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Ring-Opening Hydrofluorination of 2,3- and 3,4-Epoxy Amines by $HBF_4 \cdot OEt_2$: Application to the Asymmetric Synthesis of (*S*,*S*)-3-Deoxy-3-fluorosafingol

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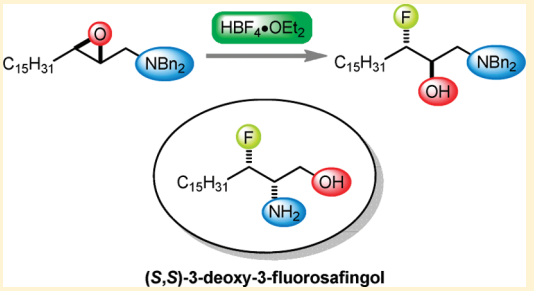
Supporting Information

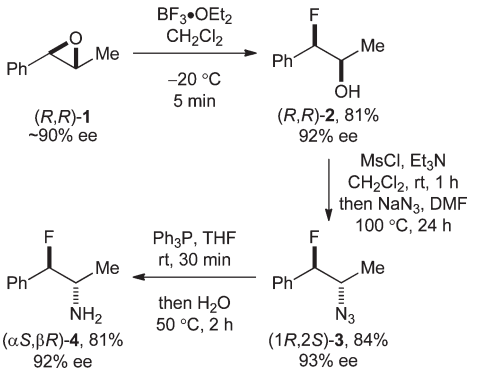
ABSTRACT: Treatment of a range of 2,3- and 3,4-epoxy amines with $HBF_4 \cdot OEt_2$ at room temperature results in fast and efficient S_N2-type ring-opening hydrofluorination to give stereodefined amino fluorohydrins. Operational simplicity, scalability, and short reaction time at ambient temperature are notable features of this method. The utility of this methodology is exemplified in a concise asymmetric synthesis of (*S*,*S*)-3-deoxy-3-fluorosafingol.



INTRODUCTION

Fluorine, perhaps more so than any other element, has generated huge interest across practically every discipline in organic chemistry. The dramatic effect that fluorine can impart on the physical, chemical, and biological properties of molecules is well-documented,[1] and fluoro-organics are now ubiquitous in medicinal chemistry,[2] agrochemistry,[3] and materials science.[4] Recent estimates suggest that 20−25% of drugs (including 5 of the top 10 drugs sold in 2005) and 30−40% of agrochemicals contain at least one fluorine atom.[5] In light of this plethora of applications, practical and safe methods for the regio- and stereocontrolled installation of fluorine atoms into organic substrates are in high demand: to meet this need, several fluorination protocols have been developed,[6] including asymmetric procedures.[7] However, many of the existing methodologies for stereoselective fluorination suffer from economical or practical setbacks, often relating to the fluorinating agents themselves. Considering the significant benefits (i.e., low cost, high fluorine content, and ease of handling in standard glassware), we recently embarked upon investigations into the utility of $BF_3 \cdot OEt_2$ as a nucleophilic fluorine source[8] and reported the stereoselective ring-opening hydrofluorination of substituted aryl epoxides with $BF_3 \cdot OEt_2$ under mild conditions for the synthesis of β-fluoroamphetamines.[9] For instance, treatment of β-methylstyrene oxide (*R*,*R*)-**1** (~90% ee) with 0.33 equiv of $BF_3 \cdot OEt_2$ in CH_2Cl_2 at −20 °C for 5 min gave *syn*-fluorohydrin **2** as the major product in 81% isolated yield, >99:1 dr, and 92% ee, consistent with a stereoselective S_N1-type process that results in retention of configuration. Mesylation of the free hydroxyl group within **2** followed by displacement with azide gave **3**, with Staudinger reduction giving β-fluoroamphetamine **4** in 68% yield from **2** and with no erosion of the stereochemical purity of the starting epoxide **1** (Scheme 1).

Scheme 1



Despite the extremely low nucleophilicity of the BF_4^- anion, the nucleophilic trapping of highly reactive cationic intermediates by fluorine transfer from BF_4^- has featured in a number of fluorination procedures. Aside from C(sp^2)−F bond-forming protocols such as the classic Balz−Schiemann synthesis of aryl fluorides,[10] the construction of C(sp^3)−F bonds by fluorine transfer from BF_4^- to carbocationic intermediates has been reported in the nitrosative decomposition of aliphatic azides with $NOBF_4$[11] and as the termination step in a variety of cation-π cyclizations.[12] S_N1-type fluorinations involving the trapping of oxocarbenium[13] and halocarbenium[14] ion intermediates by fluorine transfer from BF_4^- to generate glycosyl fluorides and

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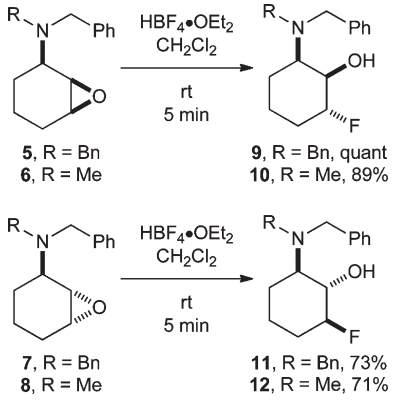
gem-difluorides, respectively, have also been described. In terms of S_N2-type processes, Ohmori and co-workers have developed a variant of the Mitsunobu reaction involving the electrochemical generation and subsequent thermal decomposition of alkoxy triphenylphosphonium tetrafluoroborate intermediates, allowing for the direct conversion of alcohols to the corresponding fluorides with inversion of configuration, although the isolated yields were low in most cases.[15] An attractive strategy in terms of stereoselective fluorination has been the stereospecific ring opening of iranium ion intermediates with nucleophilic fluorine sources, and S_N2-type fluorine transfer from BF_4^- to chloriranium,[16] iodiranium,[17] and thiiranium[18] ions has previously been observed. As part of our research program aimed at the development of novel methods for nucleophilic fluorination,[9] we became interested in the possibility of effecting the ring opening of 2,3-epoxy amines (previously prepared in our laboratories during investigations into our ammonium-directed oxidation protocol)[19] using $HBF_4 \cdot OEt_2$ as a nucleophilic source of fluorine for the preparation of amino fluorohydrins.[20] We describe herein our endeavors within this area, which culminate in a short asymmetric synthesis of (*S*,*S*)-3-deoxy-3-fluorosafingol.[21]

RESULTS AND DISCUSSION

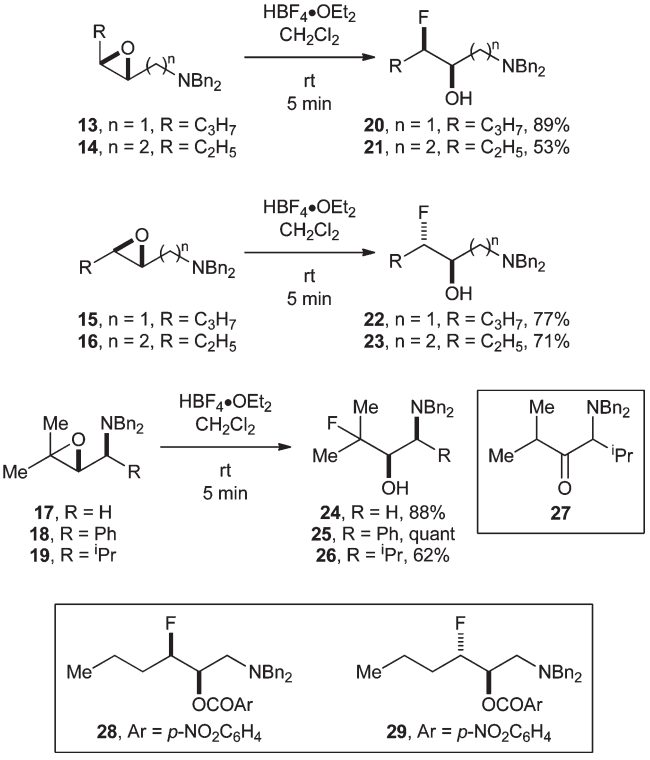
The ring-opening hydrofluorination of 2,3-epoxy amine **5**[22] as a model system was investigated. Treatment of **5** with 2 equiv of $HBF_4 \cdot OEt_2$ in CH_2Cl_2 at rt for 5 min gave amino fluorohydrin **9** as a single diastereoisomer (>99:1 dr) in quantitative yield (Scheme 2). The relative configuration within **9** was unambiguously established via single crystal X-ray diffraction analysis[23] and is consistent with the ring opening proceeding via an S_N2-type mechanism with intermolecular transfer of fluorine from BF_4^- and inversion of configuration. This is in contrast to our previously reported ring-opening hydrofluorination of aryl epoxides using $BF_3 \cdot OEt_2$, which proceeds via a stereoselective S_N1-type process (intramolecular transfer of fluorine from the in situ formed alkoxyfluoroborate complex and retention of configuration),[9] although the speed and mild reaction conditions of both of these transformations are notable. The importance of the amino moiety within **5** in promoting this transformation was underscored by attempted ring-opening hydrofluorination of cyclohexene oxide and *syn*-1,2-epoxy-3-benzyloxycyclohexane, which gave only nonfluorinated polymeric products upon treatment with $HBF_4 \cdot OEt_2$.[24] The role of the amino group in promoting the transformation of 2,3-epoxy amine **5** to amino fluorohydrin **9** may therefore lie in its capacity to form an ammonium moiety *in situ*, which would discourage ionization of the oxirane and suppress polymerization or rearrangement pathways from competing with transfer of fluorine from the BF_4^- ion.[25]

The generality of this process was explored by application to a range of 2,3-epoxy amines **6**−**8**.[22] In each case, the ring-opening reaction proceeded via attack of fluorine at the oxirane carbon atom distal to the ammonium moiety (formed in situ) to give amino fluorohydrins **10**-**12** in 71−89% isolated yield after chromatography.[26] The relative configurations within **11** and **12** were unambiguously established by single crystal X-ray diffraction analyses.[23] On this basis, the relative configuration within **10** could be confidently assigned. NMR ^3J coupling constant analyses ($^1H-^1H$ and $^1H-^{19}F$) were also supportive of this assignment. The stereochemical outcomes of these reactions are therefore consistent, in each case, with the reaction

Scheme 2



Scheme 3



proceeding via an S_N2-type mechanism. The regioselectivities of the ring-opening processes are consistent with our previous observations concerning ring opening of a range of 2,3-epoxy amines (including **5** and **7**) with a variety of Brønsted acids:[19,27] the destabilizing electron-withdrawing influence of the ammonium moiety on the late transition state[28] is less pronounced if ring opening occurs at the carbon atom distal to it.

The suitability of the conformationally more labile 2,3- and 3,4-epoxy amines **13**−**19** as substrates for this transformation was also examined.[29] Reaction of the diastereoisomeric 2,3-epoxy amines **13** and **15** gave the diastereoisomeric amino fluorohydrins **20** and **22**, respectively (Scheme 3). The relative configurations within **20** and **22** were unambiguously established by single crystal X-ray diffraction analyses of the corresponding *p*-nitrobenzoate esters **28** and **29**[30] and are consistent with both

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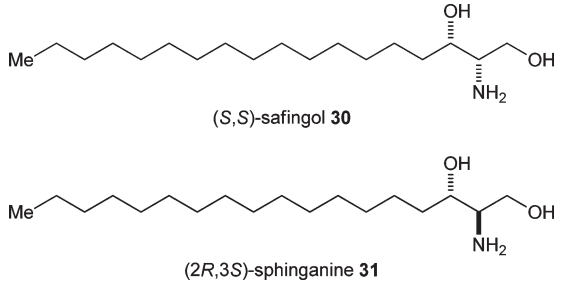
of these ring-opening reactions traversing an S_N2-type pathway. The diastereoisomeric 3,4-epoxy amines **14** and **16** also proved amenable to this transformation, proceeding to give the corresponding amino fluorohydrins **21** and **23** as the major products.[31] The relative configurations within **21** and **23** were assigned by analogy to those unambiguously established for **20** and **22** (i.e., on the assumption that both reactions proceed via S_N2-type ring openings). Meanwhile, ring opening of 2,3-epoxy amine **17** with $HBF_4 \cdot OEt_2$ gave amino fluorohydrin **24** (having fluorine at a quaternary center) in 88% yield, and similar treatment of the diastereoisomerically pure 2,3-epoxy amine **18** gave the corresponding diastereoisomerically pure amino fluorohydrin **25**, which was isolated in quantitative yield. The relative configuration within **25** was confirmed unambiguously by single crystal X-ray diffraction analysis.[30] Treatment of 2,3-epoxy amine **19** with $HBF_4 \cdot OEt_2$ resulted in formation of an 83:17 mixture of the desired fluorohydrin **26** and ketone **27**, presumably a result of a rearrangement reaction. Chromatographic purification facilitated isolation of **26** in 62% yield, and ketone **27** in 6% yield (Scheme 3).

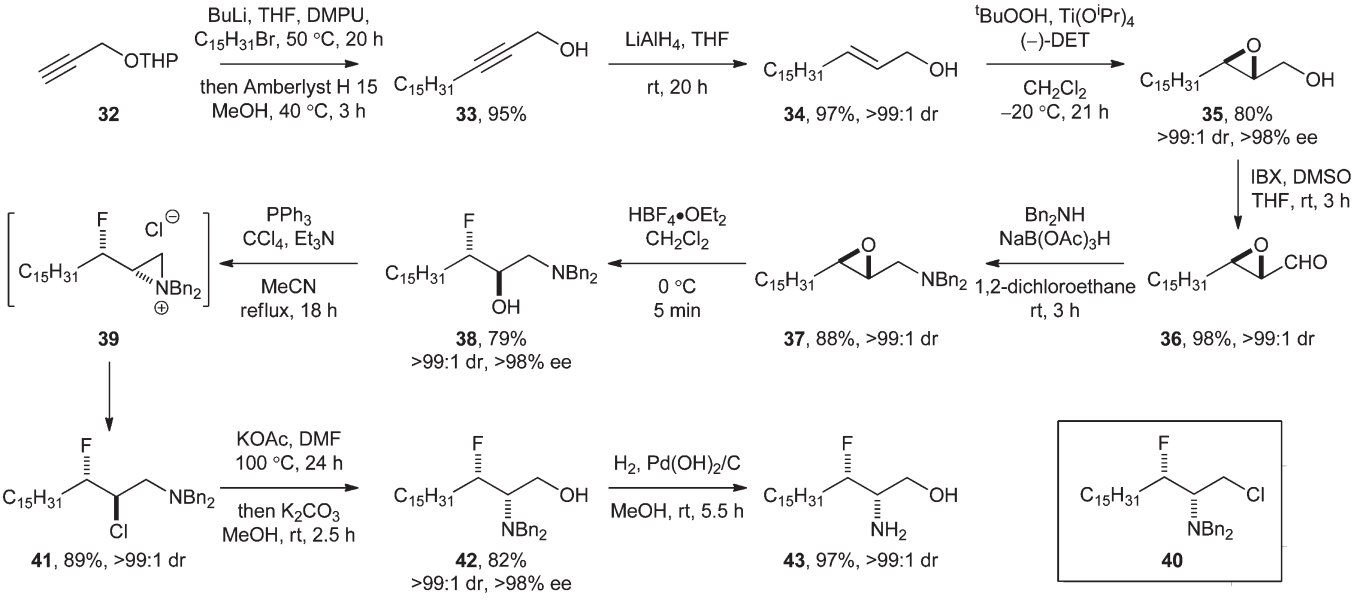
The utility of this methodology was next demonstrated by application to an asymmetric synthesis of (*S*,*S*)-3-deoxy-3-fluorosafingol.[21] (*S*,*S*)-Safingol **30** is an antineoplastic and antipsoriatic agent and is a non-naturally occurring diastereoisomer of the sphingoid base (2*R*,3*S*)-sphinganine **31**. Given the ubiquity of sphingoid bases in all eukaryotic cells,[32] there is extensive interest in the synthesis and evaluation of the biological properties of sphingoid bases and their analogues:[33] safingol **30**, for instance, has been investigated for its role in cell regulation, signal transduction, and protein kinase C inhibition[34] (Scheme 4).

Our synthesis of (*S*,*S*)-3-deoxy-3-fluorosafingol **43** (Scheme 5) began with alkylation of *O*-THP protected propargylic alcohol **32** (commercially available) by treatment with BuLi in the presence of DMPU and 1-bromopentadecane, which was followed by *O*-THP deprotection to give propargylic alcohol **33** in 95% yield. Reduction of **33** with $LiAlH_4$ gave allylic alcohol (*E*)-**34** in 97% yield and >99:1 dr. Sharpless asymmetric epoxidation[35] of **34** gave, after recrystallization, 2,3-epoxy alcohol **35** in 80% isolated yield and >98% ee.[36] Oxidation of the hydroxyl functionality within **35** with IBX[37] followed by reductive amination of the resultant aldehyde **36** with dibenzylamine and $NaB(OAc)_3H$[38] gave 2,3-epoxy amine **37** in 86% yield (2 steps). Ring-opening hydrofluorination of **37** using $HBF_4 \cdot OEt_2$ gave amino fluorohydrin **38** in 79% yield and as a single diastereoisomer (>99:1 dr) in >98% ee.[36] The relative configuration within **38** was assigned on the assumption that the ring opening proceeds via an S_N2-type process, and this assignment was supported by inspection of the $^1H-^{19}F$ ^3J coupling constant between C(2)*H* and C(3)*F* within **20** (^3J = 20.7 Hz), **22** (^3J = 11.5 Hz), and **38** (^3J = 11.4 Hz). Chlorination of **38** under Appel conditions[39] for 40 min resulted in complete conversion to an 83:17 mixture of chlorides **40** and **41**, presumably via the intermediacy of aziridinium **39**. When the reaction time was extended to 18 h, clean conversion to chloride **41** was observed, consistent with reversible ring opening of aziridinium **39** resulting initially in primary chloride **40** as the kinetic product and secondary chloride **41** as the thermodynamic product.[40] Treatment of **41** with KOAc in DMF at 100 °C followed by transesterification with K_2CO_3 in MeOH gave **42** as a single regio- and diastereoisomer (>99:1 dr), which was isolated in 82% yield and >98% ee[36] after chromatographic purification. Presumably, this reaction also proceeds via the intermediacy of aziridinium **39**, which undergoes irreversible ring opening by acetate, with attack occurring at the least substituted carbon atom. Finally, hydrogenolytic removal of the *N*-benzyl protecting groups within **42** completed the synthesis of (*S*,*S*)-3-deoxy-3-fluorosafingol **43**, which was isolated in 97% yield (36% overall yield in 11 steps from *O*-THP protected propargylic

Scheme 4



Scheme 5



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alcohol **32**) as a single diastereoisomer. The relative configuration within **43** was unambiguously established by single crystal X-ray diffraction analysis.[41] Given the known enantiomeric purities of **35**, **38** and **42** (i.e., >98% ee)[36] the enantiomeric purities of **36**, **37**, **39**−**41**, and **43** can confidently be inferred as >98% ee.

CONCLUSION

In conclusion, treatment of a range of 2,3- and 3,4-epoxy amines with $HBF_4 \cdot OEt_2$ at room temperature results in fast and efficient S_N2-type ring-opening hydrofluorination to give stereodefined amino fluorohydrins. Operational simplicity, scalability, and short reaction time at ambient temperature are notable features of this method. The utility of this methodology is exemplified in a concise asymmetric synthesis of (*S*,*S*)-3-deoxy-3-fluorosafingol.

EXPERIMENTAL SECTION

General Experimental Details. Reactions involving moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame-dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[42] *m*-CPBA was supplied as a 70−77% slurry in water and titrated according to the procedure of Swern[43] before use. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminum plates coated with 60 F_{254} silica. Flash column chromatography was performed either on Kieselgel 60 silica on a glass column or on an automated flash column chromatography platform.

Melting points are uncorrected. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded as either a thin film on NaCl plates (film) or a KBr disk (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. $^1H-^1H$ COSY and $^1H-^{13}C$ HMQC analyses were used to establish atom connectivity.

General Procedure 1 for Ring-Opening Hydrofluorination of Epoxy Amines with $HBF_4 \cdot OEt_2$. $HBF_4 \cdot OEt_2$ (2 equiv) was added in one portion to a stirred solution of the requisite epoxy amine (1 equiv, 0.25 M in CH_2Cl_2) at rt (unless specified otherwise), and the reaction mixture was stirred at this temperature for 5 min. Saturated aqueous $NaHCO_3$ was then added, and the layers were separated. The organic layer was washed twice with saturated aqueous $NaHCO_3$, and the combined aqueous layers were extracted twice with CH_2Cl_2. The combined organic layers were then dried and concentrated *in vacuo*.

General Procedure 2 for Epoxidation of Alkenyl Alcohols with *m*-CPBA. *m*-CPBA (1.5 equiv) was added to a stirred solution of the requisite alkenyl alcohol (1 equiv, 0.25 M in CH_2Cl_2) at 0 °C, and the reaction mixture was allowed to warm to rt over 24 h. Saturated aqueous Na_2SO_3 was then added until starch-iodide paper indicated no remaining oxidant, and then 5% aqueous NaOH was added and the layers were separated. The organic layer was washed twice with 5% aqueous NaOH, and the combined aqueous layers were saturated with NaCl and extracted twice with CH_2Cl_2. The combined organic layers were then dried and concentrated *in vacuo*.

General Procedure 3 for Mesylation of Alcohols. Et_3N (2 equiv) and MsCl (1.5 equiv) were added sequentially to a stirred solution of the requisite alcohol (1 equiv, 0.6 M in CH_2Cl_2) at 0 °C, and the reaction mixture was allowed to warm to rt over 1 h. Aqueous HCl (1 M) was then added, and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic layers were then dried and concentrated *in vacuo*.

General Procedure 4 for Amination of Mesylates. Dibenzylamine (2.5 equiv) was added to a stirred solution of the requisite mesylate (1 equiv, 0.4 M in EtOH), and the reaction mixture was heated at reflux for 48 h. After this time the mixture was allowed to cool to rt and was concentrated *in vacuo*. The residue was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were then dried and concentrated *in vacuo*.

(*RS*,*RS*,*RS*)-2-(*N*,*N*-Dibenzylamino)-6-fluorocyclohexan-1-ol 9. Following *General Procedure 1*, **5** (108 mg, 0.37 mmol) in CH_2Cl_2 (1.47 mL) was treated with $HBF_4 \cdot OEt_2$ (100 μL, 0.74 mmol). Purification via flash column chromatography (gradient elution, 5→40% EtOAc in 30−40 °C petrol) gave **9** as a colorless syrup which solidified on standing to a white crystalline solid (117 mg, quant, >99:1 dr); R_f 0.46 (30−40 °C petrol/EtOAc, 4:1); $C_{20}H_{24}FNO$ requires C, 76.65; H, 7.7; N, 4.5%; found C, 76.7; H, 7.8; N, 4.4%; mp 74−77 °C; ν_{max} (KBr) 3443 (O−H), 3085, 3062, 3028, 3004, 2941, 2869, 2805, 2730 (C−H), 1494, 1453; δ_H (400 MHz, $CDCl_3$) 1.43−1.87 (6H, m, C(3)H_2, C(4)H_2, C(5)H_2), 2.95 (1H, br s, O*H*), 3.01−3.09 (1H, m, C(2)*H*), 3.82 (4H, A_2, N(CH_2Ph)$_2$), 4.17−4.24 (1H, app dt, *J* 6.3, 3.3, C(1)*H*), 4.84 (1H, app dq, *J* 45.5, 3.0, C(6)*H*), 7.22−7.37 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.3 (*C*(4)), 23.8 (*C*(3)), 25.6 (d, *J* 20.8, *C*(5)), 54.7 (N(CH_2Ph)$_2$), 59.3 (*C*(2)), 67.2 (d, *J* 28.8, *C*(1)), 90.8 (d, *J* 166, *C*(6)), 127.0 (*p*-*Ph*), 128.4, 128.6 (*o*,*m*-*Ph*), 139.8 (*i*-*Ph*); δ_F (377 MHz, $CDCl_3$) −191.8 (app t, *J* 45.9); *m*/*z* (ESI$^+$) 649 ([2M + Na]$^+$, 100%), 314 ([M + H]$^+$, 82%); HRMS (ESI$^+$) $C_{20}H_{25}FNO^+$ ([M + H]$^+$) requires 314.1915; found 314.1912.

(*RS*,*RS*,*RS*)-2-(*N*-Benzyl-*N*-methylamino)-6-fluorocyclohexan-1-ol 10. Following *General Procedure 1*, **6** (217 mg, 1.00 mmol) in CH_2Cl_2 (4.00 mL) was treated with $HBF_4 \cdot OEt_2$ (272 μL, 2.00 mmol). Purification via flash column chromatography on neutralized silica gel (gradient elution, 7→60% EtOAc in 30−40 °C petrol) gave **10** as a yellow oil (211 mg, 89%, >99:1 dr); R_f 0.28 (30−40 °C petrol/EtOAc, 7:3); $C_{14}H_{20}FNO$ requires C, 70.9; H, 8.5; N, 5.9%; found C, 71.0; H, 8.6; N, 5.85%; ν_{max} (film) 3424 (O−H), 3086, 3063, 3028, 2943, 2869, 2797 (C−H), 1454, 1070, 1002; δ_H (400 MHz, $CDCl_3$) 1.44−1.93 (6H, m, C(3)H_2, C(4)H_2, C(5)H_2), 2.21 (3H, s, N*Me*), 2.63 (1H, dddd, *J* 11.6, 4.7, 2.9, 2.6, C(2)*H*), 3.43 (1H, br s, O*H*), 3.56 (1H, d, *J* 13.4, NCH_A), 3.74 (1H, d, *J* 13.4, NCH_B), 4.20 (1H, app dt, *J* 6.1, 3.1, C(1)*H*), 4.93 (1H, app dq, *J* 45.4, 3.1, C(6)*H*), 7.24−7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.7 (*C*(4)), 23.9 (*C*(3)), 25.3 (d, *J* 20.8, *C*(5)), 38.3 (N*Me*), 58.2 (NCH_2), 60.8 (*C*(2)), 65.7 (d, *J* 30.4, *C*(1)), 90.5 (d, *J* 165, *C*(6)), 127.2 (*p*-*Ph*), 128.4, 128.9 (*o*,*m*-*Ph*), 138.9 (*i*-*Ph*); δ_F (377 MHz, $CDCl_3$) −193.8 (app td, *J* 44.7, 9.2); *m*/*z* (ESI$^+$) 507 (100%), 238 ([M + H]$^+$, 69%); HRMS (ESI$^+$) $C_{14}H_{21}FNO^+$ ([M + H]$^+$) requires 238.1602, found 238.1599.

(1*RS*,2*SR*,6*RS*)-2-(*N*,*N*-Dibenzylamino)-6-fluorocyclohexan-1-ol 11. Following *General Procedure 1*, 7 (402 mg, 1.37 mmol) in CH_2Cl_2 (5.48 mL) was treated with $HBF_4 \cdot OEt_2$ (373 μL, 2.74 mmol). Purification via flash column chromatography (gradient elution, 5→40% Et_2O in 30−40 °C petrol) gave **11** as a colorless oil that solidified on standing to a white crystalline solid (314 mg, 73%, >99:1 dr); R_f 0.26 (30−40 °C petrol/Et_2O, 4:1); $C_{20}H_{24}FNO$ requires C, 76.65; H, 7.7; N, 4.5%; found C, 76.5; H, 7.6; N, 4.3%; mp 77−79 °C; ν_{max} (KBr) 3453 (O−H), 3085, 3062, 3028, 2941, 2866 (C−H), 1454, 1068, 1027, 750, 700; δ_H (400 MHz, $CDCl_3$) 1.08−1.22 (1H, m, C(4)H_A), 1.29 (1H, app qd, *J* 12.6, 3.3, C(3)H_A), 1.40−1.54 (1H, m, C(5)H_A), 1.80−1.90 (1H, m, C(4)H_B), 1.90−1.98 (1H, m, C(3)H_B), 2.03−2.13 (1H, m, C(5)H_B), 2.37−2.47 (1H, app td, *J* 11.0, 2.8, C(2)*H*), 3.40 (2H, d, *J* 13.1, N(CH_ACH_BPh)$_2$), 3.62 (1H, ddd, *J* 13.0, 10.0, 8.4, C(1)*H*), 3.76 (1H, br s, O*H*), 3.90 (2H, d, *J* 13.1, N(CH_ACH_BPh)$_2$), 4.23 (1H, dddd, *J* 51.5, 11.3, 8.4, 5.2, C(6)*H*), 7.24−7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.7 (d, *J* 12.8, *C*(4)), 21.3 (*C*(3)), 30.2 (d, *J* 17.6, *C*(5)), 53.7

($N(CH_2Ph)_2$), 61.2 (d, *J* 9.6, *C*(2)), 72.4 (d, *J* 17.6, *C*(1)), 95.1 (d, *J* 176, *C*(6)), 127.4 (*p-Ph*), 128.6, 129.0 (*o,m-Ph*), 138.9 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −179.0 (app d, *J* 51.5); *m*/*z* (FI^+) 313 ($[M]^+$, 100%); HRMS (FI^+) $C_{20}H_{24}FNO^+$ ($[M]^+$) requires 313.1836, found 313.1843.

(1*RS*,2*SR*,6*RS*)-2-(*N*-Benzyl-*N*-methylamino)-6-fluorocyclohexan-1-ol 12. Following *General Procedure 1*, **8** (217 mg, 1.00 mmol) in CH_2Cl_2 (4.00 mL) was treated with $HBF_4 \cdot OEt_2$ (272 μL, 2.00 mmol). Purification via flash column chromatography on neutralized silica gel (gradient elution, 2→20% EtOAc in 30−40 °C petrol) gave **12** as a colorless oil which solidified on standing to a white crystalline solid (169 mg, 71%, >99:1 dr); R_f 0.13 (30−40 °C petrol/EtOAc, 9:1); $C_{14}H_{20}FNO$ requires C, 70.9; H, 8.5; N, 5.9%; found C, 71.0; H, 8.35; N, 5.95%; mp 77−79 °C; ν_{max} (KBr) 3441 (O−H), 3086, 3062, 3028, 2943, 2867, 2801 (C−H), 1453, 1079, 1010; δ_H (400 MHz, $CDCl_3$) 1.15−1.32 (2H, m, C(3)H_A, C(4)H_A), 1.40−1.56 (1H, m, C(5)H_A), 1.76−1.94 (2H, m, C(3)H_B, C(4)H_B), 2.07−2.17 (1H, m, C(5)H_B), 2.22 (3H, s, N*Me*), 2.35−2.45 (1H, m, C(2)*H*), 3.47 (1H, d, *J* 13.0, NCH_A), 3.55 (1H, ddd, *J* 12.8, 10.2, 8.3, C(1)*H*), 3.74 (1H, d, *J* 13.0, NCH_B), 4.37 (1H, dddd, *J* 51.5, 11.2, 8.3, 5.2, C(6)*H*), 7.24−7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.6 (d, *J* 12.0, *C*(4)), 20.6 (d, *J* 2.4, *C*(3)), 30.3 (d, *J* 18.4, *C*(5)), 36.5 (N*Me*), 58.2 (NCH_2), 65.8 (d, *J* 9.6, *C*(2)), 72.6 (d, *J* 16.0, *C*(1)), 95.2 (d, *J* 177, *C*(6)), 127.3 (*p-Ph*), 128.5, 128.8 (*o,m-Ph*), 138.7 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −178.7 (app d, *J* 51.5); *m*/*z* (ESI^+) 497 ($[2M + Na]^+$, 100%), 238 ($[M + H]^+$, 74%); HRMS (ESI^+) $C_{14}H_{21}FNO^+$ ($[M + H]^+$) requires 238.1602, found 238.1599.

(*RS*,*SR*)-1-(*N*,*N*-Dibenzylamino)-2,3-epoxyhexane 13. Following *General Procedure 2*, (*Z*)-hex-2-en-1-ol (5.90 mL, 49.9 mmol) in CH_2Cl_2 (200 mL) was treated with *m*-CPBA (75% w/w in H_2O, 17.2 g, 74.9 mmol). Purification via distillation at reduced pressure (1.2 mmHg) gave (*RS*,*SR*)-2,3-epoxyhexan-1-ol as a colorless oil (4.39 g, 76%, >99:1 dr);[44] bp 63−65 °C (1.2 mmHg); {lit.[45] bp 103−104 °C (20 mmHg)}; δ_H (400 MHz, $CDCl_3$) 0.91−1.03 (3H, m, C(6)H_3), 1.39−1.64 (4H, m, C(4)H_2, C(5)H_2), 1.92 (1H, br s, O*H*), 3.01−3.08 (1H, m, C(3)*H*), 3.16 (1H, app dt, *J* 7.1, 4.1, C(2)*H*), 3.68 (1H, ddd, *J* 10.6, 7.2, 3.4, C(1)H_A), 3.86 (1H, ddd, *J* 11.9, 7.2, 4.1, C(1)H_B). Following *General Procedure 3*, (*RS*,*SR*)-2,3-epoxyhexan-1-ol (2.00 g, 17.2 mmol) in CH_2Cl_2 (29 mL) was treated with Et_3N (4.80 mL, 34.4 mmol) and MsCl (2.00 mL, 25.8 mmol). Purification via filtration through a pad of silica gel (eluent CH_2Cl_2) gave (*RS*,*SR*)-2,3-epoxyhexyl methanesulfonate as a yellow oil (3.20 g, 96%, >99:1 dr);[46] δ_H (400 MHz, $CDCl_3$) 0.96−1.02 (3H, m, C(6)H_3), 1.41−1.62 (4H, m, C(4)H_2, C(5)H_2), 3.06−3.12 (1H, m, C(3)*H*) overlapping 3.11 (3H, s, SO_2Me), 3.28 (1H, app dt, *J* 7.6, 4.0, C(2)*H*), 4.24 (1H, dd, *J* 11.7, 7.6, C(1)H_A), 4.47 (1H, dd, *J* 11.7, 3.9, C(1)H_B). Following *General Procedure 4*, (*RS*,*SR*)-2,3-epoxyhexyl methanesulfonate (500 mg, 2.57 mmol) in EtOH (6.44 mL) was treated with dibenzylamine (1.24 mL, 6.44 mmol). Purification via flash column chromatography (gradient elution, 2→20% Et_2O in 30−40 °C petrol) gave **13** as a colorless oil (429 mg, 56%, >99:1 dr);[47] R_f 0.33 (30−40 °C petrol/Et_2O, 9:1); δ_H (400 MHz, $CDCl_3$) 0.96 (3H, app t, *J* 6.7, C(6)H_3), 1.30−1.60 (4H, m, C(4)H_2, C(5)H_2), 2.51 (1H, dd, *J* 13.6, 6.5, C(1)H_A), 2.82 (1H, dd, *J* 13.6, 3.8, C(1)H_B), 2.87−2.94 (1H, m, C(3)*H*), 3.17 (1H, app dt, *J* 6.5, 4.1, C(2)*H*), 3.56 (2H, d, *J* 13.6, N(CH_AH_BPh)$_2$), 3.87 (2H, d, *J* 13.6, N(CH_AH_BPh)$_2$), 7.27 (2H, app t, *J* 7.2, *Ph*), 7.35 (4H, app t, *J* 7.5, *Ph*), 7.43 (4H, app d, *J* 7.8, *Ph*).

(*RS*,*SR*)-1-(*N*,*N*-Dibenzylamino)-3,4-epoxyhexane 14. Following *General Procedure 2*, (*Z*)-hex-3-en-1-ol (4.54 g, 45.3 mmol) in CH_2Cl_2 (181 mL) was treated with *m*-CPBA (75% w/w in H_2O, 15.6 g, 68.0 mmol). Purification via flash column chromatography (gradient elution, 10→80% EtOAc in 30−40 °C petrol) gave (*RS*,*SR*)-3,4-epoxyhexan-1-ol as a colorless oil (4.38 g, 83%, >99:1 dr);[48] R_f 0.16 (30−40 °C petrol/EtOAc, 3:2); δ_H (400 MHz, $CDCl_3$) 1.03 (3H, app td, *J* 7.5, 1.4, C(6)H_3), 1.44−1.74 (3H, m, C(2)H_A, C(5)H_2), 1.80−1.91 (1H, m, C(2)H_B), 2.34 (1H, br s, O*H*), 2.87−2.94 (1H, m, C(4)*H*), 3.05−3.13 (1H, m, C(3)*H*), 3.75−3.90 (2H, m, C(1)H_2). Following *General Procedure 3*, (*RS*,*SR*)-3,4-epoxyhexan-1-ol (2.00 g, 17.2 mmol) in CH_2Cl_2 (29 mL) was treated with Et_3N (4.80 mL, 34.4 mmol) and MsCl (2.00 mL, 25.8 mmol). Purification via filtration through a pad of silica gel (eluent CH_2Cl_2) gave (*RS*,*SR*)-3,4-epoxyhexyl methanesulfonate as an orange oil (2.96 g, 89%, >99:1 dr);[46] δ_H (400 MHz, $CDCl_3$) 1.05 (3H, app td, *J* 7.5, 1.4, C(6)H_3), 1.46−1.63 (2H, m, C(5)H_2), 1.79−1.90 (1H, m, C(2)H_A), 2.09 (1H, ddddd, *J* 14.7, 8.2, 6.3, 4.7, 1.6, C(2)H_B), 2.92−2.98 (1H, m, C(4)*H*), 3.04 (3H, s, SO_2Me) overlapping 3.03−3.10 (1H, m, C(3)*H*), 4.33−4.46 (2H, m, C(1)H_2). Following *General Procedure 4*, (*RS*,*SR*)-3,4-epoxyhexyl methanesulfonate (500 mg, 2.57 mmol) in EtOH (6.44 mL) was treated with dibenzylamine (1.24 mL, 6.44 mmol). Purification via flash column chromatography (gradient elution, 2→20% Et_2O in 30−40 °C petrol) gave **14** as a colorless oil (558 mg, 74%, >99:1 dr); R_f 0.38 (30−40 °C petrol/Et_2O, 9:1); ν_{max} (film) 3085, 3062, 3027, 2970, 2935, 2876, 2798 (C−H), 1494, 1453, 1368, 745, 699; δ_H (400 MHz, $CDCl_3$) 0.97 (3H, app t, *J* 7.5, C(6)H_3), 1.34−1.59 (2H, m, C(5)H_2), 1.63−1.86 (2H, m, C(2)H_2), 2.56−2.70 (2H, m, C(1)H_2), 2.79−2.87 (1H, m, C(4)*H*), 2.95−3.03 (1H, m, C(3)*H*), 3.62 (4H, AB system, J_{AB} 13.6, N(CH_2Ph)$_2$), 7.19−7.48 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 10.6 (*C*(6)), 21.1 (*C*(5)), 25.7 (*C*(2)), 50.6 (*C*(1)), 55.8 (*C*(3)), 58.2 (*C*(4)), 58.4 (N(CH_2Ph)$_2$), 126.9 (*p-Ph*), 128.2, 128.8 (*o,m-Ph*), 139.6 (*i-Ph*); *m*/*z* (ESI^+) 318 ($[M + Na]^+$, 61%), 312 (100%), 296 ($[M + H]^+$, 64%); HRMS (ESI^+) $C_{20}H_{26}NO^+$ ($[M + H]^+$) requires 296.2009, found 296.2010.

(*RS*,*RS*)-1-(*N*,*N*-Dibenzylamino)-2,3-epoxyhexane 15. Following *General Procedure 2*, (*E*)-hex-2-en-1-ol (5.89 mL, 49.9 mmol) in CH_2Cl_2 (200 mL) was treated with *m*-CPBA (75% w/w in H_2O, 17.2 g, 74.9 mmol). Purification via distillation at reduced pressure (1.2 mmHg) gave (*RS*,*RS*)-2,3-epoxyhexan-1-ol as a colorless oil (4.55 g, 78%, >99:1 dr);[44] bp 54−56 °C (1.2 mmHg); {lit.[49] bp 57 °C (1.2 mmHg)}; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, app t, *J* 7.2, C(6)H_3), 1.40−1.61 (4H, m, C(4)H_2, C(5)H_2), 1.94 (1H, br s, O*H*), 2.90−3.00 (2H, m, C(2)*H*, C(3)*H*), 3.58−3.68 (1H, m, C(1)H_A), 3.92 (1H, ddd, *J* 12.6, 5.1, 2.4, C(1)H_B). Following *General Procedure 3*, (*RS*,*RS*)-2,3-epoxyhexan-1-ol (2.00 g, 17.2 mmol) in CH_2Cl_2 (29 mL) was treated with Et_3N (4.80 mL, 34.4 mmol) and MsCl (2.00 mL, 25.8 mmol). Purification via filtration through a pad of silica gel (eluent CH_2Cl_2) gave (*RS*,*RS*)-2,3-epoxyhexyl methanesulfonate as a yellow oil (3.20 g, 96%, >99:1 dr);[46] δ_H (400 MHz, $CDCl_3$) 0.97 (3H, app t, *J* 7.2, C(6)H_3), 1.39−1.65 (4H, m, C(4)H_2, C(5)H_2), 2.92 (1H, app td, *J* 5.5, 2.1, C(3)*H*), 3.06 (1H, app dt, *J* 6.5, 2.6, C(2)*H*), 3.08 (3H, s, SO_2Me), 4.12 (1H, dd, *J* 12.0, 6.5, C(1)H_A), 4.48 (1H, dd, *J* 12.0, 3.1, C(1)H_B). Following *General Procedure 4*, (*RS*,*RS*)-2,3-epoxyhexyl methanesulfonate (500 mg, 2.57 mmol) in EtOH (6.44 mL) was treated with dibenzylamine (1.24 mL, 6.44 mmol). Purification via flash column chromatography (gradient elution, 2→20% Et_2O in 30−40 °C petrol) gave **15** as a colorless oil (280 mg, 37%, >99:1 dr);[47] R_f 0.35 (30−40 °C petrol/Et_2O, 9:1); δ_H (400 MHz, $CDCl_3$) 0.92−1.01 (3H, m, C(6)H_3), 1.38−1.55 (4H, m, C(4)H_2, C(5)H_2), 2.53 (1H, dd, *J* 13.6, 5.8, C(1)H_A), 2.62−2.69 (1H, br m, C(3)*H*), 2.73 (1H, dd, *J* 13.6, 4.0, C(1)H_B), 2.86−2.92 (1H, br m, C(2)*H*), 3.60 (2H, d, *J* 13.8, N-(CH_AH_BPh)$_2$), 3.81 (2H, d, *J* 13.8, N(CH_AH_BPh)$_2$), 7.18−7.50 (10H, m, *Ph*).

(*RS*,*RS*)-1-(*N*,*N*-Dibenzylamino)-3,4-epoxyhexane 16. Following *General Procedure 2*, (*E*)-hex-3-en-1-ol (3.72 g, 37.1 mmol) in CH_2Cl_2 (148 mL) was treated with *m*-CPBA (75% w/w in H_2O, 12.8 g, 55.7 mmol). Purification via flash column chromatography (gradient elution, 10→80% EtOAc in 30−40 °C petrol) gave (*RS*,*RS*)-3,4-epoxyhexan-1-ol as a colorless oil (3.89 g, 90%, >99:1 dr);[44] R_f 0.18 (30−40 °C petrol/EtOAc, 3:2); δ_H (400 MHz, $CDCl_3$) 0.98 (3H, app td, *J* 7.6, 1.5, C(6)H_3), 1.48−1.73 (3H, m, C(2)H_A, C(5)H_2), 1.89−2.00

(1H, m, C(2)H_B), 2.39 (1H, br s, O*H*), 2.73−2.79 (1H, m, C(4)*H*), 2.86 (1H, app ddt, *J* 6.4, 4.3, 2.0, C(3)*H*), 3.75 (2H, app td, *J* 6.0, 2.0, C(1)H_2). Following *General Procedure 3*, (*RS*,*RS*)-3,4-epoxyhexan-1-ol (2.00 g, 17.2 mmol) in CH_2Cl_2 (29 mL) was treated with Et_3N (4.80 mL, 34.4 mmol) and MsCl (2.00 mL, 25.8 mmol). Purification via filtration through a pad of silica gel (eluent CH_2Cl_2) gave (*RS*,*RS*)-3,4-epoxyhexyl methanesulfonate as an orange oil (2.73 g, 82%, >99:1 dr);[50] δ_H (400 MHz, $CDCl_3$) 1.00 (3H, app t, *J* 7.5, C(6)H_3), 1.54−1.63 (2H, m, C(5)H_2), 1.85 (1H, app ddt, *J* 14.7, 6.8, 5.3, C(2)H_A), 2.11 (1H, dddd, *J* 14.7, 7.7, 6.6, 4.4, C(2)H_B), 2.74 (1H, app td, *J* 5.5, 2.2, C(4)*H*), 2.83 (1H, ddd, *J* 6.7, 4.4, 2.2, C(3)*H*), 3.04 (3H, s, SO_2Me), 4.35 (1H, dd, *J* 5.1, 1.4, C(1)H_A), 4.37 (1H, d, *J* 5.5, C(1)H_B). Following *General Procedure 4*, (*RS*,*RS*)-3,4-epoxyhexyl methanesulfonate (500 mg, 2.57 mmol) in EtOH (6.44 mL) was treated with dibenzylamine (1.24 mL, 6.44 mmol). Purification via flash column chromatography (gradient elution, 2→20% Et_2O in 30−40 °C petrol) gave **16** as a colorless oil (500 mg, 66%, >99:1 dr); R_f 0.41 (30−40 °C petrol/Et_2O, 9:1); ν_{max} (film) 3085, 3062, 3027, 2968, 2934, 2876, 2798 (C−H), 1494, 1453, 1367, 745, 699; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, app t, *J* 7.5, C(6)H_3), 1.45−1.74 (3H, m, C(2)H_A, C(5)H_2), 1.82 (1H, app dq, *J* 13.6, 6.8, C(2)H_B), 2.57−2.65 (3H, m, C(1)H_2, C(4)*H*), 2.72 (1H, app td, *J* 5.7, 2.0, C(3)*H*), 3.60 (4H, AB system, J_{AB} 13.9, N(CH_2Ph)$_2$), 7.22−7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 9.8 (C(5)*Me*), 25.0 (*C*(5)), 30.1 (*C*(2)), 50.4 (*C*(1)), 57.2 (*C*(3)), 58.3 (N(CH_2Ph)$_2$), 60.0 (*C*(4)), 126.9 (*p-Ph*), 128.2, 128.7 (*o*, *m-Ph*), 139.6 (*i-Ph*); *m*/*z* (ESI^+) 318 ($[M + Na]^+$, 48%), 312 (100%), 296 ($[M + H]^+$, 98%); HRMS (ESI^+) $C_{20}H_{26}NO^+$ ($[M + H]^+$) requires 296.2009, found 296.2009.

(*RS*)-1-(*N*,*N*-Dibenzylamino)-2,3-epoxy-3-methylbutane 17. H_2O_2 (35% in H_2O, 1.46 mL, 16.5 mmol) was added dropwise to a stirred mixture of 3-methylbut-2-enal (1.45 mL, 15.0 mmol) and $KHCO_3$ (1.35 g, 13.5 mmol) in H_2O (9.38 mL) at 0 °C, and the resultant mixture was stirred at this temperature for 2.5 h. Saturated aqueous Na_2SO_3 was then added until starch-iodide paper indicated no remaining oxidant. The mixture was saturated with NaCl and extracted with CH_2Cl_2 (5 × 10 mL), and the combined organic layers were dried and carefully concentrated *in vacuo*. The residue was dissolved in 1,2-dichloroethane (50 mL), and dibenzylamine (3.17 mL, 16.5 mmol) and NaB(OAc)$_3$H (4.45 g, 21.0 mmol) were then sequentially added. The resultant mixture was stirred at rt for 16 h. Saturated aqueous $NaHCO_3$ (50 mL) was then added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 2→20% Et_2O in 30−40 °C petrol) gave **17** as a colorless oil (1.66 g, 39%); R_f 0.41 (30−40 °C petrol/Et_2O, 9:1); ν_{max} (film) 3085, 3062, 3028, 2961, 2925, 2884, 2797 (C−H), 1494, 1453, 1377, 738, 698; δ_H (400 MHz, $CDCl_3$) 1.20 (3H, s, C(3)Me_A), 1.26 (3H, s, C(3)Me_B), 2.58 (1H, dd, *J* 13.6, 5.8, C(1)H_A), 2.76 (1H, dd, *J* 13.6, 4.5, C(1)H_B), 2.97 (1H, app t, *J* 5.2, C(2)*H*), 3.57 (2H, d, *J* 13.6, N(CH_AH$_B$Ph)$_2$), 3.83 (2H, d, *J* 13.6, N(CH_AH$_B$Ph)$_2$), 7.23−7.49 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.9, 24.7 (C(3)Me_2), 52.9 (*C*(1)), 57.5 (*C*(3)), 58.9 (N(CH_2Ph)$_2$), 63.0 (*C*(2)), 127.0 (*p-Ph*), 128.3, 128.8 (*o*,*m-Ph*), 139.4 (*i-Ph*); *m*/*z* (ESI^+) 304 ($[M + Na]^+$, 86%), 282 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{24}NO^+$ ($[M + H]^+$) requires 282.1852, found 282.1851.

(*RS*,*RS*)-1-(*N*,*N*-Dibenzylamino)-3-fluorohexan-2-ol 20. Following *General Procedure 1*, **13** (286 mg, 0.97 mmol) in CH_2Cl_2 (3.87 mL) was treated with $HBF_4 \cdot OEt_2$ (263 μL, 1.94 mmol). Purification via flash column chromatography (gradient elution, 2→20% Et_2O in 30−40 °C petrol) gave **20** as a colorless oil (271 mg, 89%, >99:1 dr); R_f 0.28 (30−40 °C petrol/Et_2O, 4:1); $C_{20}H_{26}FNO$ requires C, 76.2; H, 8.3; N, 4.4%; found C, 76.3; H, 8.4; N, 4.3%; ν_{max} (film) 3443 (O−H), 3086, 3063, 3028, 2960, 2934, 2873, 2833, 2806 (C−H), 1453, 748, 699; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, app t, *J* 7.1, C(6)H_3), 1.31−1.57 (3H, m, C(4)H_2, C(5)H_A), 1.64−1.80 (1H, m, C(5)H_B), 2.53 (1H, dd, *J* 12.6, 3.7, C(1)H_A), 2.75 (1H, dd, *J* 12.6, 9.8, C(1)H_B), 3.18 (1H, br s, O*H*), 3.50 (2H, d, *J* 13.5, N(CH_AH$_B$Ph)$_2$), 3.69 (1H, dddd, *J* 21.5, 9.8, 3.7, 3.5, C(2)*H*), 3.84 (2H, d, *J* 13.5, N(CH_AH$_B$Ph)$_2$), 4.33 (1H, dddd, *J* 48.5, 9.0, 3.5, 3.4, C(3)*H*), 7.22−7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.9 (C(6)), 18.4 (d, *J* 4.8, *C*(5)), 32.9 (d, *J* 22.4, *C*(4)), 55.4 (d, *J* 6.4, *C*(1)), 58.6 (N(CH_2Ph)$_2$), 68.7 (d, *J* 20.8, *C*(2)), 93.9 (d, *J* 174, *C*(3)), 127.4 (*p-Ph*), 128.5, 129.1 (*o*,*m-Ph*), 138.3 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −196.5 (m); *m*/*z* (FI^+) 315 ($[M]^+$, 100%); HRMS (FI^+) $C_{20}H_{26}FNO^+$ ($[M]^+$) requires 315.1993, found 315.2006.

(*RS*,*RS*)-1-(*N*,*N*-Dibenzylamino)-4-fluorohexan-3-ol 21. Following *General Procedure 1*, **14** (200 mg, 0.68 mmol) in CH_2Cl_2 (2.72 mL) was treated with $HBF_4 \cdot OEt_2$ (184 μL, 1.35 mmol). Purification via flash column chromatography (gradient elution, 5→40% Et_2O in 30−40 °C petrol) gave **21** as a colorless oil (114 mg, 53%, >99:1 dr); R_f 0.23 (30−40 °C petrol/Et_2O, 4:1); ν_{max} (film) 3386 (O−H), 3086, 3063, 3029, 2968, 2935, 2880, 2824 (C−H), 1495, 1453, 1377, 1137, 1109, 1075, 1028, 953, 749, 733, 699; δ_H (400 MHz, $CDCl_3$) 0.98 (3H, app t, *J* 7.5, C(6)H_3), 1.47−1.78 (3H, m, C(2)H_A, C(5)H_2), 1.94 (1H, app dtd, *J* 14.4, 10.5, 3.9, C(2)H_B), 2.62 (1H, app dt, *J* 12.9, 4.2, C(1)H_A), 2.76−2.85 (1H, m, C(1)H_B), 3.29 (2H, d, *J* 13.1, N(CH_AH$_B$Ph)$_2$), 3.64 (1H, dddd, *J* 20.7, 10.0, 3.8, 2.6, C(3)*H*), 3.89 (2H, d, *J* 13.1, N(CH_AH$_B$Ph)$_2$), 4.16 (1H, app ddt, *J* 48.1, 8.4, 4.1, C(4)*H*), 5.59 (1H, br s, O*H*), 7.25−7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 9.7 (d, *J* 6.4, C(6)), 23.6 (d, *J* 20.8, *C*(5)), 27.9 (d, *J* 4.8, *C*(2)), 52.2 (*C*(1)), 58.5 (N(CH_2Ph)$_2$), 73.4 (d, *J* 24.0, *C*(3)), 97.2 (d, *J* 173, *C*(4)), 127.4 (*p-Ph*), 128.5, 129.3 (*o*,*m-Ph*), 137.9 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −195.9 (m); *m*/*z* (ESI^+) 653 ($[2M + Na]^+$, 100%), 338 ($[M + Na]^+$, 92%), 316 ($[M + H]^+$, 68%); HRMS (ESI^+) $C_{20}H_{27}FNO^+$ ($[M + H]^+$) requires 316.2071, found 316.2071.

(*RS*,*SR*)-1-(*N*,*N*-Dibenzylamino)-3-fluorohexan-2-ol 22. Following *General Procedure 1*, **15** (156 mg, 0.53 mmol) in CH_2Cl_2 (2.11 mL) was treated with $HBF_4 \cdot OEt_2$ (144 μL, 1.06 mmol). Purification via flash column chromatography (gradient elution, 2→20% Et_2O in 30−40 °C petrol) gave **22** as a colorless oil (129 mg, 77%, >99:1 dr); R_f 0.28 (30−40 °C petrol/Et_2O, 4:1); $C_{20}H_{26}FNO$ requires C, 76.2; H, 8.3; N, 4.4%; found C, 76.3; H, 8.45; N, 4.3%; ν_{max} (film) 3444 (O−H), 3086, 3063, 3029, 2960, 2935, 2874, 2838, 2807 (C−H), 1454, 1076, 1027, 749, 700; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, app t, *J* 7.2, C(6)H_3), 1.27−1.69 (4H, m, C(4)H_2, C(5)H_2), 2.58−2.76 (2H, m, C(1)H_2), 3.36 (1H, br s, O*H*), 3.49 (2H, d, *J* 13.4, N(CH_AH$_B$Ph)$_2$), 3.72 (1H, dddd, *J* 11.5, 9.6, 5.8, 3.8, C(2)*H*), 3.83 (2H, d, *J* 13.4, N(CH_AH$_B$Ph)$_2$), 4.29 (1H, dddd, *J* 48.5, 8.1, 5.8, 3.6, C(3)*H*), 7.23−7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.9 (C(6)), 18.3 (d, *J* 3.2, *C*(5)), 33.3 (d, *J* 20.8, *C*(4)), 55.3 (d, *J* 4.8, *C*(1)), 58.6 (N(CH_2Ph)$_2$), 68.3 (d, *J* 24.0, *C*(2)), 95.1 (d, *J* 169, *C*(3)), 127.4 (*p-Ph*), 128.5, 129.1 (*o*,*m-Ph*), 138.3 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −194.6 (m); *m*/*z* (FI^+) 315 ($[M]^+$, 100%); HRMS (FI^+) $C_{20}H_{26}FNO^+$ ($[M]^+$) requires 315.1993, found 315.2003.

(*RS*,*SR*)-1-(*N*,*N*-Dibenzylamino)-4-fluorohexan-3-ol 23. Following *General Procedure 1*, **16** (236 mg, 0.80 mmol) in CH_2Cl_2 (3.20 mL) was treated with $HBF_4 \cdot OEt_2$ (218 μL, 1.60 mmol). Purification via flash column chromatography (gradient elution, 5→40% Et_2O in 30−40 °C petrol) gave **23** as a colorless oil (179 mg, 71%, >99:1 dr); R_f 0.33 (30−40 °C petrol/Et_2O, 4:1); ν_{max} (film) 3260 (O−H), 3086, 3063, 3029, 3005, 2967, 2935, 2881, 2826 (C−H), 1495, 1454, 1375, 1105, 1075, 1028, 952, 749, 733, 699; δ_H (400 MHz, $CDCl_3$) 0.95 (3H, app t, *J* 7.5, C(5)*Me*), 1.49−1.87 (4H, m, C(2)H_2, C(5)H_2), 2.68−2.81 (2H, m, C(1)H_2), 3.46 (2H, d, *J* 13.1, N(CH_AH$_B$Ph)$_2$), 3.54−3.64 (1H, m, C(3)*H*), 3.72 (2H, d, *J* 13.1, N(CH_AH$_B$Ph)$_2$), 3.84−4.05 (1H, m, C(4)*H*), 6.17 (1H, br s, O*H*), 7.22−7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 9.3 (d, *J* 4.8, C(6)), 24.3 (d, *J* 20.8, *C*(5)), 27.0 (d, *J* 3.2, *C*(2)), 51.7 (*C*(1)), 58.5 (N(CH_2Ph)$_2$), 73.8 (d, *J* 25.6, *C*(3)), 96.3 (d, *J* 171, *C*(4)), 127.5 (*p-Ph*), 128.5, 129.4 (*o*,*m-Ph*), 137.7 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −193.6 (m); *m*/*z* (ESI^+) 338 ($[M + Na]^+$, 93%), 316 ($[M + H]^+$,

100%); HRMS (ESI^+) $C_{20}H_{27}FNO^+$ ($[M + H]^+$) requires 316.2071, found 316.2073.

(*RS*)-1-(*N*,*N*-Dibenzylamino)-3-fluoro-3-methylbutan-2-ol 24. Following *General Procedure 1*, **17** (200 mg, 0.71 mmol) in CH_2Cl_2 (2.84 mL) was treated with $HBF_4 \cdot OEt_2$ (193 μL, 1.42 mmol). Purification via flash column chromatography (gradient elution, 5→40% Et_2O in 30−40 °C petrol) gave **24** as a colorless oil (189 mg, 88%); R_f 0.36 (30−40 °C petrol/Et_2O, 4:1); ν_{max} (film) 3442 (O−H), 3086, 3063, 3029, 2982, 2936, 2889, 2838, 2807 (C−H), 1495, 1453, 1372, 1241, 1155, 1096, 1074, 1028, 749, 699; δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, *J* 22.2, C(3)Me_A), 1.29 (3H, d, *J* 22.0, C(3)Me_B), 2.55−2.68 (2H, m, C(1)H_2), 3.48 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 3.61 (1H, br s, O*H*), 3.65−3.75 (1H, m, C(2)*H*), 3.88 (2H, d, *J* 13.4, N(CH$_A$$H_B$Ph)$_2$), 7.25−7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.5 (d, *J* 24.0, C(3)Me_A), 23.5 (d, *J* 24.0, C(3)Me_B), 53.8 (d, *J* 4.8, *C*(1)), 58.3 (N(*C*H$_2$Ph)$_2$), 71.5 (d, *J* 25.6, *C*(2)), 96.1 (d, *J* 168, *C*(3)), 127.4 (*p-Ph*), 128.5, 129.1 (*o,m-Ph*), 138.2 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −149.7 (m); *m*/*z* (ESI^+) 324 ($[M + Na]^+$, 100%), 302 ($[M + H]^+$, 74%); HRMS (ESI^+) $C_{19}H_{25}FNO^+$ ($[M + H]^+$) requires 302.1915, found 302.1916.

(*RS*,*SR*)-1-(*N*,*N*-Dibenzylamino)-1-phenyl-3-fluoro-3-methylbutan-2-ol 25. Following *General Procedure 1*, **18** (143 mg, 0.40 mmol) in CH_2Cl_2 (1.60 mL) was treated with $HBF_4 \cdot OEt_2$ (109 μL, 0.80 mmol). Purification via flash column chromatography (gradient elution, 2→20% Et_2O in 30−40 °C petrol) gave **25** as a colorless oil which solidified on standing to a white crystalline solid (151 mg, quant, >99:1 dr); R_f 0.23 (30−40 °C petrol/Et_2O, 9:1); $C_{25}H_{28}FNO$ requires C, 79.5; H, 7.5; N, 3.7%; found C, 79.65; H, 7.3; N, 3.7%; mp 114−120 °C; ν_{max} (KBr) 3316 (O−H), 3105, 3087, 3063, 3029, 3004, 2980, 2934, 2896, 2847 (C−H), 1548, 1495, 1370, 1241, 1151, 1074, 1029, 761, 752, 701; δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 22.0, C(3)Me_A), 1.11 (3H, d, *J* 22.2, C(3)Me_B), 3.04 (2H, d, *J* 13.1, N(C$H_A$$H_B$Ph)$_2$), 3.81 (1H, d, *J* 10.1, C(1)*H*), 3.96 (2H, d, *J* 13.1, N(CH$_A$$H_B$Ph)$_2$), 4.27 (1H, app t, *J* 10.1, C(2)*H*), 5.41 (1H, br s, O*H*), 7.24−7.50 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.0 (d, *J* 24.0, C(3)Me_A), 24.4 (d, *J* 25.6, C(3)Me_B), 53.6 (N(*C*H$_2$Ph)$_2$), 62.2 (*C*(1)), 71.9 (d, *J* 24.0, *C*(2)), 96.8 (d, *J* 171, *C*(3)), 127.5, 128.0, 128.3, 128.7, 129.2, 130.2 (*p,o,m-Ph*), 134.4, 138.2 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −144.3 (app septet d, *J* 21.8, 9.2); *m*/*z* (FI^+) 377 ($[M]^+$, 100%); HRMS (FI^+) $C_{25}H_{28}FNO^+$ ($[M]^+$) requires 377.2149, found 377.2168.

(*RS*,*SR*)-2-Fluoro-2,5-dimethyl-4-(*N*,*N*-dibenzylamino)hexan-3-ol 26. Following *General Procedure 1*, **19** (241 mg, 0.75 mmol) in CH_2Cl_2 (3.00 mL) was treated with $HBF_4 \cdot OEt_2$ (203 μL, 1.49 mmol) to give an 83:17 mixture of **26**:**27**. Purification via flash column chromatography (gradient elution, 2→20% Et_2O in 30−40 °C petrol) gave **27** as a colorless oil (15 mg, 6%); R_f 0.24 (30−40 °C petrol/Et_2O, 24:1); ν_{max} (film) 3086, 3063, 3028, 2966, 2932, 2871, 2838, 2807 (C−H), 1705 (C═O), 1494, 1465, 1454, 1382, 1366, 1071, 1028, 745, 699; δ_H (400 MHz, $CDCl_3$) 0.76 (3H, d, *J* 6.6, C(5)Me_A), 0.90 (3H, d, *J* 7.1, C(2)Me_A), 1.10 (3H, d, *J* 6.6, C(2)Me_B), 1.16 (3H, d, *J* 6.6, C(5)Me_B), 2.24−2.38 (1H, m, C(5)*H*), 2.53 (1H, septet, *J* 6.9, C(2)*H*), 3.20 (1H, d, *J* 10.4, C(4)*H*), 3.58 (2H, d, *J* 14.2, N(C$H_A$$H_B$Ph)$_2$), 3.96 (2H, d, *J* 14.2, N(CH$_A$$H_B$Ph)$_2$), 7.20−7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.7, 18.1, 20.58, 20.64 (C(2)Me_2, C(5)Me_2), 27.0 (*C*(5)), 41.2 (*C*(2)), 54.6 (N(*C*H$_2$Ph)$_2$), 68.8 (*C*(4)), 127.0 (*p-Ph*), 128.3, 128.8 (*o,m-Ph*), 139.8 (*i-Ph*), 214.3 (*C*(3)); *m*/*z* (FI^+) 323 ($[M]^+$, 100%); HRMS (FI^+) $C_{22}H_{29}NO^+$ ($[M]^+$) requires 323.2244; found 323.2246. Further elution gave **26** as a colorless oil (159 mg, 62%, >99:1 dr); R_f 0.12 (30−40 °C petrol/Et_2O, 24:1); $C_{22}H_{30}FNO$ requires C, 76.9; H, 8.8; N, 4.1%; found C, 77.0; H, 8.85; N, 4.0%; ν_{max} (film) 3241 (O−H), 3107, 3087, 3064, 3029, 2980, 2958, 2881, 2842, 2812 (C−H), 1455, 1368, 1153, 1062, 750, 700; δ_H (400 MHz, $CDCl_3$) 0.79 (3H, d, *J* 21.5, C(2)Me_A), 1.12 (3H, dd, *J* 7.3, 0.5, C(5)Me_A), 1.17 (3H, dd, *J* 7.1, 0.8, C(5)Me_B), 1.45 (3H, d, *J* 23.0, C(2)Me_B), 2.34 (1H, app septet d, *J* 7.3, 2.3, C(5)*H*), 2.77 (1H, dd, *J* 8.3, 2.3, C(4)*H*), 3.54 (2H, d, *J* 12.9, N(C$H_A$$H_B$Ph)$_2$), 3.74 (1H, dd, *J* 8.3, 3.0, C(3)*H*), 3.96 (2H, d, *J* 12.9, N(CH$_A$$H_B$Ph)$_2$), 5.40 (1H, br s, O*H*), 7.23−7.36 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.7 (d, *J* 24.0, C(2)Me_A), 20.0 (d, *J* 4.8, C(5)Me_B), 22.4 (d, *J* 6.4, C(5)Me_A), 26.5 (*C*(5)), 27.4 (d, *J* 24.0, C(2)Me_B), 54.3 (N(*C*H$_2$Ph)$_2$), 61.1 (*C*(4)), 70.4 (d, *J* 30.4, *C*(3)), 96.8 (d, *J* 168, *C*(2)), 127.4 (*p-Ph*), 128.5, 129.4 (*o,m-Ph*), 138.7 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −145.8 (app septet, *J* 21.8); *m*/*z* (FI^+) 343 ($[M]^+$, 100%); HRMS (FI^+) $C_{22}H_{30}FNO^+$ ($[M]^+$) requires 343.2306, found 343.2318.

(*RS*,*RS*)-1-(*N*,*N*-Dibenzylamino)-3-fluorohexan-2-yl 4′-nitrobenzoate 28. *p*-Nitrobenzoyl chloride (263 mg, 1.42 mmol) was added to a stirred solution of **20** (224 mg, 0.71 mmol) in pyridine (3.5 mL), and the resultant mixture was stirred at rt for 24 h and then concentrated *in vacuo*. The residue was partitioned between saturated aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 2→20% Et_2O in 30−40 °C petrol) gave **28** as a pale yellow oil that solidified on standing to a white crystalline solid (252 mg, 77%, >99:1 dr); R_f 0.36 (30−40 °C petrol/Et_2O, 9:1); mp 105−107 °C; ν_{max} (KBr) 3111, 3086, 3062, 3029, 2962, 2935, 2875, 2832, 2802 (C−H), 1727 (C═O), 1528, 1273; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, app t, *J* 7.1, C(6)H_3), 1.31−1.52 (3H, m, C(4)H_A, C(5)H_2), 1.55−1.72 (1H, m, C(4)H_B), 2.83 (1H, dd, *J* 13.6, 5.0, C(1)H_A), 2.92 (1H, dd, *J* 13.6, 7.6, C(1)H_B), 3.52 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 3.80 (2H, d, *J* 13.4, N(CH$_A$$H_B$Ph)$_2$), 4.70 (1H, app ddt, *J* 47.2, 8.8, 3.3, C(3)*H*), 5.36 (1H, dddd, *J* 24.3, 7.6, 5.0, 2.9, C(2)*H*), 7.20−7.33 (10H, m, *Ph*), 8.19 (2H, d, *J* 8.8, *Ar*), 8.31 (2H, d, *J* 8.8, *Ar*); δ_C (100 MHz, $CDCl_3$) 13.7 (C(6)), 18.3 (d, *J* 4.8, C(5)), 33.1 (d, *J* 20.8, C(4)), 53.9 (d, *J* 4.8, *C*(1)), 59.1 (N(*C*H$_2$Ph)$_2$), 73.2 (d, *J* 19.2, *C*(2)), 91.8 (d, *J* 176, *C*(3)), 123.5 (*C*(3′), *C*(5′)), 127.1 (*p-Ph*), 128.3, 128.9 (*o,m-Ph*), 131.0 (*C*(2′), *C*(6′)), 135.4 (*C*(1′)), 138.8 (*i-Ph*), 150.7 (*C*(4′)), 164.1 (*C*═O); δ_F (377 MHz, $CDCl_3$) −196.2 (m); *m*/*z* (ESI^+) 487 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{27}H_{29}FN_2NaO_4^+$ ($[M + Na]^+$) requires 487.2004, found 487.1999.

(*RS*,*SR*)-1-(*N*,*N*-Dibenzylamino)-3-fluorohexan-2-yl 4′-nitrobenzoate 29. *p*-Nitrobenzoyl chloride (110 mg, 0.59 mmol) was added to a stirred solution of **22** (93 mg, 0.30 mmol) in pyridine (1.5 mL), and the resultant mixture was stirred at rt for 24 h then concentrated *in vacuo*. The residue was partitioned between saturated aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 2% →20% Et_2O in 30−40 °C petrol) gave **29** as a pale yellow oil that solidified on standing to a white, crystalline solid (104 mg, 74%, >99:1 dr); R_f 0.36 (30−40 °C petrol/Et_2O, 9:1); mp 79−80 °C; ν_{max} (KBr) 3111, 3086, 3062, 3029, 2962, 2935, 2875, 2834, 2802 (C−H), 1727 (C═O), 1528, 1273; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, app t, *J* 7.3, C(6)H_3), 1.18−1.39 (2H, m, C(4)H_A, C(5)H_A), 1.43−1.73 (2H, m, C(4)H_B, C(5)H_B), 2.76 (1H, dd, *J* 13.9, 4.8, C(1)H_A), 2.86 (1H, ddd, *J* 13.9, 7.8, 1.5, C(1)H_B), 3.59 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 3.70 (2H, d, *J* 13.4, N(CH$_A$$H_B$Ph)$_2$), 4.67 (1H, app ddt, *J* 48.0, 9.9, 2.9, C(3)*H*), 5.47−5.58 (1H, m, C(2)*H*), 7.21−7.32 (10H, m, *Ph*), 8.15 (2H, d, *J* 8.8, *Ar*), 8.31 (2H, d, *J* 8.8, *Ar*); δ_C (100 MHz, $CDCl_3$) 13.7 (C(6)), 18.6 (d, *J* 3.2, C(5)), 32.1 (d, *J* 20.8, C(4)), 52.6 (d, *J* 6.4, C(1)), 59.0 (N(*C*H$_2$Ph)$_2$), 73.9 (d, *J* 20.8, C(2)), 93.2 (d, *J* 174, *C*(3)), 123.5 (*C*(3′), *C*(5′)), 127.2 (*p-Ph*), 128.3, 129.0 (*o,m-Ph*), 131.0 (*C*(2′), *C*(6′)), 135.5 (*C*(1′)), 138.8 (*i-Ph*), 150.6 (*C*(4′)), 164.0 (*C*═O); δ_F (377 MHz, $CDCl_3$) −192.9 (m); *m*/*z* (ESI^+) 487 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{27}H_{29}FN_2NaO_4^+$ ($[M + Na]^+$) requires 487.2004, found 487.2002.

Octadec-2-yn-1-ol 33. BuLi (2.5 M in hexanes, 14.3 mL, 35.8 mmol) was added dropwise to a stirred solution of **32** (5.03 mL, 35.8 mmol) in

THF (40 mL) at −78 °C, and the resultant mixture was stirred at this temperature for 30 min. DMPU (4.72 mL, 39.0 mmol) was then added, and stirring was continued for a further 10 min. 1-Bromopentadecane (9.33 mL, 32.5 mmol) was then added dropwise, and the resultant mixture was allowed to warm to rt and then heated at 50 °C for 20 h. The mixture was allowed to cool to rt, and saturated aqueous NH_4Cl (50 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were then dried and filtered through a pad of silica gel (eluent Et_2O), and the filtrate was concentrated *in vacuo*. The residue was dissolved in MeOH (80 mL), and Amberlyst H 15 (1.08 g) was added. The resultant mixture was stirred at 40 °C for 3 h, then filtered, and concentrated *in vacuo*. The residue was dissolved in hot 30−40 °C petrol, and the resultant solution was allowed to cool to rt. Cooling of the solution to −78 °C and collection of the resultant precipitate by filtration (eluent 30−40 °C petrol) gave **33** as a cream-colored solid (8.25 g, 95%). Purification of an aliquot via flash column chromatography (gradient elution, 5→40% Et_2O in 30−40 °C petrol) gave an analytical sample of **30** as a white solid;[51] R_f 0.24 (30−40 °C petrol/Et_2O, 4:1); mp 59−60 °C; {lit.[51] mp 62−64 °C}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.8, C(18)H_3), 1.21−1.42 (24H, m, C(6)−C(17)H_2), 1.47−1.55 (2H, m, C(5)H_2), 2.21 (2H, tt, *J* 7.1, 2.1, C(4)H_2), 4.26 (1H, br s, C(1)H_2).

(*E*)-Octadec-2-en-1-ol 34. A solution of **33** (8.25 g, 31.0 mmol) in THF (80 mL) was added dropwise to a stirred solution of $LiAlH_4$ (1.0 M in THF, 34.1 mL, 34.1 mmol) in THF (25 mL) at 0 °C, and the resultant mixture was allowed to warm to rt over 20 h. Saturated aqueous Rochelle's salt (100 mL) was then added dropwise (*cautiously!*), and the resultant mixture was stirred at rt for 18 h. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were dried and filtered through a pad of silica gel (eluent Et_2O), and the filtrate was concentrated *in vacuo* to give **34** as a white solid (8.05 g, 97%, >99:1 dr);[52] mp 44−46 °C; {lit.[52] mp 46−48 °C}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.8, C(18)H_3), 1.20−1.43 (26H, m, C(5)−C(17)H_2), 2.04 (2H, dt, *J* 7.5, 6.1, C(4)H_2), 4.09 (2H, br m, C(1)H_2), 5.59−5.75 (2H, m, C(2)*H*, C(3)*H*).

(*R*,*R*)-2,3-Epoxyoctadecan-1-ol 35. $Ti(O^iPr)_4$ (10.6 mL, 35.7 mmol) and diethyl D-(−)-tartrate (8.14 mL, 47.6 mmol) were added sequentially to CH_2Cl_2 (330 mL) over powdered 4 Å molecular sieves (21.5 g) at a temperature between −20 and −30 °C (dry ice/acetone bath), and the resultant mixture was stirred at this temperature for 15 min. A solution of **34** (7.99 g, 29.7 mmol) in CH_2Cl_2 (60 mL) was added via syringe, and stirring was continued for a further 10 min. Precooled (−20 °C) ^tBuOOH (3.43 M solution in PhMe,[53] 26.0 mL, 89.2 mmol) was then added dropwise, and the resultant mixture was placed in a freezer at −20 °C for 21 h. The reaction was then transferred to an ice bath, and a precooled (0 °C) solution of $FeSO_4 \cdot 7H_2O$ (49.6 g, 178 mmol) and D-(−)-tartaric acid (13.4 g, 89.2 mmol) in H_2O (135 mL) was added. The resultant mixture was stirred vigorously at 0 °C for 10 min and then allowed to warm to rt over 1 h. Celite was then added until the aqueous slurry became granular, the mixture was filtered through a pad of Celite (eluent CH_2Cl_2), and the filtrate was collected. The filter cake was swirled in hot EtOAc and then filtered through a pad of Celite (eluent EtOAc), and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2, and all filtrates were combined then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (300 mL) and treated with a precooled (0 °C) solution of 1 M aqueous NaOH in brine (300 mL) at 0 °C, and the resultant mixture was stirred at this temperature for 1 h. The layers were separated, the aqueous layer was extracted with Et_2O (2 × 200 mL), and then the combined organic layers were dried and concentrated *in vacuo*. Purification via recrystallization (Et_2O) gave **35** as a white crystalline solid (6.77 g, 80%, >99:1 dr, >98% ee);[52] mp 79−80 °C; {lit.[52] mp 77−78 °C}; $[\alpha]_D^{25}$ +21.4 (*c* 1.0 in $CHCl_3$); {lit.[52] $[\alpha]_D^{23}$ +22.5 (*c* 0.8 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, app t, *J* 6.7, C(18)H_3), 1.19−1.71 (28H, m, C(4)−C(17)H_2), 2.91−2.99 (2H, m, C(2)*H*, C(3)*H*), 3.64 (1H, ddd, *J* 12.4, 7.4, 4.3, C(1)H_A), 3.92 (1H, ddd, *J* 12.4, 5.4, 2.6, C(1)H_B).

(2*S*,3*R*)-2,3-Epoxyoctadecanal 36. A solution of **35** (6.79 g, 23.9 mmol) in THF (70 mL) was added dropwise to a solution of IBX (16.7 g, 59.7 mmol) in DMSO (200 mL), and the resultant mixture was stirred at rt for 3 h. EtOAc (800 mL) and H_2O (800 mL) were then added sequentially, and the resultant mixture was filtered through a pad of Celite (eluent EtOAc). The layers were separated, the aqueous layer was extracted with EtOAc (2 × 350 mL), and the combined organic layers were washed with H_2O (4 × 500 mL), dried, and concentrated *in vacuo*. The residue was dissolved in hot Et_2O, filtered through a pad of Celite (eluent Et_2O), and then concentrated *in vacuo* to give **36** as a white solid (6.62 g, 98%, >99:1 dr); mp 58−59 °C; $[\alpha]^{25}_D$ −41.1 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 2953, 2914, 2849 (C−H), 1738, 1715, 1470, 854, 719; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, app t, *J* 6.8, C(18)H_3), 1.21−1.72 (28H, m, C(4)−C(17)H_2), 3.14 (1H, dd, *J* 6.2, 2.0, C(2)*H*), 3.24 (1H, ddd, *J* 5.9, 5.1, 2.0, C(3)*H*), 9.02 (1H, d, *J* 6.3, C(1)*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (C(18)), 22.7, 25.8, 29.2, 29.3, 29.4, 29.5, 29.58, 29.64, 29.7, 31.2, 31.9 (*C*(4)-*C*(17)), 56.8 (*C*(3)), 59.1 (*C*(2)), 198.5 (*C*(1)); *m*/*z* (FI^+) 282 ($[M]^+$, 100%); HRMS (FI^+) $C_{18}H_{34}O_2^+$ ($[M]^+$) requires 282.2553, found 282.2558.

(*R*,*R*)-1-(*N*,*N*-Dibenzylamino)-2,3-epoxyoctadecane 37. Dibenzylamine (4.51 mL, 23.4 mmol) and $NaB(OAc)_3H$ (6.95 g, 32.8 mmol) were sequentially added to a stirred solution of **36** (6.62 g, 23.4 mmol) in 1,2-dichloroethane (160 mL) at 0 °C, and the resultant mixture was allowed to warm to rt over 3 h. Saturated aqueous $NaHCO_3$ (300 mL) was then added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL), and the combined organic layers were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 2→20% Et_2O in 30−40 °C petrol) gave **37** as a colorless oil that solidified on standing to a white solid (9.60 g, 88%, >99:1 dr); R_f 0.44 (30−40 °C petrol/Et_2O, 9:1); $C_{32}H_{49}NO$ requires C, 82.9; H, 10.65; N, 3.0%; found C, 82.9; H, 10.6; N, 3.0%; mp 29−30 °C; $[\alpha]^{25}_D$ +6.5 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 3086, 3063, 3028, 2924, 2853, 2798 (C−H), 1495, 1454, 1370, 745, 698; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, app t, *J* 6.8, C(18)H_3), 1.21−1.51 (28H, m, C(4)−C(17)H_2), 2.52 (1H, dd, *J* 13.7, 6.0, C(1)H_A), 2.63 (1H, app td, *J* 5.4, 2.3, C(3)*H*), 2.70 (1H, dd, *J* 13.7, 4.0, C(1)H_B), 2.87 (1H, ddd, *J* 6.0, 4.0, 2.3, C(2)*H*), 3.58 (2H, d, *J* 13.6, N($CH_AH_BPh)_2$), 3.79 (2H, d, *J* 13.6, N($CH_AH_BPh)_2$), 7.21−7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (C(18)), 22.7, 26.0, 29.36, 29.44, 29.5, 29.6, 29.66, 29.70, 31.8, 31.9 (*C*(4)-*C*(17)), 55.5 (*C*(1)), 57.0 (*C*(2)), 57.3 (*C*(3)), 58.9 (N($CH_2Ph)_2$), 126.9 (*p*-*Ph*), 128.2, 128.8 (*o*,*m*-*Ph*), 139.4 (*i*-*Ph*); *m*/*z* (ESI^+) 464 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{32}H_{50}NO^+$ ($[M + H]^+$) requires 464.3887, found 464.3881.

(2*R*,3*S*)-1-(*N*,*N*-Dibenzylamino)-3-fluorooctadecan-2-ol 38. Following *General Procedure 1*, **37** (9.46 g, 20.4 mmol) in CH_2Cl_2 (82 mL) at 0 °C was treated with $HBF_4 \cdot OEt_2$ (5.55 mL, 40.8 mmol). Purification via recrystallization from MeCN gave **38** as a white crystalline solid (6.98 g, 71%, >99:1 dr, >98% ee). The mother liquor was concentrated *in vacuo*, and the residue was purified via flash column chromatography (gradient elution, 2→20% Et_2O in 30−40 °C petrol) to give additional **38** as a colorless oil that solidified on standing to a white crystalline solid (825 mg, 8%, >99:1 dr, >98% ee); R_f 0.21 (30−40 °C petrol/Et_2O, 9:1); mp 42−43 °C; $[\alpha]^{25}_D$ +35.0 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 3452 (O−H), 3063, 3029, 2924, 2853 (C−H), 1454, 748, 699; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, app t, *J* 6.8, C(18)H_3), 1.15−1.68 (28H, m, C(4)−C(17)H_2), 2.63 (1H, dd, *J* 12.6, 9.6, C(1)H_A), 2.70 (1H, ddd, *J* 12.6, 3.9, 1.4, C(1)H_B), 3.36 (1H, br s, O*H*), 3.48 (2H, d, *J* 13.3, N($CH_AH_BPh)_2$), 3.71 (1H, dddd, *J* 11.4, 9.7, 5.7, 3.9, C(2)*H*), 3.83 (2H, d, *J* 13.3, N($CH_AH_BPh)_2$), 4.17−4.37 (1H, m, C(3)*H*), 7.26−7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (C(18)), 22.7, 25.0 (d, *J* 3.2), 29.36, 29.44, 29.5, 29.57, 29.64, 29.66, 29.70, 31.2 (d, *J* 20.8), 31.9 (C(4)-C(17)), 55.3 (d, *J* 5.6, C(1)), 58.5 (N($CH_2Ph)_2$), 68.2 (d, *J* 24.0, C(2)), 95.4 (d, *J* 169, C(3)), 127.4 (*p*-*Ph*), 128.5, 129.1 (*o*,*m*-*Ph*), 138.3 (*i*-*Ph*); δ_F (377 MHz, $CDCl_3$) −194.3 (m); *m*/*z* (ESI^+) 484 ($[M + H]^+$, 96%), 464

([M−F]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{51}FNO^+$ ([M + H]$^+$) requires 484.3949, found 484.3946.

(2*R*,3*S*)-1-(*N*,*N*-Dibenzylamino)-2-chloro-3-fluorooctadecane 41. *Method A.* CCl_4 (289 μL, 3.00 mmol) was added dropwise to a stirred mixture of **38** (145 mg, 0.30 mmol), PPh_3 (197 mg, 0.75 mmol) and Et_3N (418 μL, 3.00 mmol) in MeCN (1.20 mL) at rt, and the resultant mixture was heated at reflux for 40 min, allowed to cool to rt, and concentrated *in vacuo*. Purification via filtration through a pad of silica gel (eluent CH_2Cl_2) gave an 83:17 mixture of **40**:**41** as a yellow oil (153 mg, quant). Data for **40**: δ_H (500 MHz, $CDCl_3$) [selected peaks] 1.88−2.01 (1H, m, C(4)H_A), 2.80−2.92 (1H, m, C(2)*H*), 3.59 (2H, d, *J* 13.4, N(CH_AH$_B$Ph)$_2$), 3.86 (1H, dd, *J* 10.9, 8.8, C(1)H_A), 3.92 (1H, dd, *J* 10.9, 4.7, C(1)H_B), 4.03 (2H, d, *J* 13.4, N(CH$_A$$H_B$Ph)$_2$), 4.79 (1H, dddd, J 48.2, 8.0, 4.7, 3.3, C(3)*H*). A solution of the 83:17 mixture of **40**:**41** (50.0 mg) in MeCN (0.40 mL) was heated at reflux for 18 h and then concentrated *in vacuo* to give **41** as a yellow oil (50.0 mg, quant, >99:1 dr).

Method B. CCl_4 (13.6 mL, 141 mmol) was added dropwise to a stirred mixture of **38** (6.81 g, 14.1 mmol), PPh_3 (9.23 g, 35.2 mmol), and Et_3N (19.6 mL, 141 mmol) in MeCN (56 mL) at 0 °C, and the resultant mixture was allowed to warm to rt and then heated at reflux for 18 h. The mixture was then allowed to cool to rt and was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2, filtered through a pad of silica gel (eluent CH_2Cl_2), and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 1→8% Et_2O in 30−40 °C petrol) gave **41** as a yellow oil (6.28 g, 89%, >99:1 dr); R_f 0.53 (30−40 °C petrol/Et_2O, 24:1); $[\alpha]^{25}_D$ −13.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3087, 3063, 3028, 2924, 2853 (C−H), 1454, 747, 698; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, app t, *J* 6.8, C(18)H_3), 0.99−1.70 (28H, m, C(4)−C(17)H_2), 2.76 (1H, ddd, *J* 13.9, 6.6, 2.3, C(1)H_A), 2.88 (1H, dd, *J* 13.9, 7.6, C(1)H_B), 3.51 (2H, d, *J* 13.5, N(CH_AH$_B$Ph)$_2$), 3.75 (2H, d, *J* 13.5, N(CH$_A$$H_B$Ph)$_2$), 4.12−4.22 (1H, m, C(2)*H*), 4.67 (1H, dddd, *J* 47.5, 9.7, 3.9, 2.3, C(3)*H*), 7.25−7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (C(18)), 22.7, 25.1 (d, *J* 2.4), 29.4, 29.5, 29.6, 29.65, 29.67, 29.69, 29.71, 29.8, 31.9 (*C*(4)-*C*(17)), 56.6 (d, *J* 6.4, *C*(1)), 59.1 (N(*C*H$_2$Ph)$_2$), 60.9 (d, *J* 21.6, *C*(2)), 93.9 (d, *J* 174, *C*(3)), 127.3 (*p-Ph*), 128.3, 129.0 (*o,m-Ph*), 138.7 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −184.8 (m); *m*/*z* (ESI$^+$) 502 ([M(^{35}Cl) + H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{50}{}^{37}ClFN^+$ ([M(^{37}Cl) + H]$^+$) requires 504.3581, found 504.3595; $C_{32}H_{50}{}^{35}ClFN^+$ ([M(^{35}Cl) + H]$^+$) requires 502.3610, found 502.3606.

(*S*,*S*)-2-(*N*,*N*-Dibenzylamino)-3-fluorooctadecan-1-ol 42. KOAc (1.67 g, 17.1 mmol) was added to a stirred solution of **41** (857 mg, 1.71 mmol) in DMF (34 mL), and the resultant suspension was stirred at 100 °C for 24 h. The mixture was allowed to cool to rt, and EtOAc (300 mL) and saturated aqueous $NaHCO_3$ (300 mL) were added sequentially. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 150 mL). The combined organic layers were washed with H_2O (4 × 200 mL), dried, and concentrated *in vacuo*. K_2CO_3 (236 mg, 1.71 mmol), MeOH (4.27 mL) and THF (4.27 mL) were added to the residue, and the resultant mixture was stirred at rt for 2.5 h and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and H_2O (50 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 2→20% EtOAc in 30−40 °C petrol) gave **42** as a yellow oil that solidified on standing to a cream solid (681 mg, 82%, >99:1 dr, >98% ee); R_f 0.28 (30−40 °C petrol/EtOAc, 9:1); $C_{32}H_{50}FNO$ requires C, 79.45; H, 10.4; N, 2.9%; found C, 79.5; H, 10.4; N, 2.8%; mp 40−41 °C; $[\alpha]^{25}_D$ −50.6 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 3423 (O−H), 3086, 3063, 3029, 2924, 2853 (C−H), 1455, 750, 699; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, app t, *J* 6.8, C(18)H_3), 1.22−1.68 (28H, m, C(4)−C(17)H_2), 3.00 (1H, app dq, *J* 12.8, 7.9, C(2)*H*), 3.13 (1H, br s, O*H*), 3.42 (2H, app d, *J* 7.6, C(1)H_2), 3.82 (2H, d, *J* 12.9, N(CH_AH$_B$Ph)$_2$), 3.92 (2H, d, *J* 12.9, N(CH$_A$$H_B$Ph)$_2$), 4.79 (1H, app dtd, *J* 50.0, 8.5, 2.3, C(3)*H*), 7.24−7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (C(18)), 22.7, 24.6 (d, *J* 4.0), 29.37, 29.44, 29.5, 29.56, 29.64, 29.66, 29.70, 31.9, 32.9 (d, *J* 20.8) (*C*(4)-*C*(17)), 54.5 (d, *J* 3.2, N(*C*H$_2$Ph)$_2$), 57.7 (d, *J* 10.4, *C*(1)), 61.0 (d, *J* 16.8, *C*(2)), 94.4 (d, *J* 173, *C*(3)), 127.3 (*p-Ph*), 128.5, 129.3 (*o*, *m-Ph*), 139.2 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −186.9 (m); *m*/*z* (ESI$^+$) 484 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{51}FNO^+$ ([M + H]$^+$) requires 484.3949, found 484.3940.

(*S*,*S*)-2-Amino-3-fluorooctadecan-1-ol [(*S*,*S*)-3-deoxy-3-fluorosafingol] 43. $Pd(OH)_2$/C (100 mg, 50% w/w wrt **42**) was added to a vigorously stirred solution of **42** (200 mg, 0.41 mmol) in degassed MeOH (2.08 mL), and the resultant suspension was stirred at rt under H_2 (5 atm) for 5.5 h. The reaction mixture was then filtered through a pad of Celite (eluent hot MeOH) and concentrated *in vacuo* to give **43** as a white solid (121 mg, 97%, >99:1 dr); $C_{18}H_{38}FNO$ requires C, 71.2; H, 12.6; N, 4.6%; found C, 71.3; H, 12.8; N, 4.5%; mp 80−81 °C; $[\alpha]^{25}_D$ −6.2 (*c* 1.0 in MeOH); ν_{max} (KBr) 3354, 3270, 3196, 3095, 2953, 2918, 2847 (C−H), 1626, 1468, 1071, 1052, 938, 907, 872, 722; δ_H (400 MHz, MeOH-d_4) 0.91 (3H, app t, *J* 6.8, C(18)H_3), 1.23−1.84 (28H, m, C(4)−C(17)H_2), 2.76−2.88 (1H, m, C(2)*H*), 3.51 (1H, dd, *J* 10.9, 6.3, C(1)H_A), 3.60 (1H, dd, *J* 10.9, 5.8, C(1)H_B), 4.50 (1H, app ddt, *J* 48.8, 8.8, 4.2, C(3)*H*); δ_C (100 MHz, MeOH-d_4) 13.5 (C(18)), 22.7, 25.4 (d, *J* 4.0), 29.5, 29.6, 29.68, 29.71, 29.77, 29.79, 31.7 (d, *J* 20.8), 32.1 (*C*(4)-*C*(17)), 55.8 (d, *J* 19.2, *C*(2)), 62.9 (d, *J* 5.6, *C*(1)), 94.0 (d, *J* 169, *C*(3)); δ_F (377 MHz, MeOH-d_4) −198.7 (m); *m*/*z* (ESI$^+$) 304 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{39}FNO^+$ ([M + H]$^+$) requires 304.3010, found 304.3006.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra and files in CIF format for structures CCDC 810176−810182. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3. Mikami, K.; Itoh, Y.; Yamamaka, Y. M. *Chem. Rev.* **2004**, *104*, 1. O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.

(2) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637. Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013. Morgenthaler, M.; Schweizer, E.; Hoffmann-Röder, A.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Müller, K. *ChemMedChem* **2007**, *2*, 1100. Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. Kirk, K. L. *Org. Process. Res. Dev.* **2008**, *12*, 305. Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.

(3) Jeschke, P. *ChemBioChem* **2004**, *5*, 570.

(4) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004.

(5) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071.

(6) Wilkinson, J. A. *Chem. Rev.* **1992**, *92*, 505. Mascaretti, O. A. *Aldrichimica Acta* **1993**, *26*, 47. Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem.*

Rev. **1996**, *96*, 1737. Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr. Opin. Drug. Discovery Dev.* **2008**, *11*, 803.

(7) Bobbio, C.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 2065. Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1.

(8) Other examples of fluorine transfer from $BF_3 \cdot OEt_2$ have been reported. For selected examples in cation-π cyclizations, see: Mann, A.; Muller, C.; Tyrrell, E. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1427. Franck-Neumann, M.; Geoffroy, P.; Hanss, D. *Tetrahedron Lett.* **1999**, *40*, 8487. Pearson, A. J.; Alimardanov, A. R.; Kerber, W. D. *J. Organomet. Chem.* **2001**, *630*, 23. Lu, Y.; Green, J. R. *Synlett* **2001**, 243. Yadav, V. K.; Vijaykumar, N. *J. Am. Chem. Soc.* **2004**, *126*, 8652. Launay, G. G.; Slawin, A. M. Z.; O'Hagan, D. *Beilstein J. Org. Chem.* **2010**, *6*. Luo, H.-Q.; Hu, X.-H.; Loh, T.-P. *Tetrahedron Lett.* **2010**, *51*, 1041. For selected examples in the halofluorination of alkenes, see: Heasley, V. L.; Gipe, R. K.; Martin, J. L.; Wiese, H. C.; Oakes, M. L.; Shellhamer, D. F.; Heasley, G. L.; Robinson, B. L. *J. Org. Chem.* **1983**, *48*, 3195. Heasley, G. L.; Janes, J. M.; Stark, S. R.; Robinson, B. L.; Heasley, V. L.; Shellhamer, D. F. *Tetrahedron Lett.* **1985**, *26*, 1811. For selected examples in the ring-opening hydrofluorination of epoxides and aziridines, see: Goldsmith, D. J. *J. Am. Chem. Soc.* **1962**, *84*, 3913. Sharts, C. M.; Sheppard, W. A. *Org. React.* **1974**, *21*, 1. Takaishi, N.; Takahashi, H.; Inamoto, Y. *Tetrahedron Lett.* **1985**, *26*, 2361. Ashwell, M.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron* **1990**, *46*, 7429. Duhamel, P.; Leblond, B.; Bidois-Séry, L.; Poirier, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2265. Ding, C.-H.; Dai, L.-X.; Hou, X.-L. *Synlett* **2004**, 2218.

(9) Cresswell, A. J.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Tyte, M. J. *Org. Lett.* **2010**, *12*, 2936.

(10) Balz, G.; Schiemann, G. *Ber. Deutsch. Chem. Ges.* **1927**, *60*, 1186.

(11) Doyle, M. P.; Whitefleet, J. L.; Bosch, R. J. *J. Org. Chem.* **1979**, *44*, 2923.

(12) For selected examples, see: Barluenga, J.; González, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem., Int. Ed.* **1988**, *27*, 1546. Faller, J. W.; Linebarrier, D. L. *Organomet.* **1990**, *9*, 3182. Yoshida, J.-I.; Ishichi, Y.; Isoe, S. *J. Am. Chem. Soc.* **1992**, *114*, 7594. Olier, C.; Gastaldi, S.; Christie, S. D. R.; Bertrand, M. P. *Synlett* **2007**, *2007*, 423. Olier, C.; Gastaldi, S.; Gil, G.; Bertrand, M. P. *Tetrahedron Lett.* **2007**, *48*, 7801. Yadav, J. S.; Subba Reddy, B. V.; Ramesh, K.; Narayana Kumar, G. G. K. S.; Grée, R. *Tetrahedron Lett.* **2010**, *51*, 1578.

(13) Igarashi, K.; Honma, T.; Irisawa, J. *Carbohyd. Res.* **1970**, *13* 49. Kunz, H.; Sager, W. *Helv. Chim. Acta* **1985**, *68*, 283. Blomberg, L.; Norberg, T. *J. Carbohydr. Chem.* **1992**, *11*, 751. Huang, K.-T.; Winssinger, N. *Eur. J. Org. Chem.* **2007**, 1887. López, J. C.; Uriel, C.; Guillamón-Martín, A.; Valverde, S.; Gómez, A. M. *Org. Lett.* **2007**, *9*, 2759.

(14) Bloodworth, A. J.; Bower, K. J.; Mitchell, J. C. *Tetrahedron Lett.* **1987**, *28*, 5347.

(15) Maeda, H.; Koide, T.; Matsumoto, S.; Ohmori, H. *Chem. Pharm. Bull.* **1996**, *44*, 1480.

(16) Koch, V. R.; Miller, L. L.; Clark, D. B.; Fleischmann, M.; Joslin, T.; Pletcher, D. *J. Electroanal. Chem. Interfacial Electrochem.* **1973**, *43*, 318.

(17) Evans, R. D.; Schauble, J. H. *Synthesis* **1987**, 551. Barluenga, J.; Campos, P. J.; González, J. M.; Suárez, J. L.; Asensio, G. *J. Org. Chem.* **1991**, *56*, 2234.

(18) Fujie, S.; Matsumoto, K.; Suga, S.; Yoshida, J.-I. *Chem. Lett.* **2009**, *38*, 1186.

(19) (a) Aciro, C.; Claridge, T. D. W.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3751. (b) Aciro, C.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3762. (c) Bond, C. W.; Cresswell, A. J.; Davies, S. G.; Kurosawa, W.; Lee, J. A.; Fletcher, A. M.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *J. Org. Chem.* **2009**, *74*, 6735. (d) Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Thomson, J. E. *Org. Lett.* **2010**, *12*, 136. (e) Davies, S. G.; Fletcher, A. M.; Kurosawa, W.; Lee, J. A.; Poce, G.; Roberts, P. M.; Thomson, J. E.; Williamson, D. M. *J. Org. Chem.* **2010**, *75*, 7745. (f) Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Scott, P. M.; Thomson, J. E. *J. Org. Chem.* **2010**, *75*, 8133. (g) Kurosawa, W.; Roberts, P. M.; Davies, S. G. *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem. Jpn.)* **2010**, *68*, 1295. (h) Bagal, S. K.; Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Roberts, P. M.; Scott, P. M.; Thomson, J. E. *Tetrahedron Lett.* **2011**, *52*, 2216.

(20) For reviews concerning the ring opening hydrofluorination of epoxides, see: Bonini, C.; Righi, G. *Synthesis* **1994**, 225. Haufe, G. *J. Fluorine Chem.* **2004**, *125*, 875. Haufe, G. Product Subclass 9: β-Fluoro Alcohols. In *Science of Synthesis*, Vol. 34: Fluorine; Percy, J., Ed.; Thieme: Stuttgart, 2006; pp 345.

(21) For examples of previous syntheses of other fluorinated sphingoid bases and analogues, see: Kozikowski, A. P.; Wu, J.-P. *Tetrahedron Lett.* **1990**, *31*, 4309. De Jonghe, S.; Overmeire, I. V.; Van Calenbergh, S.; Hendrix, C.; Busson, R.; De Kukeleire, D.; Herdewijn, P. *Eur. J. Org. Chem.* **2000**, 3177. Olendorf, J.; Haufe, G. *Eur. J. Org. Chem.* **2006**, 4463. Teare, H.; Huguet, F.; Tredwell, M.; Thibaudeau, S.; Luthra, S.; Gouverneur, V. *ARKIVOC* **2007**, 232.

(22) 2,3-Epoxy amines **5**−**8** were prepared from the corresponding cyclic allylic amines following our previously reported protocols; see refs 19a and 19b.

(23) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 810176 (**9**), CCDC 810177 (**11**), and CCDC 810178 (**12**).

(24) Malhotra, S. L.; Blanchard, L. P. *J. Macromol. Sci., Chem.* **1978**, *A12*, 1379. Abu-Abdoun, I. I.; Ali, A. *Eur. Polm. J.* **1992**, *28*, 73.

(25) For related examples of this phenomenon, see: Henbest, H. B.; Wrigley, T. I. *J. Chem. Soc.* **1957**, 4765. Bowers, A.; Cuéllar Ibáñez, L.; Ringold, H. J. *Tetrahedron* **1959**, *7*, 138.

(26) Ring-opening hydrofluorination of 2,3-epoxy amines **7** and **8** was accompanied by the formation of a minor (∼5%) unidentified fluorinated species that was not isolated.

(27) For other related examples, see: Wolinsky, J.; Thorstenson, J. H.; Killinger, T. A. *J. Org. Chem.* **1978**, *43*, 875. Calvani, F.; Crotti, P.; Gardelli, C.; Pineschi, M. *Tetrahedron* **1994**, *50*, 12999.

(28) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737. Addy, J. K.; Parker, R. E. *J. Chem. Soc.* **1963**, 915.

(29) 2,3-Epoxy amines **13**−**16** were prepared from the corresponding commercially available allylic or homoallylic alcohols, via a three-step procedure involving epoxidation, mesylation, and displacement with dibenzylamine. 2,3-Epoxy amine **17** was prepared from commercially available 3-methylbut-2-enal via a two-step procedure involving epoxidation and reductive amination with dibenzylamine. 2,3-Epoxy amines **18** and **19** were prepared from the corresponding allylic amines following our previously reported protocols; see: Davies, S. G.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Woods, P. A. *Tetrahedron* **2010**, *66*, 6806 (allylic amine syntheses) and ref 19e (ammonium-directed oxidations).

(30) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 810179 (**25**), CCDC 810180 (**28**), and CCDC 810181 (**29**).

(31) In both of these cases, the mass balance comprised a complex mixture of unidentifiable products.

(32) Cinque, B.; Di Marzio, L.; Centi, C.; Di Rocco, C.; Riccardi, C.; Cifone, M. G. *Pharmacol. Res.* **2003**, *47*, 421.

(33) Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075. Howell, A. R.; Ndakala, A. J. *Curr. Org. Chem.* **2002**, *6*, 365. Howell, A. R.; So, R. C.; Richardson, S. K. *Tetrahedron* **2004**, *60*, 11327. Abraham, E.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Tetrahedron: Asymmetry* **2008**, *19*, 1027.

(34) Hannun, Y. A.; Bell, R. M. *Science* **1989**, *243*, 500. Schwartz, G. K.; Jiang, J.; Kelsen, D.; Albino, A. P. *J. Natl. Cancer Inst.* **1993**, *85*, 402.

(35) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. Hill, J. G.; Sharpless, K. B.; Exon, C. M.; Regenye, R. *Org. Synth.* **1985**, *63*, 66. Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1.

(36) The enantiomeric purities of **35**, **38** and **42** were determined by conversion to the corresponding Mosher's esters; see: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(37) Duschek, A.; Kirsch, S. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1524.

(38) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.
(39) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801.
(40) Sivaprakasham, M.; Couty, F.; Evano, G.; Srinivas, B.; Sridhar, R.; Rao, K. R. *ARKIVOC* **2007**, 71.
(41) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 810182.
(42) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
(43) Swern, D. *Org. React.* **1953**, *VII*, 392.
(44) Azzena, F.; Calvani, F.; Crotti, P.; Gardelli, C.; Macchia, F.; Pineschi, M. *Tetrahedron* **1995**, *51*, 10601.
(45) Mori, K.; Nakazono, Y. *Tetrahedron* **1986**, *42*, 6459.
(46) Miyaoka, H.; Shigemoto, T.; Shinohara, I.; Suzuki, A.; Yamada, Y. *Tetrahedron* **2000**, *56*, 8077.
(47) Liu, Q.; Marchington, A. P.; Boden, N.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 511.
(48) Takai, T.; Hata, E.; Yamada, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2513.
(49) Gorthey, L. A.; Vairamani, M.; Djerassi, C. *J. Org. Chem.* **1984**, *49*, 1511.
(50) Dennis, M.; Hall, L. M.; Murphy, P. J.; Thornhill, A. J.; Nash, R.; Winters, A. L.; Hursthouse, M. B.; Light, M. E.; Horton, P. *Tetrahedron Lett.* **2003**, *44*, 3075.
(51) Oppolzer, W.; Radinov, R. N.; El-Sayed, E. *J. Org. Chem.* **2001**, *66*, 4766.
(52) Roush, W. R.; Adam, M. A. *J. Org. Chem.* **1985**, *50*, 3752.
(53) Prepared following the procedure reported by Hill, J. G.; Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3608.