyl acetate (3×60 ml) and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified using column chromatography (5:95 ethyl acetate to petroleum ether as the eluent) to give (2*R*)-*tert*-butyldimethylsilyloxy-1,2-diphenylethanone (1.41 g, 4.32 mmol, 70%) as a clear, viscous oil. $[\alpha]_D$=+79.7° (*c*=0.018, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.00 (3H, s, SiC*H*$_3$), 0.08 (3H, s, SiC*H*$_3$), 0.89 (9H, s, 3×SiC(C*H*$_3$)), 5.74 (1H, s, PhC*H*(OTBDMS)), 7.25 (2H, m, 2×Ar*H*), 7.34 (3H, m, 3×Ar*H*), 7.45 (1H, m, Ar*H*), 7.53 (2H, d, *J*=7.8, Ar*H*), 8.00 (2H, dd, *J*=8.4, 1.2 Hz, 2×Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.1 (SiC*H*$_3$), −5.0 (SiCH$_3$), 18.3 (Si*C*), 25.7 (3×SiC(*C*H$_3$)), 80.4 (*C*H), 125.7 (2×ArCH), 127.7 (Ar*C*H), 128.1 (2×Ar*C*H), 128.5 (2×ArCH), 128.6 (2×Ar*C*H), 132.9 (Ar*C*H), 134.4 (Ar*C*), 138.9 (Ar*C*), 199.1 (*C*=O); *m/z* (CI$^+$ mode) 327 (M$^+$, 100), 269 (12%), 221 (43%), 195 (18%), 105 (10%), 90 (14%), 73 (20%); found: (M), 326.1688. $C_{20}H_{26}O_2Si$ requires *M*, 326.1697; ν_{max} (ATR) 2931 (=C–H), 2856, 1681 (C=O), 1255, 1117, 616 cm^{-1}.

4.1.11. (1R,2R)-1-(4-Bromophenyl)-2-(tert-butyldimethylsilanoxy)-1,2-diphenylethanol

Magnesium turnings (0.100 g, 4.17 mmol) and a small crystal of iodine were suspended in THF (5 ml). The suspension was cooled to 0 °C and 1,4-dibromobenzene (0.921 g, 3.90 mmol) dissolved in THF (3 ml) was added slowly with vigorous stirring and the reaction allowed to warm to room temperature. (2*R*)-*tert*-Butyldimethylsilyloxy-1,2-diphenylethanone (0.774 g, 2.37 mmol) in THF (8 ml) was cooled to 0 °C and the solution of freshly prepared Grignard (7.3 ml) was added. The solution was allowed to warm to room temperature and stirred for 2 h. The reaction was then quenched using aqueous, saturated NH_4Cl (10 ml). The layers were separated and the aqueous layer was washed with Et_2O (3×10 ml). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (5:95 ethyl acetate and petroleum ether as the eluent) gave (1*R*,2*R*)-1-(4-bromophenyl)-2-(*tert*-butyldimethyl-silanoxy)-1,2-diphenylethanol (0.799 g, 1.659 mmol, 70%) as a white solid. $[\alpha]_D$=24.8° (*c*=0.99, $CHCl_3$); mp 94–98 °C (MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.28 (3H, s, SiC*H*$_3$), 0.00 (3H, s, SiC*H*$_3$), 0.79 (9H, s, 3×SiC(C*H*$_3$)), 5.49 (1H, s, PhC*H*), 7.10–7.19 (9H, m, 9×Ar*H*), 7.23 (1H, dd, *J*=8.5, 1.5 Hz, Ar*H*), 7.54 (2H, d, *J*=8.5 Hz, Ar*H*), 7.65 (2H, d, *J*=8.8 Hz, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.2 (SiCH$_3$), −4.2 (SiCH$_3$), 18.0 (Si*C*), 25.7 (3×SiC(*C*H$_3$)), 79.9 (Ph*C*H), 80.8 (*C*OH), 121.0 (Ar*C*), 126.4 (Ar*C*H), 126.7 (Ar*C*H), 127.2 (Ar*C*H), 127.5 (Ar*C*H), 127.6 (Ar*C*H), 128.7 (Ar*C*H), 129.0 (Ar*C*H), 130.9 (Ar*C*H), 139.2 (Ar*C*), 142.6 (Ar*C*), 144.9 (Ar*C*); *m/z* (ES$^-$ mode) 481 (M$^-$, 90%), 403 (10%); found: (M$^-$), 481.1196. $C_{26}H_{30}O_2BrSi$ requires *M*, 481.1204; ν_{max} (neat) 2923 (Nujol), 1584, 1085 cm^{-1}.

4.1.12. (1R,2R)-1-(4-Bromophenyl)-1,2-diphenylethanol (**7**)

(1*R*,2*R*)-1-(4-Bromophenyl)-2-(*tert*-butyldimethylsilanoxy)-1,2-diphenylethanol (0.700 g, 1.45 mmol) was dissolved in THF (7 ml) under nitrogen atmosphere. *tert*-Butylammonium fluoride (2.17 ml, 2.0 M in THF) was added to the reaction, stirred for 5 min and then quenched with water (10 ml). The aqueous phase was washed with Et_2O (3×10 ml) and the combined organic layers were washed with brine (3×10 ml), dried (Na_2SO_4) and concentrated in vacuo. The crude product was then purified by column chromatography (10:90 ethyl acetate and petroleum ether as the eluent) to give **7** (0.51 g, 1.37 mmol, 95%) as a white solid. $[\alpha]_D$=142.3° (*c*=0.99, $CHCl_3$); mp 142–145 °C (MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45

(1H, s, PhC*H*), 6.94 (2H, d, *J*=7.3 Hz, 2×Ar*H*), 7.00–7.10 (9H, m, 9×Ar*H*), 7.42 (3H, m, 3×Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 77.9 (Ph*C*H), 80.8 (*C*OH), 121.4 (Ar*C*), 126.2 (Ar*C*H), 127.0 (Ar*C*H), 127.6 (Ar*C*H), 127.8 (Ar*C*H), 127.9 (Ar*C*H), 128.0 (Ar*C*H), 129.1 (Ar*C*H), 131.4 (Ar*C*H), 138.7 (Ar*C*), 143.0 (Ar*C*), 144.3 (Ar*C*); *m*/*z* (ES^- mode) 481 (M^-, 90%), 403 (10%); Found: (M^-), 481.1196. $C_{26}H_{30}O_2BrSi$ requires *M*, 481.1204; ν_{max} (neat) 3427 (br, O–H), 2923 (C–H), 704 cm^{-1}.

4.1.13. Crotonic acid (1S,2R)-1-{4-[5-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoro-undecylsulfanyl)-pentyl]-phenyl}-1,2-diphenyl (**8**)

(1*R*,2*S*)-[4-(5-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluoro) decylsulfanylpentyl)-phenyl]-1,2-diphenylethane-1,2-diol **1** (0.73 g, 0.87 mmol), triethylamine (0.17 ml, 1.1 mmol), 4-*N*-dimethylaminopyridine (cat.) and *trans*-crotonic anhydride (0.175 ml, 1.1 mmol) in CH_2Cl_2 (8 ml) were stirred overnight. The product mixture was washed with aqueous, saturated $NaHCO_3$ (3×10 ml). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by FSPE to give **8** (0.599 g, 0.66 mmol, 78%) as a white solid. $[\alpha]_D$=90.9° (*c*=0.018, $CHCl_3$); mp 143–145 °C (MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27–1.29 (2H, m, $ArCH_2CH_2CH_2$), 1.50 (4H, m, $ArCH_2CH_2CH_2CH_2CH_2S$), 1.75 (3H, dd, *J*=6.6, 1.9 Hz, C(O)CH=CHCH_3), 2.29 (2H, m, $SCH_2CH_2R_F$), 2.42–2.47 (4H, m, $ArCH_2CH_2CH_2CH_2CH_2S$), 2.64 (2H, m, $SCH_2CH_2R_F$), 5.73 (1H, dd, *J*=15.4, 1.9 Hz, C(O)C*H*=CHCH$_3$), 6.59 (1H, s, PhC*H*), 6.80–6.87 (3H, m, 2×Ar*H*, C(O)C*H*=CHCH$_3$), 6.97 (2H, m, Ar*H*), 7.03 (2H, m, Ar*H*), 7.08 (2H, m, Ar*H*), 7.18 (2H, m, Ar*H*), 7.26 (2H, m, Ar*H*), 7.46 (2H, d, *J*=8.2 Hz, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0 (*C*H$_3$CH=CHC(O)O), 22.6 ($SCH_2CH_2R_F$), 28.3 ($ArCH_2CH_2CH$), 29.2 (CH_2CH_2S), 30.8 ($ArCH_2CH_2$), 32.1 ($SCH_2CH_2R_F$), 32.2 (*C*H$_2$S), 35.2 (Ar*C*H$_2$), 78.3 (Ph*C*H), 80.3 (*C*OH), 122.2 (OC(O)CH=*C*HCH$_3$), 126.3 (Ar*C*H), 126.5 (Ar*C*H), 127.2 (Ar*C*H), 127.3 (Ar*C*H), 127.4 (Ar*C*H), 127.8 (Ar*C*H), 128.2 (Ar*C*H), 128.5 (Ar*C*H), 136.2 (Ar*C*), 140.4 (Ar*C*), 141.1 (Ar*C*), 144.9 (Ar*C*), 145.9 (OC(O)*C*H=CHCH$_3$), 165.2 (O*C*=O); *m*/*z* (ES^+ mode) 929 (MNa, 100%), 928 (45%), 924 (20%); found: (MNa^+), 929.1931. $C_{39}H_{35}O_3F_{17}NaS$ requires *M*, 929.1928; ν_{max} (neat) 2929, 1685 (C=O), 1204 (C–F) cm^{-1}.

4.1.14. Acrylic acid (1S,2R)-1-{4-[5-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoro-undecylsulfanyl)-pentyl]-phenyl}-1,2-diphenyl (**9**)

(1*R*,2*S*)-[4-(5-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluoro)decylsulfanylpentyl)-phenyl]-1,2-diphenylethane-1,2-diol **1** (0.13 g, 0.16 mmol), triethylamine (0.03 ml, 0.25 mmol) and acryloyl chloride (0.02 ml, 0.22 mmol) in CH_2Cl_2 (2 ml) was stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (5 ml) and washed with aqueous, saturated $NaHCO_3$ (3×5 ml). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification using FSPE gave **9** (0.094 g, 0.11 mmol, 65%) as a white solid. $[\alpha]_D$=81.9° (*c*=0.018, $CHCl_3$); mp 147–150 °C (MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27–1.31 (2H, m, $ArCH_2CH_2CH_2$), 1.50 (4H, m, $ArCH_2CH_2CH_2CH_2CH_2S$), 2.29 (2H, m, $SCH_2CH_2R_F$), 2.43–2.47 (4H, m, $ArCH_2CH_2CH_2CH_2CH_2S$), 2.64 (2H, m, $SCH_2CH_2R_F$), 5.80 (1H, d, *J*=10.7 Hz, C(O)CH=C*H*H), 6.00 (1H, dd, *J*=17.0, 10.7 Hz, C(O)C*H*=CH$_2$), 6.25 (1H, d, *J*=17.0 Hz, C(O)CH=CH*H*), 6.64 (1H, s, PhC*H*), 6.87 (2H, m, Ar*H*), 6.98 (2H, m, Ar*H*), 7.04 (2H, m, Ar*H*), 7.11 (2H, m, Ar*H*), 7.20 (2H, m, Ar*H*), 7.27 (2H, m, Ar*H*), 7.47 (2H, d, *J*=7.9 Hz, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6 ($SCH_2CH_2R_F$), 28.3 ($ArCH_2CH_2CH_2$), 29.2 (CH_2CH_2S), 30.8 ($ArCH_2CH_2$), 32.1 ($SCH_2CH_2R_F$), 32.2 (*C*H$_2$S), 35.2 (Ar*C*H$_2$), 78.7 (Ph*C*H), 80.2 (*C*OH), 126.3 (Ar*C*H), 126.5 (Ar*C*H), 127.3 (Ar*C*H), 127.4 (Ar*C*H), 127.8 (Ar*C*H), 127.9 (Ar*C*H), 128.0 (C(O)CH=CH$_2$), 128.2 (Ar*C*H), 128.4 (Ar*C*H), 131.6 (C(O)CH=*C*H$_2$), 135.9 (Ar*C*), 140.3 (Ar*C*), 141.2 (Ar*C*), 144.6 (Ar*C*), 164.9 (O*C*=O); *m*/*z* (ES^+ mode) 915 (MNa, 65%), 914 (100%), 921 (10%); found: (MNa^+), 915.1755. $C_{38}H_{33}O_3F_{17}NaS$ requires *M*, 915.1771; ν_{max} (neat) 2929, 1701 (C=O), 1204 (C–F) cm^{-1}.

4.2. General procedure

SmI_2-mediated coupling of aldehydes with **8** or **9** to give γ-butyrolactones.

To a solution of samarium(II) iodide (0.1 M in THF, 2.2 equiv) under nitrogen atmosphere at −15 °C was added dropwise a mixture of aldehyde (1 equiv), *t*-BuOH (6 equiv) and **8/9** (1 equiv) dissolved in THF. The dark blue reaction was stirred for 5 h. The reaction was quenched with aqueous, saturated NaCl solution (5 ml) and the aqueous phase was washed with Et_2O (3×5 ml). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude was purified by FSPE to give the lactone product.

For the synthesis of the racemic lactone standards for determination of enantiomeric excess using chiral GC, methyl acrylate and methylcrotonate were used in the above procedure.

4.2.1. (4R,5S)-5-Isopropyl-4-methyl dihydrofuran-2-one[6] (**10**)

See general procedure: the reaction of isobutyraldehyde (0.017 ml, 0.18 mmol, 1 equiv) with **8** (0.165 g, 0.18 mmol, 1 equiv) gave, after FSPE, (4*R*,5*S*)-5-isopropyl-4-methyl dihydrofuran-2-one **10** (19.1 mg, 75%, 98% ee) as a clear oil. Data is in agreement with that in the literature. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, d, *J*=6.6 Hz, C*H*$_3$CHCH$_3$), 1.00 (3H, d, *J*=7.0 Hz, C*H*$_3$CHCH$_2$), 1.09 (3H, d, *J*=6.5 Hz, C*H*$_3$CHCH$_3$), 1.86–1.93 (1H, m, C*H*(CH$_3$)$_2$), 2.21 (1H, dd, *J*=16.9 Hz, 1.1 Hz, 1H from C*H*$_2$C=O), 2.53–2.58 (1H, m, C*H*CH$_2$C=O), 2.74 (1H, dd, *J*=16.9 Hz, 7.4 Hz, 1H from C*H*$_2$C=O), 3.94 (1H, dd, *J*=10.2 Hz, 4.8 Hz, C*H*O).

4.2.2. (S)-5-tert-Butyl-4-methyl dihydrofuran-2-one[6] (**11**)

See general procedure: the reaction of pivaldehyde (0.02 ml, 0.18 mmol, 1 equiv) with **8** (0.165 g, 0.15 mmol, 1 equiv) gave, after FSPE, (4*R*,5*S*)-*tert*-butyl-4-methyl dihydrofuran-2-one **11** (17.2 mg, 60%, 97% ee) as a clear oil. Data is in agreement with that in the literature. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (9H, s, C(C*H*$_3$)$_3$), 1.14 (3H, d, *J*=7.1 Hz, C*H*$_3$CH), 2.20 (1H, dd, *J*=16.6, 1.6 Hz, 1H from C*H*$_2$C=O), 2.64–2.69 (1H, m, C*H*CH$_2$C=O), 2.76 (1H, dd, *J*=16.6, 7.6 Hz, 1H from C*H*$_2$C=O), 4.09 (1H, d, *J*=4.9 Hz, C*H*O).

4.2.3. (4R,5S)-5-Cyclohexyl-4-methyl dihydrofuran-2-one[6] (**12**)

See general procedure: the reaction of cyclohexyl carboxaldehyde (0.02 ml, 0.15 mmol, 1 equiv) with **8** (0.135 g, 0.15 mmol, 1 equiv) gave, after FSPE, (4*R*,5*S*)-5-cyclohexyl-4-methyl dihydrofuran-2-one **12** (17.5 mg, 82%, 99% ee) as a clear oil. Data is in agreement with that in the literature. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83–0.92 (1H, m, 1H of C*H*$_2$ of cyclohexane ring), 0.95 (3H, d, 6.9 Hz, C*H*$_3$CH), 0.99–1.00 (1H, m, 1H of C*H*$_2$ of cyclohexane ring), 1.07–1.22 (2H, m, C*H*$_2$ of cyclohexane ring), 1.53–1.58 (3H, m, CH$_2$ and 1H of CH$_2$ of cyclohexane ring), 1.62–1.71 (4H, m, 2×C*H*$_2$ of cyclohexane ring), 1.96–2.00 (1H, m, 1H of C*H*$_2$ of cyclohexane ring), 2.12 (1H, dd, *J*=16.9 Hz, 1.1 Hz, 1H from C*H*$_2$C=O), 2.47–2.50 (1H, m, C*H*CH$_2$C=O), 2.65 (1H, dd, *J*=16.9, 7.4 Hz, 1H from C*H*$_2$C=O), 3.95 (1H, dd, *J*=9.8, 4.7 Hz, C*H*O).

4.2.4. (4R,5S)-5-n-Butyl-4-methyl dihydrofuran-2-one[6] (**13**)

See general procedure: the reaction of valeraldehyde (0.02 ml, 0.18 mmol, 1 eq.) with **8** (0.165 g, 0.18 mmol, 1 equiv) gave, after FSPE, (4*R*,5*S*)-5-*n*-butyl-4-methyl dihydrofuran-2-one **13** (14.4 mg, 51%, 98% ee) as a clear oil. Data is in agreement with that in the literature. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, t, *J*=7.3 Hz, C*H*$_3$CH$_2$), 0.93 (3H, d, *J*=7.0 Hz, CHC*H*$_3$), 1.36–1.42 (3H, m, C*H*$_2$), 1.45–1.58 (2H, m, C*H*$_2$), 1.61–1.70 (1H, m, 1H of C*H*$_2$), 2.21 (1H, dd, *J*=16.9, 3.9 Hz, 1H from C*H*$_2$C=O), 2.54–2.63 (1H, m, C*H*CH$_2$C=O), 2.70 (1H, dd, *J*=16.9, 7.8 Hz, 1H from C*H*$_2$C=O), 4.41–4.46 (1H, m, C*H*O).

4.2.5. (4R,5S)-5-Cyclopropyl-4-methyl dihydrofuran-2(3H)-one (**14**)

See general procedure: the reaction of cyclopropane carboxaldehyde (0.007 ml, 0.0933 mmol, 1 equiv) with **8** (0.0845 g, 0.0933 mmol, 1 equiv) gave, after FSPE, (4*R*,5*S*)-5-cyclopropyl-4-methyldihydrofuran-2(3*H*)-one **14** (9.0 mg, 69%, 99% ee) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.29 (1H, m, 1H of cyclopropyl CH_2), 0.46 (1H, m, 1H of cyclopropyl CH_2), 0.64 (1H, m, 1H of cyclopropyl CH_2), 0.71 (1H, m, 1H of cyclopropyl CH_2), 1.00 (1H, m, CH of cyclopropyl), 1.19 (3H, d, J=6.9 Hz, CH_3), 2.29 (1H, m, 1H from CH_2C=O), 2.68 (2H, m, 1H from CH_2 and CHCH$_3$), 3.94 (1H, dd, J=9.1, 6.0 Hz, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.0 (CH_2 of cyclopropyl), 1.8 (CH_2 of cyclopropyl), 8.4 (CH of cyclopropyl), 12.9 (Me), 31.8 (*C*HMe), 35.2 (C(O)CH_2), 86.8 (CHO), 175.1 (C=O); m/z (ES$^+$ mode) 141 (MH$^+$, 70%), 123 (10%), 109 (10%), 83 (15%), 69 (15%); found: (M), 140.0836. $C_8H_{12}O_2$ requires M, 140.0832; ν_{max} (neat) 2938, 1712 (C=O) cm^{-1}.

4.2.6. (S)-5-tert-Butyl dihydrofuran-2-one[6] (**15**)

See general procedure: the reaction of pivaldehyde (0.02 ml, 0.18 mmol, 1 equiv) with **9** (0.134 g, 0.15 mmol, 1 equiv) gave, after FSPE, (*S*)-5-*tert*-butyl dihydrofuran-2-one **15** (17.2 mg, 60%, 82% ee) as a clear oil. Data is in agreement with that in the literature. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (9H, s, 3×(CH_3)C), 1.94–2.02 (1H, m, 1H from CH_2), 2.08–2.16 (1H, m, 1H from CH_2), 2.50–2.55 (2H, m, CH_2C=O), 4.19 (1H, dd, J=6.9 Hz, 8.8 Hz, CHO).

4.2.7. (S)-5-Cyclohexyl dihydrofuran-2-one[6] (**16**)

See general procedure: the reaction of cyclohexane carboxaldehyde (0.02 ml, 0.18 mmol, 1 equiv) with **9** (0.134 g, 0.15 mmol, 1 equiv) gave, after FSPE, (*S*)-5-cyclohexyl dihydrofuran-2-one **16** (23.3 mg, 77%, 86% ee) as clear oil. Data is in agreement with that in the literature. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00–1.06 (2H, m, CH_2), 1.16–1.29 (2H, m, CH_2), 1.51–1.57 (2H, m, CH_2), 1.65–1.72 (2H, m, CH_2), 1.76–1.80 (2H, m, CH_2), 1.90–1.98 (2H, m, 1H from CH_2CH$_2$C=O and 1H from CH_2), 2.25 (1H, apparent sextet, J=6.7 Hz, 1H from CH_2CH$_2$C=O), 2.50–2.54 (2H, m, CH_2C=O), 4.14 (1H, dt, J=7.4, 8.0 Hz, CHO).

4.2.8. (5S)-5-Cyclopentyl dihydrofuran-2(3H)-one (**17**)

See general procedure: the reaction of cyclopentane carboxaldehyde (0.001 ml, 0.0952 mmol, 1 equiv) with **9** (0.085 g, 0.0952 mmol, 1 equiv) gave, after FSPE, (5*S*)-5-cyclopentyl dihydrofuran-2(3*H*)-one (10.8 mg, 74%, 88% ee) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20–1.99 (10H, m, cyclopentyl group, 1H of CH_2), 2.23 (1H, m, 1H of CH_2), 2.47 (2H, m, CH_2C=O), 4.25 (1H, m, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4 (CH_2 of cyclopentyl), 25.5 (CH_2 of cyclopentyl), 27.1 (CH_2CH$_2$C=O), 29.1 (CH of cyclopentyl), 29.2 (CH_2 of cyclopentyl), 29.4 (CH_2 of cyclopentyl), 44.8 (CH_2C=O), 84.9 (CHO), 177.5 (C=O); m/z (Cl$^+$ mode) 155 (MH$^+$, 100%), 136 (10%), 108 (10%), 84 (25%), 64 (10%); found: (M), 154.0986. $C_9H_{14}O_2$ requires M, 154.0988; ν_{max} (neat) 2976, 1724 (C=O) cm^{-1}.

4.2.9. (5S)-5-Methyl-5-phenyl dihydrofuran-2(3H)-one[6] (**21**)

See general procedure: the reaction of acetophenone (0.013 ml, 0.011 mmol, 1 equiv) with **9** (0.0978 g, 0.011 mmol, 1 equiv) gave, after FSPE (5*S*)-5-methyl-5-phenyldihydrofuran-2(3*H*)-one **21** (17.2 mg, 97%, 46% ee) as a clear oil. Data is in agreement with that in the literature. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.66 (3H, s, CH_3C), 2.31–2.62 (4H, m, CH_2CH$_2$C=O), 7.21–7.31 (5H, m, ArH).

4.2.10. (4R,5R)-1-Benzyl-5-isopropyl-4-methylpyrrolidin-2-one (**23**)

N-Benzyl-*N*-[(1*Z*)-2-methylpropylidene]amine oxide **22** (0.040 g, 0.22 mmol), **8** (0.0825 g, 0.091 mmol) and degassed water (0.06 ml, 3.19 mmol) were dissolved in THF (3 ml), pre-cooled to −78 °C and the solution added to SmI_2 (6.40 ml, 1.0 M in THF, 0.64 mmol) at −78 °C. The reaction was kept at −78 °C for 4 h and subsequently allowed to warm to room temperature and left overnight. The reaction was quenched with saturated $Na_2S_2O_3$ solution (5 ml), the aqueous layer was washed with Et_2O (3×5 ml) and the combined organic layers were washed with saturated, aqueous NaCl solution (3×5 ml), dried (Na_2SO_4), filtered and concentrated in vacuo. The resultant crude mixture was dissolved in THF (3 ml) and formic acid (0.1 ml) was added. The reaction was stirred for 3 h at 40 °C and quenched with saturated, aqueous $NaHCO_3$ solution (5 ml). The aqueous layer was washed with Et_2O (3×5 ml) and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude mixture was purified by FSPE to give *cis*-1-benzyl-5-isopropyl-4-methylpyrrolidin-2-one (0.0152 g, 0.0658 mmol, 73%, 45% ee) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, d, J=7.0 Hz, CHCH_3), 0.97 (3H, d, J=7.2 Hz, CHCH_3), 1.03 (3H, d, J=6.9 Hz, CHCH_3), 1.97 (1H, m, CH(CH$_3$)$_2$), 2.18 (1H, m, C(O)CHH), 2.34–2.44 (2H, m, C(O)CHH, CHMe), 3.22 (1H, dd, J=7.9, 2.4 Hz, CHN), 3.83 (1H, d, J=15.1 Hz, PhCHH), 5.20 (1H, d, J=15.1 Hz, PhCHH), 7.14 (2H, d, J=7.2 Hz, 2×ArH), 7.19 (1H, m, ArH), 7.25 (2H, m, 2×ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.2 (Me), 18.0 (CHCH_3 of *i*-Pr), 21.4 (CHCH_3 of *i*-Pr), 29.1 (*C*HMe), 32.7 (*C*H(CH$_3$)$_2$), 38.8 (C(O)CH_2), 45.7 (PhCH_2), 64.4 (*C*HN), 127.4 (ArCH), 127.9 (2×Ar*C*H), 128.6 (2×ArCH), 136.8 (Ar*C*), 175.6 (*C*=O); m/z (Cl$^+$ mode), 232 (M$^+$, 100%), 187 (20%), 90 (10%); found: (M$^+$), 232.1692. $C_{15}H_{22}ON$ requires M, 232.1696; ν_{max} (neat) 2932 (C–H), 2360, 1734, 1423 cm^{-1}.

Acknowledgements

We thank the University of Manchester and Novartis (studentship to J.C.V.) and Dr. Glynn Williams for preliminary studies on the synthesis of 1.

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