Synthesis of Fluorinated Sphinganine and Dihydroceramide Analogues

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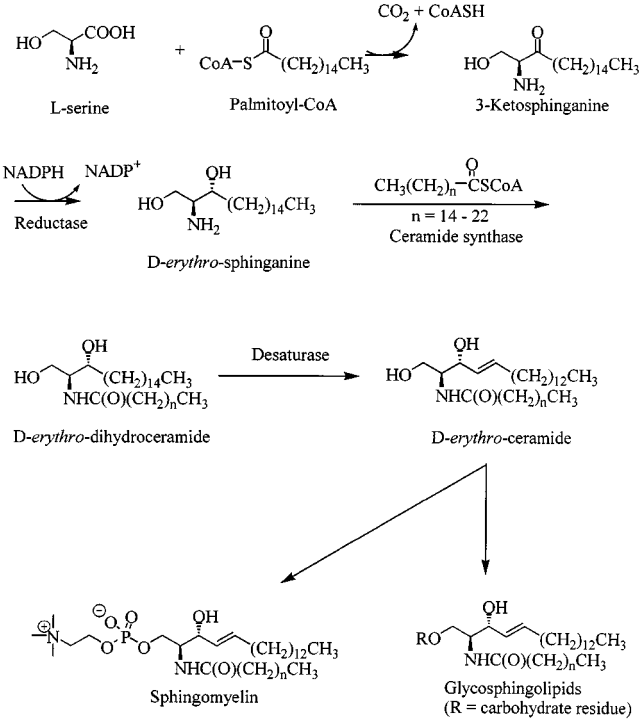
With the aim of uncovering inhibitors of dihydroceramide desaturase and ceramide synthase and studying their substrate specificity, the synthesis of short-chain 3-fluorosphinganine and 3-fluorodihydroceramide analogues was effected. The synthesis starts from the known alkynols **1** and **10**, respectively, and from the Garner aldehyde **15**. The key step is the introduction of a fluorine atom using diethylaminosulfur trifluoride, which proceeds efficiently for *erythro*-alcohols **2** and **16**, but gives rise to cyclization reactions for *threo* compounds **11** and **17**.

Introduction

Dihydroceramides and sphinganine are intermediates in the biosynthesis of ceramides. The de novo biosynthesis of ceramides takes place in the endoplasmic reticulum and involves the condensation of L-serine and palmitoylCoA, which is catalyzed by a pyridoxalphosphate-dependent serine palmitoyl transferase. The resulting 3-oxosphinganine is subsequently reduced by an NADPH-dependent reductase to D-*erythro*-sphinganine.[1] Acylation by sphinganine-*N*-acyltransferase (also known as ceramide synthase)[2] leads to the formation of D-*erythro*-dihydroceramide. Dihydroceramide desaturase[3] introduces the 4,5-*trans*-carbon−carbon double bond to yield D-*erythro*-ceramide (Scheme 1).

Ceramides are potent bioactive molecules that intervene in a number of biological processes such as cell proliferation, cell differentiation, and apoptosis.[4] It is commonly believed that dihydroceramides, lacking the 4,5-*trans*-carbon−carbon double bond, are biologically inactive,[5] although this issue is controversial.[6] Ceramides can be further converted in the Golgi apparatus to glycosphingolipids[7] and sphingomyelin,[8] which are transported to the plasma membrane to exert their biological function.

The enzymes in the sphingolipid metabolism (including dihydroceramide desaturase and ceramide synthase) are poorly characterized. In this paper, we wish to report the synthesis of fluorinated sphinganine and dihydroceramide analogues. These compounds are useful to delineate the characteristics of ceramide synthase and dihydroceramide desaturase and to study their substrate specificity. Because of the poor aqueous solubility of natural dihydroceramides, it is necessary to provide derivatives with increased solubility in aqueous media in order to facilitate the study of the metabolism of sphingolipids. This goal can be achieved by shortening the sphingoid backbone (C_{12} and a phenyl residue instead of C_{18}) and by introducing a short *N*-acyl chain (C_2 and C_6 instead of the naturally occurring $C_{16}-C_{24}$). Similar short-chain ceramides have already been synthesized to study the influence of ceramide analogues on the axonal growth of hippocampal neurons.[9] The synthesis of the D-*erythro* (the naturally occurring configuration) as well as the L-*threo* epimers was envisaged to probe the stereospecificity of the enzymes. As organofluoro compounds frequently function as enzyme inhibitors and substrate analogues, it should be of interest to access fluorinated sphinganines and dihydroceramides. Furthermore, the substitution of a hydroxy group for a fluorine atom is one of the



Scheme 1. Biosynthesis of glycosphingolipids and sphingomyelin

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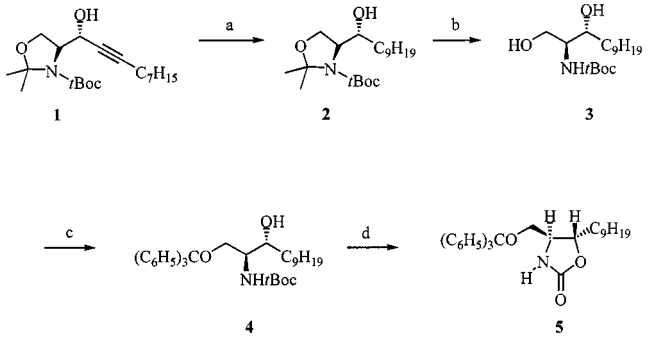
most frequently used isosteric replacements often leading to new compounds with interesting biological properties.[10]

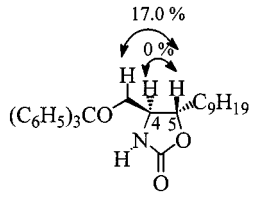
Results and Discussion

The synthesis of fluorinated sphinganine and dihydroceramide analogues involves *erythro*-alkynol **1** (Scheme 2) as a key substance, which is available according to a recently adapted procedure, originally developed by Herold.[9,11] Catalytic hydrogenation of **1** led to the formation of the saturated alcohol **2**. Cleavage of the oxazolidine under acidic conditions (Amberlyst 15[11] or *p*-TsOH[12]) yielded the *N*-*t*Boc-protected sphinganine analogue **3**. Conversion of the primary hydroxy group to a trityl ether is mandatory prior to substitution of the secondary hydroxy group for a fluorine atom. A wide variety of fluorinating reagents is available.[13] We opted for the use of diethylaminosulfur trifluoride (DAST),[14] as it is a highly effective reagent for direct, one-step, and high yielding conversion of alcohols into fluorides under mild conditions. DAST has been used for the synthesis of fluorinated prostaglandins,[15] fluorinated carbohydrates,[16] fluorinated nucleosides,[17] and fluorinated sterols.[18] To the best of our knowledge, the synthesis of fluorinated (dihydro)ceramides using DAST has not been described yet. In our hands, reaction of **4** with DAST afforded only oxazolidinone derivative **5**.



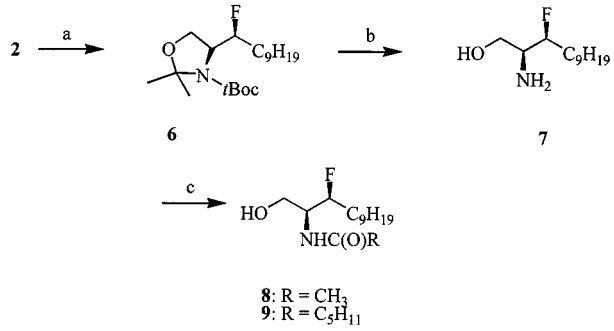
Scheme 2. Formation of oxazolidinone **5**: a: H_2, Pt/C, MeOH, 98%; b: Amberlyst 15, MeOH, room temp., 79% or *p*-TsOH, MeOH, room temp., 76%; c: TrCl, DMAP, pyridine, reflux, 82%; d: DAST, CH_2Cl_2, −78 °C to room temp., 88%

The relative configuration of the protons 4-H and 5-H was deduced from the vicinal ^1H-^1H coupling constant and from NOE measurements. Based on the small coupling constant ($^3J_{4,5}$ = 5.87 Hz), the relative configuration of 4-H and 5-H was assigned as *trans*.[19] Confirmation of this *trans* relationship was obtained from NOE experiments (Scheme 3). The 5-H signal exhibited a strong NOE effect to 1′-H, while no NOE correlation could be detected between 4-H and 5-H. These findings are consistent with the *trans* configuration of 4-H and 5-H, resulting from an intramolecular S_N2-type nucleophilic reaction of the alcohol to the carbamate moiety. Similar cyclization reactions have been observed on treatment of *N*-*t*Boc derivatives of β-amino alcohols with *p*-toluenesulfonyl chloride.[20]



Scheme 3. NOE effects in oxazolidinone **5**

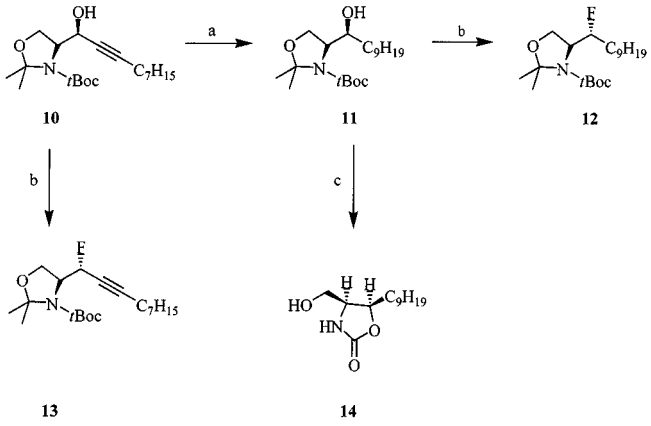
To obviate cyclizations, we decided to introduce the fluorine atom when the *N*-*t*Boc and the primary hydroxy group occurred in a protected form as the oxazolidine (Scheme 4). Fluorination of alcohol **2**, using DAST, afforded oxazolidine **6**. As DAST reactions are concomitant with inversion of configuration (S_N2-type),[16,17] we infer that the *threo*-fluoride **6** must be formed. Simultaneous cleavage of the oxazolidine and deprotection of the *t*Boc group by treatment of **6** with trifluoroacetic acid[21] gave the L-*threo*-3-fluorosphinganine analogue **7**. To study the effect of the *N*-acyl chain length on the biological activity, we acylated the amino group (Schotten−Baumann procedure[22]) with acetyl chloride and with hexanoyl chloride to afford L-*threo*-3-fluorodihydroceramides **8** and **9**, respectively.



Scheme 4. Synthesis of aliphatic L-*threo*-3-fluorosphinganine and -dihydroceramide analogues: a: DAST, CH_2Cl_2, −78 °C to room temp., 81%; b: TFA/H_2O (3:1), room temp., 82%; c: RC(O)Cl, THF, 50% aq. NaOAc, room temp., 83% (**8**), 88% (**9**)

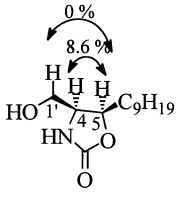
The synthesis of the corresponding *erythro*-fluorides starts from the known *threo*-alkynol **10** (Scheme 5),[9] which, upon catalytic hydrogenation, afforded *threo*-alcohol **11**. Introduction of fluorine atom yielded the desired *erythro*-fluoride **12**, although the reaction gave a very poor yield (5%) and is not useful for preparative purposes. The low reactivity of **11** is probably due to the existence of an intramolecular hydrogen bond between the hydroxy group and the urethane carbonyl group.[23] Alternative routes were investigated for improved yields. Fluorination of *threo*-alkynol **10** gave rise to *erythro*-fluoride **13** in a slightly better yield (32%). However, reduction of alkyne **13** by catalytic hydrogenation to its saturated counterpart proved to be cumbersome. Alternatively, a two-step sequence was attempted involving reaction with tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF)[24] subsequent to transformation of alcohol **11** to the triflate. However, reaction of **11** with trifluoromethanesulfonic anhydride did not afford a triflate, but cleavage of the oxazolidine and intramolecular

cyclization gave cyclic urethane **14** in near quantitative yield.



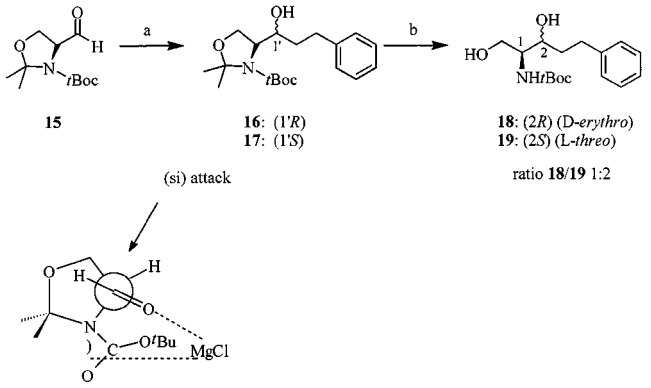
Scheme 5. Synthesis of aliphatic D-*erythro*-3-fluorosphinganine and -dihydroceramide analogues: a: H_2, Pt/C, MeOH, 92%; b: DAST, CH_2Cl_2, −78 °C to room temp., 5% (**12**), 32% (**13**); c: $(CF_3SO_2)_2O$, CH_2Cl_2, pyridine, 0 °C, 93%

The stereochemistry of **14** was verified by double irradiation experiments and NOE correlations (Scheme 6). On irradiation of 4-H (δ = 3.76−3.85), the signal of 5-H reduced to a double doublet (J = 3.8 Hz and 9.7 Hz) from a doublet of double doublets (J = 3.7 Hz, 7.6 Hz and 9.7 Hz). It follows that $^3J_{4,5}$ = 7.6 Hz. This observation provided a first indication for a *cis* relationship.[19] Moreover, a strong NOE contact was observed between 4-H and 5-H, while no NOE effect was apparent between 1′-H and 5-H. Based on these results, we assigned the stereochemical relationship of 4-H and 5-H to be *cis*.



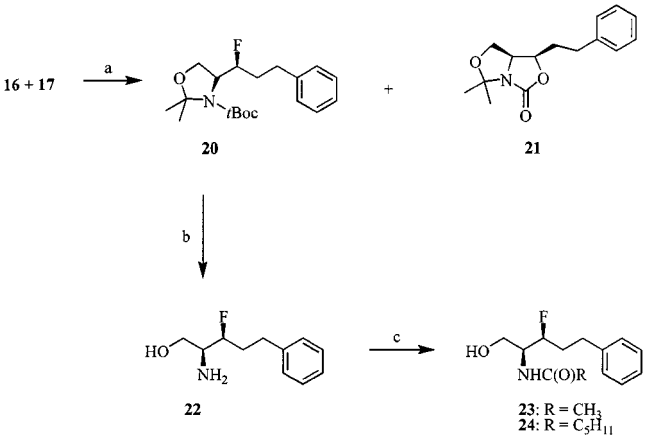
Scheme 6. NOE-effects in oxazolidinone **14**

With the aim of studying the structure-activity relationship of the sphinganine and dihydroceramide analogues, we decided to synthesize derivatives in which the alkyl chain was replaced by an aromatic residue. The well-known Garner aldehyde **15** (synthesized from L-serine by using an established procedure[25]) was treated with phenylethylmagnesium chloride to afford a mixture of epimeric alcohols **16** and **17** (Scheme 7), which could not be separated by silica chromatography. Because of overlap of NMR signals, it was not possible to determine the epimeric ratio. Therefore, we cleaved the oxazolidine with *p*-TsOH and obtained the *N*-*t*Boc-protected aromatic sphinganine analogues **18** + **19**. Again, the epimers could not be separated by HPLC on silica. Analysis of the ^{1}H NMR spectrum of the epimeric mixture **18** + **19** was difficult because of extensive overlap of signals and therefore the ^{1}H NMR spectrum was only used to determine the epimeric ratio. Based on previous observations that L-*threo* and D-*erythro* epimers can be distinguished by the upfield resonance of the NH proton of the L-*threo* epimer,[9,11] [δ = 5.35 (*erythro*), 5.25 (*threo*)], the *threo*/*erythro* ratio was found to be 2:1. The ^{13}C NMR spectrum of the epimeric mixture **18** + **19** proved to be very useful for unambiguous differentiation between the two epimers. C-2 of the L-*threo* epimer (δ = 71.7) resonates at a higher field with respect to its corresponding D-*erythro* epimer (δ = 73.2), which is in agreement with previous observations.[26] The *threo* selectivity of the Grignard reaction can be attributed to chelation control taking into account that the Grignard reagent acts as a Lewis acid.[23] In the transition state, interaction between the *N*-*t*Boc group and the aldehyde favours addition from the *si* face to yield the *threo* stereochemistry (chelation-controlled Cram product).



Scheme 7. Grignard reaction to the Garner aldehyde **15**: a: $C_6H_5(CH_2)_2MgCl$, THF, −78 °C to room temp., 73%; b: *p*-TsOH, MeOH, room temp., 64%

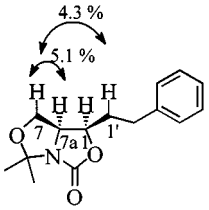
The mixture of **16** + **17** was used in the fluorination reaction with DAST (Scheme 8), whereby a fluorinated product and a bicyclic compound were isolated.



Scheme 8. Synthesis of aromatic L-*threo*-3-fluorosphinganine and -dihydroceramide analogues: a: DAST, CH_2Cl_2, −78 °C to room temp., 26% (**20**), 60% (**21**); b: TFA/H_2O (3:1), room temp., 76%; c: RC(O)Cl, THF, 50% aq. NaOAc, room temp., 81% (**23**), 77% (**24**)

Apparently, *erythro*-alcohol **16** was fluorinated to yield *threo*-fluoride **20**, while *threo*-alcohol **17** underwent intramolecular cyclization to afford **21**. Both reaction products could easily be separated by flash chromatography on silica. The ^{1}H-^{1}H coupling constant $^3J_{1,7a}$ of **21** was established as 8.6 Hz, which is indicative of a *cis* relationship.[19] Further confirmation was achieved by NOE experiments

(Scheme 9). Selective irradiation of 1-H or 7a-H was not possible due to the small chemical shift differences. Thus, irradiation at δ = 3.78 (7-H) caused enhancements for 7a-H and for 1′-H. No NOE contact was observed between 7-H and 1-H.



Scheme 9

The *threo*-fluoride **20** was deprotected with a mixture of trifluoroacetic acid and water to yield L-*threo*-3-fluorosphinganine **22**, which was acylated by suitable acyl chlorides to the desired L-*threo*-3-fluorodihydroceramides **23** and **24**.

Compounds **8** and **9** have been evaluated as potential inhibitors of dihydroceramide desaturase by an in vitro assay using rat liver microsomes.[27] Both compounds showed a slight inhibition of the desaturase activity, evidence of a decrease of enzymatic activity from 100% (control) to 91% (for compound **8**) and to 73% (for compound **9**), when equimolar concentrations of the substrate and inhibitors were used. Studies with compounds **7** and **22** as inhibitors and/or substrates of ceramide synthase are in progress and will be reported elsewhere. Additionally, we have measured the apoptogenic potential of fluorinated dihydroceramides **8** and **9**. Isosteric substitution of a hydroxy group for a fluorine atom led to enhancement of the apoptogenic activity. On the other hand, ceramide analogues **23** and **24**, carrying an aromatic residue, showed loss of apoptogenic potential. It is commonly believed that only ceramides induce apoptosis, while dihydroceramides, lacking the 4,5-*trans*-carbon−carbon double bond, are biologically inactive. However, by introduction of a fluorine atom for a hydroxy group, we were able to obtain dihydroceramide analogues that show strong apoptogenic activity.[28]

Conclusion

The DAST-mediated synthesis of fluorinated sphinganine and dihydroceramide analogues is described. Only the L-*threo*-fluorinated compounds could be obtained, since *threo*-alcohols **11** and **17** are very prone to undergo intramolecular cyclization, thus obviating formation of the D-*erythro*-fluorinated epimers. We found that compounds **8** and **9** were weak inhibitors of the in vitro conversion of dihydroceramide to ceramide. To the best of our knowledge, no inhibitors of dihydroceramide desaturase are known. Further exploration of the structure-activity relationships of dihydroceramide analogues could lead to more potent dihydroceramide desaturase inhibitors. Such inhibitors can be considered as potential biochemical tools to further elucidate the biological significance of ceramides and dihydroceramides.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker WH360 spectrometer (^{1}H NMR: 360 MHz; ^{13}C NMR: 90 MHz), with a Bruker AN500 spectrometer (^{1}H NMR: 500 MHz; ^{13}C NMR: 125 MHz) or with a Varian Gemini 200 spectrometer (^{1}H NMR: 200 MHz; ^{13}C NMR: 50 MHz) using tetramethylsilane as internal standard for the ^{1}H NMR spectra and [D$_6$]DMSO (δ = 39.7) or CDCl$_3$ (δ = 76.9) for the ^{13}C NMR spectra. − Liquid secondary-ion mass spectra (LSIMS) were obtained using a Kratos concept ^{1}H mass spectrometer (Kratos, Manchester, UK). − Elemental analyses were performed at the University of Konstanz, Germany (Prof. Pfleiderer, Laboratory of Anorganische Chemie). − Precoated Merck silica gel F254 plates were used for TLC and spots were examined with UV light at 254 nm and/or ninhydrin (0.5% in EtOH) solution or phosphomolybdic acid (0.5% in EtOH) solution. − Column chromatography was performed on SÜD-Chemie silica gel (0.2−0.05 mm). − Anhydrous solvents were obtained as follows: THF was distilled from sodium/benzophenone; pyridine was refluxed overnight over potassium hydroxide and then distilled; dichloromethane was stored over calcium hydride, refluxed and distilled.

3-*tert*-Butyl (4*S*)-4-[(1*R*)-1-Hydroxydecyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (2): Compound **1** (471 mg, 1.3324 mmol) was dissolved in MeOH (110 mL). The catalyst (5% Pt/C, 40 mg) was added and the mixture was stirred for 24 h at 35 atm H_2. The catalyst was removed by filtration through Celite. The filtrate was concentrated and the residue was chromatographed on silica gel with EtOAc/pentane (13:87) to afford **2** as an oil (467 mg, 98%). − ^{1}H NMR (360 MHz, CDCl$_3$): δ = 0.90 (t, 3 H, CH$_3$), 1.25 (br. s, 16 H, 8 × CH$_2$), 1.45 (br. s, 12 H, *t*Bu and CH$_3$), 1.60 (br. s, 3 H, CH$_3$), 3.50 (br. s, 1 H, OH), 3.70−4.10 (m, 4 H, C*H*OH, 4-H and 2 × 5-H). − MS (LSIMS, thioglycerol); *m*/*z* (%): 358 (13) [M + H]$^+$, 302 (83) [M + H − isobutene]$^+$, 244 (100), 200 (14), 147 (23), 100 (33) [*t*Boc]$^+$, 57 (93) [*t*Bu]$^+$. − Exact mass (LSIMS, thioglycerol) calculated for $C_{20}H_{40}NO_4$ [M + H]$^+$ 358.2957, found 358.2999.

***tert*-Butyl *N*-[(1*S*,2*R*)-2-Hydroxy-1-(hydroxymethyl)undecyl]carbamate (3). − Method A:** Compound **2** (1.112 g, 3.1102 mmol) was dissolved in MeOH (25 mL). Amberlyst 15 (1.630 g) was added and the heterogeneous mixture was stirred at room temperature for 2 d. After filtration through Celite and concentration of the filtrate in vacuo, the residue was purified by silica gel flash chromatography (MeOH/CH$_2$Cl$_2$, 5:95) to yield **3** as a white solid (987 mg, 79%). − **Method B:** Compound **2** (204 mg, 0.5706 mmol) and *p*-toluenesulfonic acid monohydrate (13 mg, 0.0685 mmol) were dissolved in MeOH (5 mL). The solution was stirred at room temperature for 5 h. The reaction mixture was concentrated in vacuo and the residue was diluted with diethyl ether. The ether solution was washed successively with a saturated NaHCO$_3$ solution and water, dried with MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography (silica, MeOH/CH$_2$Cl$_2$, 5:95) yielded compound **3** as a white solid (138 mg, 76%). − ^{1}H NMR (360 MHz, [D$_6$]DMSO): δ = 0.85 (t, *J* = 6.7 Hz, 3 H, CH$_3$), 1.15−1.25 (m, 16 H, 8 × CH$_2$), 1.40 [s, 9 H, (CH$_3$)$_3$], 3.37−3.45 (m, 3 H, C*H*$_2$OH and 1-H), 3.47−3.55 (m, 1 H, 2-H), 4.36 (t, *J* = 5.4 Hz, 1 H, CH$_2$O*H*), 4.46 (d, *J* = 5.3 Hz, 1 H, 2-OH), 6.29 (d, *J* = 8.9 Hz, 1 H, NH). − ^{13}C NMR (90 MHz, CDCl$_3$): δ = 14.0 (CH$_3$), 22.6,

25.9, 28.3 [C(CH_3)$_3$], 29.2, 29.4, 31.8, 34.4 (alkyl carbon atoms), 54.8 (C-1), 62.5 (CH_2OH), 74.3 (C-2), 79.8 [C(CH$_3$)$_3$], 156.0 (C=O). − MS (LSIMS, thioglycerol); *m*/*z* (%): 318 (42) [M + H]$^+$, 262 (100) [M + H − isobutene]$^+$, 218 (61) [M + H − *t*Boc]$^+$, 200 (19), 57 (20) [*t*Bu]$^+$. − Exact mass (LSIMS, thioglycerol) calculated for $C_{17}H_{36}NO_4$ [M + H]$^+$ 318.2644, found 318.2622.

***tert*-Butyl *N*-{(1*S*,2*R*)-2-Hydroxy-1-[(trityloxy)methyl]undecyl}-carbamate (4):** A solution of **3** (107 mg, 0.3370 mmol), trityl chloride (188 mg, 0.6750 mmol), and 4-(dimethylamino)pyridine (123 mg, 1.0110 mmol) in pyridine (3 mL) was refluxed for 3 h. The mixture was then diluted with ethyl acetate and washed successively with a saturated $NaHCO_3$ solution and brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (silica, EtOAc/pentane, 7:93) afforded **4** as an oil (155 mg, 82%). − ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 0.85 (t, *J* = 6.2 Hz, 3 H, CH_3), 1.20 (br. s, 14 H, 7 × CH_2), 1.45 [s, 9 H, (CH$_3$)$_3$], 1.75 [quint, 2 H, CH_2CH$_2$C(O)], 3.15 (m, 1 H, 1-H), 3.55−3.65 (m, 3 H CH_2OH and 2-H), 4.38 (d, *J* = 5.9 Hz, 1 H, OH), 6.55 (d, *J* = 9.7 Hz, 1 H, NH), 7.23 [t, *J* = 6.8 Hz, 3 H, arom H (*para*)], 7.29 [t, *J* = 7.3 Hz, 6 H, arom H (*meta*)], 7.38 [d, *J* = 7.6 Hz, 6 H, arom H (*ortho*)]. − ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 14.0 (CH_3), 19.9, 22.2, 23.9, 24.8 (alkyl carbon atoms), 28.8 [C(CH_3)$_3$], 31.4, 32.4, 33.0, 33.6 (alkyl carbon atoms), 55.1 (C-1), 63.6 (CH_2OH), 70.1 (C-2), 77.5 [C(CH$_3$)$_3$], 85.8 [C(C$_6$H$_5$)$_3$], 123.9 (arom C), 127.8 (arom C), 128.4 (arom C), 144.2 (C$_{ipso}$), 155.6 (C=O). − MS (LSIMS, thioglycerol/NaOAc); *m*/*z* (%): 584 (6) [M + H + Na]$^+$, 560 (6) [M + H]$^+$, 243 (100) [trityl]$^+$, 165 (20), 105 (8), 57 (12) [*t*Bu]$^+$.

(4*S*,5*R*)-5-Nonyl-4-[(trityloxy)methyl]-1,3-oxazolidin-2-one (5): A solution of **4** (105 mg, 0.1876 mmol) in dry CH_2Cl_2 (4 mL) was added dropwise to a cooled solution (−78 °C) of DAST (75 μL, 0.5628 mmol) in dry CH_2Cl_2 (4 mL). The reaction mixture was warmed to room temperature over 2 h and then mixed with water (4 mL). The organic layer was separated, washed with water, dried with $MgSO_4$, and concentrated. Purification of the residue by flash chromatography (silica, EtOAc/pentane, 2:8) yielded **5** as an oil (80 mg, 88%). − ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 0.85 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.25 (br. s, 14 H, 7 × CH_2), 2.98−3.02 (m, 2 H, CH_2O), 3.51 (q, *J* = 4.9 Hz, 1 H, 4-H), 4.10 (q, *J* = 5.9 Hz, 1 H, 5-H), 7.28 [t, *J* = 7.1 Hz, 3 H, arom H (*para*)], 7.31−7.40 [m, 12 H, arom H (*ortho* and *meta*)], 7.82 (s, 1 H, NH). − ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 14.0 (CH_3), 22.2, 24.1, 28.7, 28.7, 29.0, 31.4, 34.4, 56.4 (C-4), 65.0 (CH_2O), 78.2 (C-5), 86.2 [C(C$_6$H$_5$)$_3$], 127.2 (arom C), 128.0 (arom C), 128.3 (arom C), 143.5 (C$_{ipso}$), 158.2 (C=O). − MS (LSIMS, thioglycerol/NaOAc); *m*/*z* (%): 486 (32) [M + H]$^+$, 243 (100) [trityl]$^+$, 165 (8). − Exact mass (LSIMS, thioglycerol) calculated for $C_{32}H_{40}NO_3$ [M + H]$^+$ 486.3008; found 486.3028.

***tert*-Butyl (4*S*)-4-[(1*S*)-1-Fluorodecyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (6):** A solution of **2** (178 mg, 0.4979 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to a cooled solution (−78 °C) of DAST (198 μL, 1.4937 mmol) in dry CH_2Cl_2 (5 mL). The mixture was allowed to warm to room temperature and stirred overnight. The organic layer was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (silica, EtOAc/hexane, 2.5:97.5) yielded compound **6** as an oil (145 mg, 81%). − ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 0.88 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.25 (m, 16 H, 8 × CH_2), 1.45 (m, 15 H, *t*Bu and 2 × CH_3), 3.85−3.95 (m, 3 H, 2 × 5-H and 4-H), 4.50−4.58 (d, *J* = 12.7 Hz, $^2J_{H,F}$ = 50.5 Hz, 0.5 H, C*H*F), 4.60−4.69 (d, *J* = 12.7 Hz, 0.5 H, C*H*F). − MS (LSIMS, NBA); *m*/*z* (%): 360 (10) [M + H]$^+$, 344 (15), 304 (100) [M + H − isobutene]$^+$, 288 (55), 260 (66) [M + H − *t*Boc]$^+$, 246 (30), 73 (43), 57 (91) [*t*Bu]$^+$. − Exact mass (LSIMS, NBA) calculated for $C_{20}H_{39}FNO_3$ [M + H]$^+$ 360.2914; found 360.2893.

(2*S*,3*S*)-2-Amino-3-fluoro-1-dodecanol (7): A solution of **6** (716 mg, 1.9915 mmol) in trifluoroacetic acid (33 mL) and water (11 mL) was stirred at room temperature for 30 min. Aqueous ammonia solution (33%) was then added until pH = 8−9 with concomitant ice cooling, and the resulting mixture was extracted several times with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (silica, MeOH/CH_2Cl_2, 5:95) yielded the title compound as a white solid (358 mg, 82%). − ^{1}H NMR (500 MHz, CD_3OD): δ = 0.89 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.30 (br. s, 14 H, 7 × CH_2), 1.60−1.70 (m, 2 H, CH_2), 2.88 (m, $^3J_{H,F}$ = 20.0 Hz, 1 H, 2-H), 3.49 (m, 1 H, 1-H$_a$), 3.68 (dd, *J* = 3.8 Hz and 10.6 Hz, 1 H, 1-H$_b$), 4.33−4.38 (m, $^2J_{H,F}$ = 48.5 Hz, 0.5 H, 3-H), 4.43−4.47 (m, 0.5 H, 3-H). − MS (LSIMS, thioglycerol/NBA); *m*/*z* (%): 220 (100) [M + H]$^+$, 91 (6), 57 (9). − Exact mass (LSIMS, thioglycerol/NBA) calculated for $C_{12}H_{27}FNO$ [M + H]$^+$ 220.2077, found 220.2041.

***N*-[(1*S*,2*S*)-2-Fluoro-1-(hydroxymethyl)undecyl]acetamide (8):** To a solution of **7** (270 mg, 1.2309 mmol) in THF (7 mL) was added a 50% aqueous NaOAc solution (7 mL) and acetyl chloride (88 μL, 1.2309 mmol). After completion of the reaction (3 h), the mixture was diluted with THF and brine. The organic phase was separated, washed with water, dried with $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (silica, MeOH/CH_2Cl_2, 4:96) yielded the title compound as a white solid (267 mg, 83%). − ^{1}H NMR (500 MHz, CD_3OD): δ = 0.90 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.25 (br. s, 14 H, 7 × CH_2), 1.55−1.65 (m, 2 H, CH_2), 2.00 [s, 3 H, C(O)CH_3], 3.62−3.69 (m, 2 H, CH_2OH), 3.98−4.03 (m, $^3J_{H,F}$ = 20.4 Hz, 1 H, 1-H), 4.43−4.46 (m, $^2J_{H,F}$ = 48.5 Hz, 0.5 H, 2-H), 4.52−4.56 (m, 0.5 H, 2-H). − ^{13}C NMR (125 MHz, CD_3OD): δ = 14.4 (CH_2CH_3), 22.7, 23.7, 26.3, 30.4, 30.5, 30.6, 32.7, 32.9, 33.1 (alkyl carbon atoms), 55.2 (d, $^2J_{C,F}$ = 23.9 Hz, C-1), 61.2 (d, $^3J_{C,F}$ = 3.9 Hz, CH_2OH), 93.8 (d, $^1J_{C,F}$ = 170.8 Hz, C-2), 173.3 (C=O). − MS (LSIMS, thioglycerol/NBA); *m*/*z* (%): 262 (100) [M + H]$^+$, 220 (7), 137 (7), 91 (8), 60 (19). − Exact mass (LSIMS, thioglycerol/NBA) calculated for $C_{14}H_{29}NO_2F$ [M + H]$^+$ 262.2182; found 262.2151. − $C_{14}H_{28}FNO_2$: calcd. C 64.33, H 10.80, N 5.36; found C 64.06, H 10.67, N 4.83.

***N*-[(1*S*,2*S*)-2-Fluoro-1-(hydroxymethyl)undecyl]hexanamide (9):** Compound **9** was prepared from **7** (68 mg, 0.3100 mmol) and hexanoyl chloride (44 μL, 0.3100 mmol) according to the procedure described for the synthesis of compound **8**. Purification by silica gel flash chromatography (MeOH/CH_2Cl_2, 1:99) yielded **9** as a white solid (87 mg, 88%). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85−0.91 (m, 6 H, 2 × CH_3), 1.25−1.35 (m, 16 H, 8 × CH_2), 1.55−1.65 (m, 6 H, 3 × CH_2), 2.15 (br. s, 1 H, OH), 2.25 [t, *J* = 7.5 Hz, 2 H, C(O)CH_2], 3.72 (dd, *J* = 3.0 Hz and 11.5 Hz, 1 H, H$_a$−CH_2OH), 3.92 (dd, *J* = 4.0 Hz and 11.7 Hz, 1 H, H$_b$−CH_2OH), 4.02−4.12 (m, $^3J_{H,F}$ = 22.0 Hz, 1 H, 1-H), 4.51−4.56 (m, 0.5 H, 2-H), 4.61−4.66 (m, $^2J_{H,F}$ = 49.4 Hz, 0.5 H, 2-H), 6.18 (d, *J* = 8.4 Hz, 1 H, NH). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8 (CH_3), 14.0 (CH_3), 22.2, 22.5, 25.2, 29.1, 29.2, 29.3, 29.4, 31.3, 31.7, 31.9, 36.6 (alkyl carbon atoms), 53.0 (d, $^2J_{C,F}$ = 21.0 Hz, C-1), 61.1 (CH_2OH), 94.8 (d, $^1J_{C,F}$ = 170.3 Hz, C-2), 173.54 (C=O). − MS (LSIMS, thioglycerol); *m*/*z* (%): 318 (100) [M + H]$^+$, 220 (19), 200 (8), 116 (12), 99 (8), 72 (7). − Exact mass (LSIMS, thioglycerol) calculated for $C_{18}H_{37}FNO_2$ [M + H]$^+$ 318.2808, found 318.2810. − $C_{18}H_{36}NO_2F$: calcd. C 68.10, H 11.43, N 4.41; found C 67.99, H 11.43, N 3.79.

***tert*-Butyl (4*S*)-4-[(1*S*)-1-Hydroxydecyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (11):** The same procedure as described for the synthesis of **2** was followed, using 100 mg (0.2829 mmol) of **10** and 8 mg of Pt/C. Purification by flash chromatography (silica, EtOAc/pentane, 12:88) yielded **11** as an oil (93 mg, 92%). − ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.90 (t, 3 H, CH_3), 1.25 (br. s, 15 H, 2 × CH_3 and *t*Bu), 1.45−1.55 (m, 16 H, 8 × CH_2), 2.40 (br. s, 1 H, OH), 3.50 (dd, *J* = 1.8 Hz and 9.9 Hz, 1 H, 4-H), 3.75 (dd, *J* = 1.8 Hz and 11.9 Hz, 1 H, 5-H_a), 3.87−3.94 (m, 1 H, C*H*OH), 4.04 (dd, *J* = 1.9 Hz and 11.9 Hz, 1 H, 5-H_b). − MS (LSIMS, thioglycerol); *m*/*z* (%): 358 (50) [M + H]$^+$, 302 (100) [M + H − isobutene]$^+$, 244 (100), 200 (22), 100 (33) [*t*Boc]$^+$, 57 (88) [*t*Bu]$^+$.

***tert*-Butyl (4*S*)-4-[(1*R*)-1-Fluorodecyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (12):** This compound was prepared as described for compound **6**, using 1.996 g (5.5827 mmol) of **6** and DAST (2.23 mL, 0.0167 mol). Purification by flash chromatography (silica, EtOAc/hexane, 2.5:97.5) yielded pure **12** as a colourless oil (100 mg, 5%). − ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 0.85 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.25 (br. s, 12 H, 6 × CH_2), 1.35−1.55 (m, 19 H, *t*Bu, 2 × CH_3 and 2 × CH_2), 3.85−3.95 (m, 2 H, 2 5-H), 4.01−4.11 (m, 1 H, 4-H), 4.51−4.59 (d, *J* = 16.1 Hz, $^2J_{H,F}$ = 47.2 Hz, 0.5 H, CHF), 4.61−4.69 (d, *J* = 16.1 Hz, 0.5 H, CHF). − MS (LSIMS, NBA); *m*/*z* (%): 304 (25) [M + H − isobutene]$^+$, 284 (24), 244 (16), 133 (23), 57 (100) [*t*Bu]$^+$.

***tert*-Butyl (4*S*)-4-[(1*R*)-1-Fluoro-2-decynyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (13):** This compound was prepared as described for compound **12**, using 543 mg (1.5361 mmol) of **10** and DAST (612 μL, 4.6082 mmol). Purification of the residue by flash chromatography (silica, EtOAc/hexane, 1.5:98.5) yielded **13** as a colourless oil (175 mg, 32% yield). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.24−1.40 (m, 8 H, 4 × CH_2), 1.45−1.62 (m, 17 H, *t*Bu, 2 × CH_3 and CH_2), 2.24 (m, 2 H, C≡C−CH_2), 4.01 (t, *J* = 7.7 Hz, 1 H, 5-H_a), 4.11−4.24 (m, 2 H, 5-H_b and 4-H), 5.25−5.38 (d, $^2J_{H,F}$ = 46.8 Hz, 0.5 H, CHF), 5.43−5.56 (d, $^2J_{H,F}$ = 46.3 Hz, 0.5 H, CHF).

(4*S*,5*S*)-4-(Hydroxymethyl)-5-nonyl-1,3-oxazolidin-2-one (14): A solution of **11** (48 mg, 0.1343 mmol) in CH_2Cl_2 (4 mL) and pyridine (1 mL) was cooled at 0 °C. Trifluoromethanesulfonic anhydride (45 μL, 0.2686 mmol) was added dropwise. TLC monitoring indicated that the reaction was complete in less than 15 min. The reaction mixture was washed with dilute HCl (0.1 N) and water, dried with $MgSO_4$, and concentrated. Purification of the residue by flash chromatography (silica, EtOAc/pentane, 1:9) yielded **14** as a white solid (30 mg, 93%). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.4 Hz, 3 H, CH_3), 1.20−1.40 (br. s, 12 H, 6 × CH_2), 1.48−1.52 (m, 2 H, CH_2), 1.77−1.82 (m, 2 H, CH_2), 3.65−3.69 (m, 2 H, CH_2OH), 3.76−3.85 (ddd, *J* = 3.9 Hz, 6.6 Hz and 10.5 Hz, 1 H, 4-H), 4.58−4.68 (ddd, *J* = 3.7 Hz, 7.6 Hz and 9.7 Hz, 1 H, 5-H), 6.48 (br. s, 1 H, NH, D_2O-exchangeable). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.6, 26.1, 28.8, 29.2, 29.4, 31.8, 56.7 (C-4), 61.1 (CH_2OH), 79.7 (C-5), 160.6 (C=O).

***tert*-Butyl (4*S*)-4-[(1*RS*)-1-Hydroxy-3-phenylpropyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (16 and 17):** To a cooled (−78 °C) solution of crude Garner aldehyde **15** (1.800 g, 7.8508 mmol) in THF (40 mL) was added dropwise 1 M phenethylmagnesium chloride in THF (15.7 mL, 15.7016 mmol). After the addition was complete, the reaction mixture was allowed to warm up to room temperature. The reaction was quenched by the addition of a saturated ammonium chloride solution (157 mL). The aqueous phase was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (silica, EtOAc/pentane, 1:9) yielded an inseparable mixture of epimeric alcohols **16** and **17** as an oil (1.920 g, 73%). − ^{1}H NMR (360 MHz, [D$_6$]DMSO): δ = 1.12−1.45 (m, 15 H, *t*Bu and 2 × CH_3), 1.50−1.70 (m, 2 H, CH_2CH_2C$_6$H$_5$), 2.50−2.60 (m, 1 H, CH_2CH_2C$_6$H$_5$), 2.75−2.80 (m, 1 H, CH_2CH_2C$_6$H$_5$), 3.75−3.90 (m, 3 H, 2 × 5-H and 4-H), 3.95−4.00 (m, 1 H, C*H*OH), 4.85 (t, 1 H, OH, D_2O-exchangeable), 7.13−7.19 [m, 3 H, arom H (*ortho* and *para*)], 7.26 [t, *J* = 7.3 Hz, 2 H, arom H (*meta*)]. − MS (LSIMS, thioglycerol); *m*/*z* (%): 336 (8) [M + H]$^+$, 280 (28) [M + H − isobutene]$^+$, 236 (21) [M − *t*Boc]$^+$, 222 (79), 91 (44), 73 (44), 57 (100) [*t*Bu]$^+$. − Exact mass (LSIMS, thioglycerol) calculated for $C_{19}H_{30}NO_4$ [M + H]$^+$ 336.2175, found 336.2161.

***tert*-Butyl *N*-[(1*S*,2*RS*)-2-Hydroxy-1-hydroxymethyl-4-phenylbutyl]carbamate (18 and 19):** The mixture of **16** + **17** (120 mg, 0.3578 mmol) and *p*-toluenesulfonic acid monohydrate (8 mg, 0.0429 mmol) was dissolved in MeOH (4 mL). The solution was stirred at room temperature for 5 h. The reaction mixture was concentrated in vacuo and the residue was diluted with diethyl ether. The ether solution was washed successively with a saturated $NaHCO_3$ solution and water, dried with $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (silica, MeOH/CH_2Cl_2, 3:97) yielded an inseparable mixture of epimeric alcohols **18** and **19** as a white powder (68 mg, 64%). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.2 [(*C*H$_3$)$_3$C], 31.7 (C-4, *threo*), 32.1 (C-4, *erythro*), 35.7 (C-3), *threo*), 35.9 (C-3, *erythro*), 54.2 (C-1, *threo*), 54.9 (C-1, *erythro*), 62.5 (CH_2OH, *erythro*), 64.8 (CH_2OH, *threo*), 71.7 (C-2, *threo*), 73.2 (C-2, *erythro*), 79.6 [*C*(CH$_3$)$_3$], 125.8 (arom C), 125.8 (arom C), 128.3 (arom C), 141.5 (C$_{ipso}$), 156.4 (C=O). − MS (LSIMS, thioglycerol); *m*/*z* (%): 296 (12) [M + H]$^+$, 288 (16), 240 (51) [M + H − isobutene]$^+$, 196 (100) [M + H − *t*Boc]$^+$, 143 (21), 91 (31), 57 (43) [*t*Bu]$^+$. − Exact mass (LSIMS, thioglycerol) calculated for $C_{16}H_{26}NO_4$ [M + H]$^+$ 296.1862, found 296.1857.

***tert*-Butyl (4*S*)-4-[(1*S*)-1-Fluoro-3-phenylpropyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (20) and (1*R*,7a*S*)-5,5-Dimethyl-1-phenethyldihydro-1*H*-[1,3]oxazolo[3,4-*c*][1,3]oxazol-3-one (21):** Compounds **20** and **21** were prepared from the epimeric mixture **18** + **19** (208 mg, 0.6201 mmol) and DAST (247 μL, 1.8602 mmol) according to the procedure described for the synthesis of **6**. Purification of the residue by flash chromatography (silica, EtOAc/pentane, 3:97, followed by EtOAc/pentane, 15:85) yielded compounds **20** (54 mg, 26%) and **21** (97 mg, 60%), both as oils. − **20:** ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.25 (s, 6 H, 2 × CH_3), 1.40 (m, 9 H, *t*Bu), 1.65−2.00 (m, 2 H, CH_2CH_2C$_6$H$_5$), 2.60−2.68 (m, 1 H, CH_2CH_2C$_6$H$_5$), 2.75−2.83 (m, 1 H, CH_2CH_2C$_6$H$_5$), 3.90−4.00 (m, 3 H, 2 5-H and 4-H), 4.46−4.70 (m, $^2J_{H,F}$ = 45.0 Hz, 1 H, CHF), 7.17−7.23 [m, 3 H, arom H (*ortho* and *para*)], 7.26−7.31 [t, *J* = 7.0 Hz, 2 H, arom H (*meta*)]. − MS (LSIMS, thioglycerol/NBA); *m*/*z* (%): 338 (19) [M + H]$^+$, 282 (100) [M + H − isobutene]$^+$, 266 (26), 238 (50) [M + H − tBoc]$^+$, 222 (26), 133 (30), 91 (21), 57 (52) [*t*Bu]$^+$. − Exact mass (LSIMS, thioglycerol/NBA) calculated for $C_{19}H_{29}NO_3F$ [M + H]$^+$ 338.2131, found 338.2128. − **21:** ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 1.34 (s, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 1.82−1.97 (m, 2 H, CH_2CH_2C$_6$H$_5$), 2.56−2.80 (m, 2 H, CH_2CH_2C$_6$H$_5$), 3.71 (t, *J* = 8.7 Hz, 1 H, 7-H_a), 3.85 (dd, *J* = 6.4 Hz and 8.6 Hz, 1 H, 7-H_b), 4.33−4.44 (dt, *J* = 6.2 Hz and 8.4 Hz, 1 H, 7a-H), 4.58−4.68 (dt, *J* = 5.1 Hz and 8.1 Hz, 1 H, 1-H), 7.20−7.30 (m, 5 H, arom H). − ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 23.3 (CH_3), 28.0 (CH_3), 31.4 (CH_2*C*H$_2$C$_6$H$_5$), 31.8 (*C*H$_2$CH$_2$C$_6$H$_5$), 60.5 (C-7a), 63.2 (C-7), 74.1 (C-1), 93.9 [*C*(CH$_3$)$_2$], 126.3 (arom C), 128.6 (arom C), 141.0 (C$_{ipso}$), 156.6 (C=O).

(2*S*,3*S*)-2-Amino-3-fluoro-5-phenyl-1-pentanol (22): Compound **22** was synthesized from **20** (65 mg, 0.1926 mmol) and trifluoroacetic acid/water (3.3 mL/1.1 mL) according to the procedure described for compound **7**. Purification by flash chromatography (silica, MeOH/CH_2Cl_2, 6:94) yielded the title compound as a colourless oil (29 mg, 76%). − ^{1}H NMR (500 MHz, CD_3OD): δ = 1.90−2.00 (m, 2 H, 2 × 4-H), 2.65−2.72 (m, 1 H, 5-H_a), 2.83−2.89 (m, 1 H, 5-H_b), 2.94 (m, $^3J_{H,F}$ = 20.1 Hz, 1 H, 2-H), 3.50−3.54 (dd, *J* = 6.9 Hz and 11.1 Hz, 1 H, 1-H_a), 3.68−3.71 (dd, *J* = 3.8 Hz and 11.1 Hz, 1 H, 1-H_b), 4.39−4.42 (m, $^2J_{H,F}$ = 48.4 Hz, 0.5 H, 3-H), 4.49−4.53 (m, 0.5 H, 3-H), 7.13−7.15 [m, 1 H, arom H (*para*)], 7.20−7.27 [m, 4 H, arom H (*ortho* and *meta*)]. − MS (LSIMS, thioglycerol); *m*/*z* (%): 198 (40) $[M + H]^+$, 147 (49), 91 (50), 73 (100). − Exact mass (LSIMS, thioglycerol) calculated for $C_{11}H_{17}FNO$ $[M + H]^+$ 198.1294; found 198.1261.

***N*-[(1*S*,2*S*)-2-Fluoro-1-(hydroxymethyl)-4-phenylbutyl]acetamide (23):** The same procedure as described for the synthesis of **8** was followed using **22** (390 mg, 1.9772 mmol) and acetyl chloride (141 μL, 1.9772 mmol). Purification by flash chromatography (silica, MeOH/CH_2Cl_2, 3:97) yielded **23** as a white solid (383 mg, 81%). − ^{1}H NMR (500 MHz, CD_3OD): δ = 1.85−2.00 [m, 5 H, $C(O)CH_3$ and 2 × 3-H), 2.65 (m, 1 H, 4-H_a), 2.85 (m, 1 H, 4-H_b), 3.65 (m, 2 H, CH_2OH), 4.05 (m, 1 H, 1-H), 4.44−4.48 (m, $^2J_{H,F}$ = 48.3 Hz, 0.5 H, 2-H), 4.53−4.58 (m, 0.5 H, 2-H), 7.13−7.19 (m, 3 H, arom H), 7.23−7.27 (m, 2 H, arom H). − ^{13}C NMR (125 MHz, CD_3OD): δ = 22.7 (CH_3), 32.2 (C-4), 34.9 (d, $^2J_{C,F}$ = 20.5 Hz, C-3), 55.1 (d, $^2J_{C,F}$ = 24.5 Hz, C-1), 61.2 (CH_2OH), 92.9 (d, $^1J_{C,F}$ = 171.5 Hz, C-2), 127.0 (arom C), 129.5 (arom C), 142.5 (C_{ipso}), 173.3 (C=O). − MS (LSIMS, thioglycerol); *m*/*z* (%): 240 (21) $[M + H]^+$, 207 (17), 147 (39), 133 (14), 83 (31), 73 (100), 55 (65). − Exact mass (LSIMS, thioglycerol) calculated for $C_{13}H_{19}NO_2F$ $[M + H]^+$ 240.1400; found 240.1400. − $C_{13}H_{18}FNO_2$: calcd. C 65.25, H 7.58, N 5.85; found C 65.13, H 7.57, N 5.53.

***N*-[(1*S*,2*S*)-2-Fluoro-1-(hydroxymethyl)-4-phenylbutyl]hexanamide (24):** The same procedure as described for the synthesis of **9** was followed using **22** (179 mg, 0.9075 mmol) and hexanoyl chloride (127 μL, 0.9075 mmol). Purification by flash chromatography (silica, MeOH/CH_2Cl_2, 2:98) yielded the title compound as a white solid (206 mg, 77%). − ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 0.83 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.18−1.30 (m, 4 H, 2 × CH_2), 1.43−1.53 [m, 2 H, $C(O)CH_2CH_2$], 1.80−1.95 (m, 2 H, 2 × 3-H), 2.05−2.13 [m, 2 H, $C(O)CH_2$], 2.58−2.65 (m, 1 H, 4-H_a), 2.72−2.80 (m, 1 H, 4-H_b), 3.43−3.51 (m, 2 H, CH_2OH), 3.95−4.04 (m, 1 H, 1-H), 4.43−4.48 (m, 0.5 H, 2-H), 4.53−4.58 (m, $^2J_{H,F}$ = 48.6 Hz, 0.5 H, 2-H), 4.75 (t, *J* = 5.45 Hz, 1 H, OH), 7.18 [d, *J* = 7.5 Hz, 3 H, arom H (*ortho* and *para*)], 7.27 [t, *J* = 7.6 Hz, 2 H, arom H (*meta*)], 7.70 (d, *J* = 9.0 Hz, 1 H, NH). − MS (LSIMS, thioglycerol/NBA); *m*/*z* (%): 296 (100) $[M + H]^+$, 198 (44), 147 (28), 91 (49), 73 (73). − Exact mass (LSIMS, thioglycerol) calculated for $C_{17}H_{27}NO_2F$ $[M + H]^+$ 296.2026, found 296.2024. − $C_{17}H_{26}FNO_2$: calcd. C 69.12, H 8.87, N 4.74; found C 68.93, H 8.75, N 4.44.

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