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Sphingosine and clavaminol H derivatives bearing fluorinated chains and their cytotoxic activity

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ABSTRACT

Microwave induced cross-metathesis of perfluoroalkylated propenes with a substituted allyl alcohol is a simple and straightforward method for the synthesis of sphingosine derivatives possessing perfluoroalkyl chains. One of the prepared compounds was converted into the fluorinated clavaminol H derivative and its deacetylated congener. Selected compounds were subjected to preliminary testing for cytotoxic activity on several cancer cell lines.

1. Introduction

The presence of fluorine atoms in a molecule can deeply modify its biological properties. This fact is the underlying strategy for the synthesis of compounds possessing the fluorine atom or trifluoromethyl group in contemporary medicinal chemistry [1–4]. Although the use of compounds bearing longer perfluoroalkyl chains is rather in its infancy, there are several examples that clearly demonstrate their potential applications. Generally, they could be divided into two groups: one bearing additional perfluoroalkylated chains and the other having hydrogen atoms in their own alkyl chain substituted by fluorine (selected examples are displayed in Fig. 1).

The first group encompasses compounds bearing C_2F_5 group such as antiprogestine **I** (ZK 230211) [5], fulvestrant **II** [6], RU58668 **III** [7], substances bearing other perfluoroalkyl groups such as 7α-perfluoroalkylestradiols **IV** (*n*-C_6F_{13} and CF_3 groups) [8], 11β-perfluoroalkylestradiols **V** (*n*-C_6F_{13} [9], *n*-$C_6F_{13}(CH_2)_2$, and *n*-$C_8F_{17}(CH_2)_2$ [10] groups), and 11β isomers of fulvestrant [11]. Recently, 17α-perfluoroalkylestradiols were synthesized as selective ERα and ERβ ligands by our group [12]. Worth of mentioning is also synthesis of perfluoroalkyl ketones **VI** (CF_3, C_2F_5, and *n*-C_3F_7 groups) [13] as inhibitors of group VIA calcium-independent phospholipase A_2 and highly fluorinated amphiphilic MUC1 glycopeptide antigens (*n*-C_8F_{17} group) [14]. The second group is considerably smaller and is currently presented by brassinosteroid derivatives **VII** possessing perfluorinated side-chain instead of the alkyl one. This change had a positive effect on the metabolic stability while preserving the biological activity of the fluorinated compounds [15]. It is worth mentioning that perfluoroalkyl chains, in contrast to alkyl chains, are known to adopt a helical structure due to the electrostatic repulsion of the fluorine atoms in the relative 1,3-positions [16]. This might be another factor accounting for the unique properties of perfluoroalkylated compounds and their biological activity.

In respect to the above mentioned and our interest in synthesis and biological activity of natural compounds possessing fluorinated aliphatic chains instead of alkyl ones [12,15,20], we were interested in the preparation of sphingosines having the fluorinated alkyl chain. Our interest stemmed from the fact that sphingosines are an interesting class of compounds that play the important role in a number of biological processes [17]. Several fluorinated sphingosine derivatives bearing one [18a–d], two [18e], or three [18f] fluorine atoms in various positions have been prepared so far. In most cases fluorine atoms were used as surrogates of other functional groups (e.g. OH) or substitutes for hydrogen atoms in the close vicinity of OH and NH_2 groups. Interestingly, only little has been done to assess their biological activity in a broader scope. Another hitherto unexplored approach to modified sphingosines and their derivatives could be based on substitution of an alkyl chain for a perfluoroalkyl chain, where a

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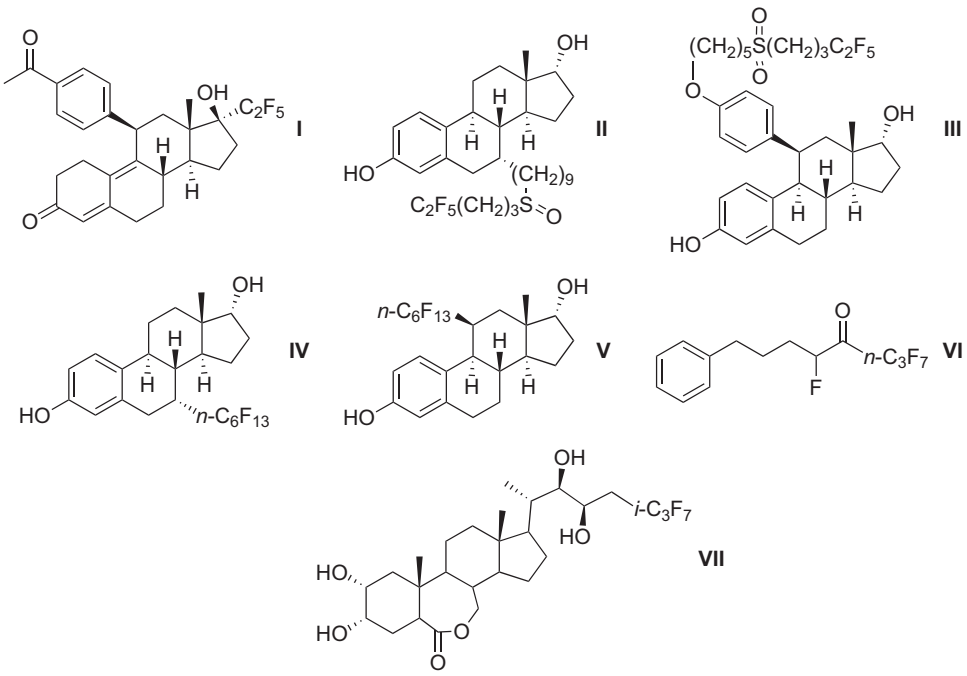


Fig. 1. Selected examples of biologically active compounds bearing perfluoroalkyl chains.

possible change of biological activity could be the result not only of different lipophilicity of the side-chain but also of its different conformation (vide supra).

2. Results and discussion

In this regard we envisioned that perfluoroalkylated sphingosines **1** could be accessed by the cross metathesis reaction of perfluoroalkylpropenes **2** with the properly substituted chiral allyl alcohols **3** (Fig. 2). It has been shown that sphingosine derivatives could be prepared by a versatile cross-metathesis reaction of two suitably substituted terminal alkenes [19]. The feasibility of this approach was supported by our previous results showing that the synthesis of perfluoroalkylated compounds could be based on the cross-metathesis reaction of a terminal alkene with the corresponding perfluoroalkylpropene catalyzed by Hoveyda-Grubbs 2nd generation catalyst (H-G II) [12,16,20].

The starting perfluoroalkylpropenes **2a**–**2d** (**2a**, $R_f = n\text{-}C_5F_{11}$, **2b**, $R_f = n\text{-}C_6F_{13}$, **2c**, $R_f = n\text{-}C_7F_{15}$) were synthesized by the previously reported procedure in good yields [20]. The synthesis of allyl alcohol **3a** proved to be a rather tedious task. Although there is a procedure for synthesis of **3a** based on diastereoselective aldol condensation [21], we opted for the 4 steps procedure using commercially available *N*-Boc-L-serine as the starting compound because it seemed to be a simpler pathway [19]. Despite the fact that we duly followed the described procedure, the isolated yields of **5** did not exceed 27%, which was three times lower than the reported yield (92%). Upon extensive experimentation, we found that the major product of the addition of vinylmagnesium bromide to the Weinreb amide, was β-aminoketone **4**, which was the product of conjugate addition of Me(MeO)NMgBr, liberated during the course of the reaction, to the formed α,β-unsaturated ketone **5** (Scheme 1, Method A).

This forced us to look for a shorter and reproducible method for the preparation of **3**. We found that the reaction of *N*-Boc-L-serine **6** with *n*-BuLi followed by the reaction with vinylmagnesium bromide provided vinyl ketone **7** in 40% yield reproducibly (Scheme 1, Method B). Its subsequent reduction with lithium[-tri-(*tert*-butoxy)aluminum]hydride gave rise selectively to the *N*-Boc protected diol **3b** in isolated 90% yield. In addition, **3c** was prepared from **3a** by simple silylation reaction in 96% yield and **3d** was prepared in 83% yield from **3b**, using Amberlyst 15.

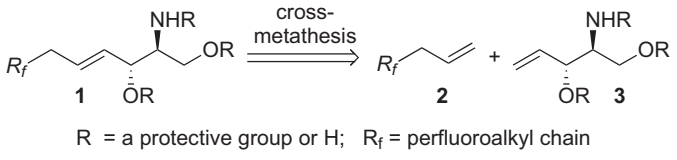
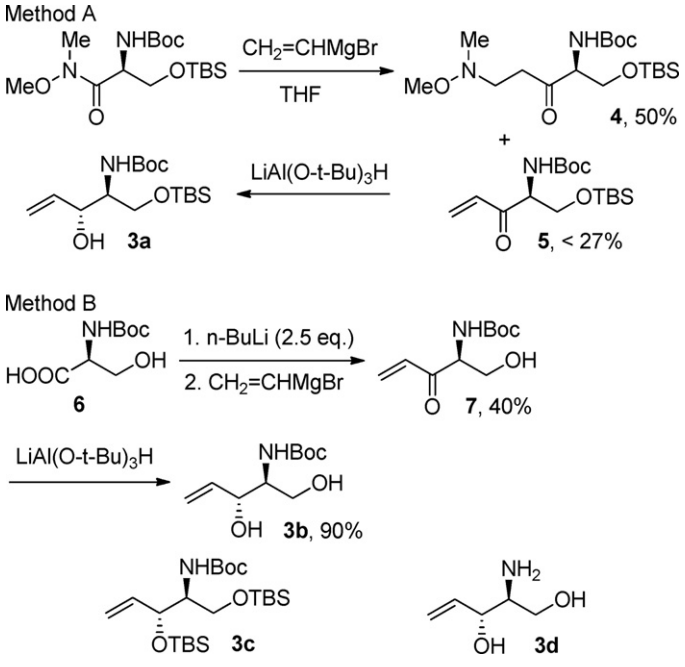


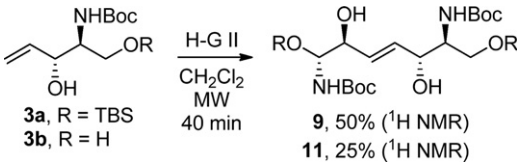
Fig. 2. Retrosynthesis of perfluoroalkylated sphingosines **1**.



Scheme 1. Synthesis of **3a** and **3b**.

The initial cross-metathesis experiments were run under thermal conditions (H-G II – 10 mol%, CH_2Cl_2, T = 42 °C, perfluoroalkylpropene – 4 equiv, 48 h) with **3a**. However, only low conversions of the starting material to the corresponding products were observed (isolated yields were with the range of 12–23%) and the starting material remained mostly unreacted. Addition of fluorinated solvents such as octafluorotoluene, which was shown to have a positive effect on the course of cross-metathesis reaction [22,23], or sequential addition of additional amounts of the catalyst did not result in better overall yields. Nonetheless, after much experimental work, reasonable conversions of the starting material to the desired products were achieved when the reactions were carried out under microwave irradiation [24] in a microwave reactor and the catalyst together with the perfluoroalkylpropenes were added in two portions during the course of the reaction. The results of cross-metathesis reaction of **3a** are summarized in Table 1 (Entries 1–3). The products with the protected terminal hydroxy groups **8a**–**8c** were obtained in 38, 46, and 47% isolated yields, respectively (Table 1, Entries 1–3). The formation of dimer **9** was observed in 7–15% yield range (Scheme 2). Although TLC analyses indicated the presence of other side-products, they were not formed in substantial amounts. Attempts to isolate them did not provide analytically pure samples to allow their structural identifications and characterization.

In order to assess the scope of the reaction with other derivatives **3**, the reactions with **3b** were carried out (Table 1, Entries 4–6). The *N*-Boc protected products **10a**–**10c** were isolated in 34, 36, and 32% yields, respectively (Table 1, Entries 4–6). Gratifyingly, the formation of dimer **11** was not observed. As far as the reactions with compounds **3c** and **3d** are concerned, they did not enter the cross-metathesis reaction at all and the starting material was recovered.



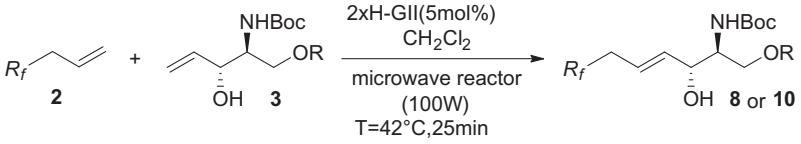
Scheme 2. Homodimerization of **3a** and **3b** to **9** and **11**.

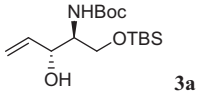
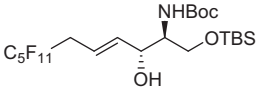
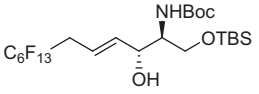
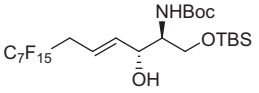
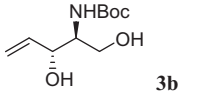
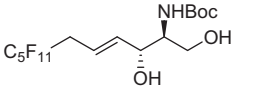
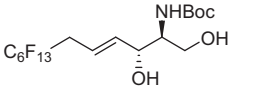
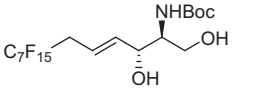
With respect to the above mentioned results, the propensity of **3a** and **3b** to homometathesis under the used reaction conditions was evaluated (Scheme 2). The obtained results clearly showed that **3b** succumbed to homometathesis less readily than **3a** indicating that it might be a better reaction partner for the selective cross-metathesis reaction with perfluoroalkylpropenes.

It should be also noted that homodimers of **2**, unlike in previous cases [20a], did not react with **3a** or **3b**. This result explained necessity for the introduction of the additional amounts of **2** into the reaction mixture during the course of the reaction. Cross-metathesis of **3a** or **3b** with perfluorohexylethene [25] was run as well. However, it proceeded only with low conversion of the starting material giving rise to a complex reaction mixture in which the expected products were not detected. Finally, the *N*-Boc protected derivatives **10a**–**10c** were converted into the sphingosine derivatives **12a**–**12c** after treatment with trifluoroacetic acid in dichloromethane in 58, 68, and 87% yields, respectively (Scheme 3) [26].

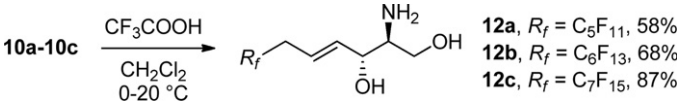
Since the structure of the prepared perfluorinated sphingosine derivative **12b** had the same carbon chain length as clavaminol H [27a], it was decided to convert it to the fluorinated clavaminol H derivative **13** and its deacetylated congener **14** (Scheme 4). Simple hydrogenation of **12b**–**Ac** (prepared by peracetylation of **12b** with

Table 1
Cross-metathesis of **2** with **3** to sphingosine derivatives **8** or **10**.

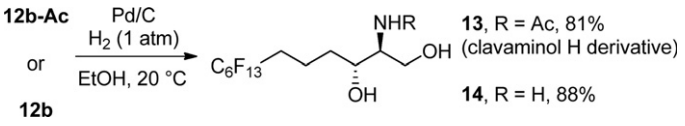


Entry	2	Allyl alcohol 3	Product	8 or 10	Yield (%)[a,b]	9 or 11	Yield (%)[b]
1	**2a**	 **3a**		**8a**	50 (38)	**9**	14
2	**2b**			**8b**	65 (46)	**9**	15
3	**2c**			**8c**	50 (47)	**9**	7
4	**2a**	 **3b**		**10a**	50 (34)	**11**	0
5	**2b**			**10b**	60 (36)	**11**	0
6	**2c**			**10c**	50 (32)	**11**	0

[a] ^{1}H NMR yields mesitylene as internal standard.
[b] Isolated yields in parentheses.



Scheme 3. Deprotection of **10a–10c** to **12a–12c**.



Scheme 4. Synthesis of clavaminol H derivatives.

Ac_2O in pyridine followed by selective removal of the acetyl group from the hydroxyl groups under basic conditions with MeONa/MeOH) or **12b** on Pd/C furnished **13** or **14** in 81 or 88% yield, respectively.

Since clavaminols [27] and sphingosines [28] are known to exhibit cytotoxic activity against various cancer cell lines, the preliminary testing of the selected perfluoroalkylated sphingosine derivatives was undertaken [29]. As model compounds were selected the sphingosine derivative **12c**, the fluorinated clavaminol H derivative **13** and its hydrolyzed congener **14**. The selected compounds were tested for the cytotoxic activity in four different cell lines: human promyelocytic leukemia HL60 cells (ATCC CCL 240), human cervix carcinoma HeLa S3 cells (ATCC CCL 2.2), human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119), and human hepatocellular carcinoma cells (HepG2) (Table 2).

Interestingly, compound **12c** showed to be active against all cell cultures (GIC50 = 6.51, 1.97, 1.19, and 10.93 mM against HL60, HeLa S3, CCRF-CEM, and HepG2 cell-lines, respectively). Compound **13** was not active at all, this result was rather expected because similar data were obtained also for clavaminol H. Compound **14** possessing free amino group showed to be active against three cell cultures (GIC50 = 3.02, 2.04, and 2.24 mM against HL60, HeLa S3, and CCRF-CEM, respectively) and inactive against HepG2 cell-lines. The detection of apoptotic/necrotic cells was evaluated by flow cytometry using Annexin V-FITC apoptosis kit (Clontech Laboratories Inc.). Although the activity of the prepared compounds **12c** and **14** possessing perfluoroalkylated chains were within the same range of deacetylated clavaminol H, its mechanism was different. It was reported that the deacetylated clavaminol H induces apoptosis [27], whereas compounds **12c** and **14** induced necrosis. Although highly speculative, this difference in the activity mode could perhaps be attributed to a different conformational geometry of the lipophilic chain in perfluoroalkylated compounds. Conformational rigidity, arising from the helical structure of a perfluoroalkylated chain [16], could thus result in a different interaction on a cell membrane inducing its irrreversible destruction leading to necrosis. A different level of the cell wall penetration by compounds bearing various perfluoroalkylated chains have been reported [30]. In addition, as far as a comparison of these results with biological activity of another biologically active compounds and their polyfluorinated analogs is concerned, there is currently no available data. To the best of our knowledge, such pairs have not been prepared and studied yet. The only exception is the synthesis of a brassinosteroid with polyfluorinated side chain instead of the alkyl one reported by this laboratory [15]. The comparison of its activity in some essays showed similar reactivity as for the natural compound, but no studies regarding the mechanism were carried out.

Table 2
Cytotoxic activity test.

Compound	GIC50[a]	$mmol^{-1}$ [b]		
	HL60	HeLaS3	CCRF-CEM	HepG2
12c	6.51 ± 0.28	1.97 ± 0.04	1.19 ± 0.28	10.93 ± 1.37
13	NA[c]	NA[c]	NA[c]	NA[c]
14	3.02 ± 0.36	2.04 ± 0.05	2.24 ± 0.358	>20

[a] Growth inhibition concentration.
[b] XTT based colorimetric assay of cell proliferation (Roche).
[c] NA – not active.

3. Conclusions

In summary, we have shown that a simple pathway for the synthesis of sphingosine analogues possessing perfluoroalkylated chains could be based on cross-metathesis of perfluoroalkylpropenes with suitable terminal alkenes. The crucial moment of this procedure is the use of microwave irradiation that allowed the reaction to provide the desired products with good selectivity and reasonable isolated yields. The cytotoxic activity test showed that the prepared compounds had interesting biological activity. Their different mode of activity in comparison with the deacylated natural claviminol, i.e. apoptosis vs. necrosis, might provide impetus for further studies on the properties of other highly fluorinated analogues of biologically active compounds.

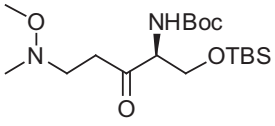
4. Experimental

4.1. General description of materials and methods

All solvents were used as obtained unless otherwise noted. THF was distilled from sodium and benzophenone. Perfluoroalkylated propenes **2a**, **2b**, and **2c** [31], *N*-Boc-1-(*O*-TBS)-(2*S*,3*R*)-2-amino-pent-4-en-3-ol **3a** [19a] were prepared according to the previously reported procedure. All other reagents were obtained from commercial sources. Metathesis reactions were carried out under an argon atmosphere using the CEM Discover microwave reactor. The NMR spectra were measured on Bruker AVANCE 400 and 500 instruments (^1H at 400 or 500 MHz; ^{13}C at 100.6 or 125.7, and ^{19}F NMR at 470.3 MHz) as solutions in MeOD, $CDCl_3$ or CD_3COCD_3 at 27 °C unless otherwise noted. Chemical shifts are given in δ-scale (^1H NMR spectra were referenced to TMS as an internal standard, ^{13}C NMR spectra to $CDCl_3$ at δ 77.0, and ^{19}F NMR to C_6F_6 δ −163.0), coupling constants *J* are given in Hz. Melting points (uncorrected) were determined using a Kofler apparatus. Infrared spectra were recorded as $CHCl_3$ solutions or as KBr tablets and are reported in wave numbers (cm^{-1}). Fluka 60 silica gel or fluorinated silica gel Fluoro*Flash* 40 μm was used for flash chromatography. TLC was performed on silica gel 60 FB_{254B}-coated aluminum sheets or Fluoro*Flash* HPTLC FB_{254B}-coated glass sheets and spots were detected by UV illumination and spraying with ninhydrin solution. Purity of the prepared compounds was determined from ^1H NMR spectra.

4.2. Synthesis of the starting materials ***3a–3d***

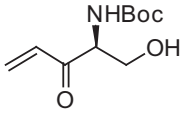
4.2.1. N-*Boc-1-(O-TBS)-(2S)-2-amino-1-hydroxy-5-[methoxy(methyl)amino]pentan-3-one (**4**)*



4 g of ketone **4** (55%) was isolated from the reaction of Weinreb amide (6.9 g, 19 mmol) with vinylmagnesium bromide as the side product during the preparation of **3a** according to the previously reported procedure [19a] as a pale yellow oil: $[\alpha]_D$ +31.6 (*c* 0.348, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.86 (s, 9H), 1.45

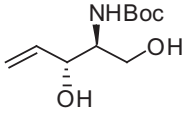
(s, 9H), 2.57 (s, 3H), 2.83 (m, 2H), 2.92 (m, 2H), 3.46 (s, 2H), 3.84 (dd, J = 10.4, 4.1 Hz, 1H), 4.08 (dd, J = 10.5, 3.3 Hz, 1H), 4.32 (m, 2H), 5.51 (bd, J = 7.2 Hz, NH); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ −5.64, 18.12, 25.71, 28.30, 37.90, 44.96, 54.73, 59.89, 61.29, 63.24, 79.68, 155.26, 206.67; IR ($CHCl_3$) ν 3435, 2982, 2896, 1705, 1472, 1464, 1446, 1408, 1393, 1380, 1368, 1234, 1256, 1006, 939, 839 cm^{-1}; HR-MS (ESI) calcd. for $C_{18}H_{39}O_5N_2Si$ [M+H$^+$] 391.26228, found 391.26217. R_f (2/1 hexane/EtOAc) = 0.7.

4.2.2. N-*Boc-(2S)-2-amino-3-oxo-pent-4-en-1-ol* (**7**)



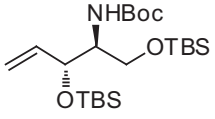
The solution of *N*-Boc-L-serine **6** (4.3 g, 21 mmol) in THF (80 mL) was cooled to −78 °C and then *n*-BuLi in hexane (33.2 mL, 53 mmol) was added dropwise under argon atmosphere [32]. After the reaction mixture was stirred at the same temperature for 15 min, vinyl magnesium bromide in THF (78 mL, 78 mmol) was added over 30 min. The resulting mixture was then allowed to come to room temperature and stirred overnight. The reaction mixture was poured into 1 M H_3PO_4 (0 °C, 100 mL) and extracted with EtOAc (3 × 50 mL). The organic extracts were combined, washed with saturated aqueous $NaHCO_3$ (1 × 100 mL) and saturated aqueous NaCl (1 × 100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography on silica gel (3/1 hexane/EtOAc) furnished 1.81 g (40%) of the title compound as a pale yellow oil: $[\alpha]_D$ +62.5 (c 0.128, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.86 (bs, OH), 3.88–3.96 (m, 2H), 4.67 (m, 1H), 5.72 (bs, NH), 5.93 (bd, J = 10.6 Hz, 1H), 6.44 (dd, J = 17.5, 1.1 Hz, 1H), 6.58 (dd, J = 17.5, 10.6 Hz, 1H); ^{13}C NMR (150.9 MHz, CD_3COCD_3) δ 28.27, 59.87, 63.65, 80.39, 130.73, 132.74, 156.05, 196.44; IR ($CHCl_3$) ν 3620, 3600, 3429, 2982, 1699, 1615, 1497, 1407, 1394, 1369, 1250, 1057, 983, 970, 935, 860 cm^{-1}; HR-MS (ESI) calcd. for $C_{10}H_{17}NO_4Na$ [M+Na$^+$] 238,10498 found 238.10494. R_f (1/1 hexane/EtOAc) = 0.5.

4.2.3. N-*Boc-(2S,3R)-2-amino-pent-4-en-1,3-diol* (**3b**)



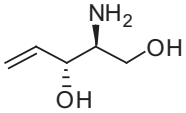
To a solution of **7** (1.81 g, 8.4 mmol) in ethanol (40 mL) was added lithium tri-*tert*-butoxyaluminiumhydride (5.1 g, 20 mmol) at −78 °C. After the reaction mixture was stirred at the same temperature for 4 h, acetone was added (20 mL), solvents were removed under reduced pressure and the residue was extracted with EtOAc (3 × 50 mL). The organic extracts were combined, washed with saturated aqueous NaCl (1 × 100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography on silica gel (2/1 hexane/EtOAc) furnished 1.63 g (90%) of the title compound as a pale yellow oil. Spectral characteristics were in agreement with the previously reported data [19a].

4.2.4. N-*Boc-1,3-bis(O-TBS)-(2S,3R)-4E-2-amino-pent-4-en-1,3-diol* (**3c**)



To a solution of **3a** (416 mg, 1.3 mmol) in DMF (15 mL) was added imidazole (188 mg, 2.8 mmol) and TBDMSCl (388 mg, 2.6 mmol) at 0 °C. The reaction mixture was allowed to come to room temperature and stirred for additional 2 h. Then ice was added and the reaction mixture was extracted with diethyl ether (3 × 20 mL). The organic extracts were combined, washed with saturated aqueous NaCl (1 × 20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica gel (3/1 hexane/EtOAc) furnished 540 mg (96%) of the title compound as a pale yellow oil: $[\alpha]_D$ +3.1 (c 0.481, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02–0.06 (m, 12H), 0.89, 0.90 (s, 2 × 9H), 1.42 (s, 9H), 3.58–3.66 (m, 2H), 3.77 (m, 1H), 4.29 (m, 1H), 4.63 (bd, J = 8.1 Hz, NH), 5.14 (dm, J = 10.3 Hz, 1H), 5.24 (dt, J = 17.2, 1.6 Hz, 1H), 5.85 (ddd, J = 17.2, 10.3, 6.3 Hz, 1H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ −5.52, −5.36, −5.06, −4.39, 18.10, 18.19, 25.80, 25.86, 28.37, 56.40, 61.28, 73.04, 78.90, 116.12, 138.27, 155.61; IR ($CHCl_3$) ν 3450, 3082, 2982, 2957, 2896, 1708, 1645, 1501, 1472, 1464, 1420, 1404, 1392, 1367, 1255, 1171, 1090, 1006, 994, 937, 929, 838, 681 cm^{-1}; HR-MS (ESI) calcd. for $C_{22}H_{47}NO_4Si_2Na$ [M+Na$^+$] 468,29358 found 468.29348. R_f (7/1 hexane/EtOAc) = 0.65.

4.2.5. (2S,3R)-4E-*2-amino-pent-4-en-1,3-diol* (**3d**)



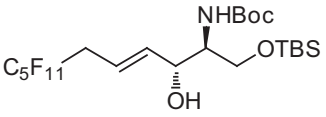
To a solution of **3b** (137 mg, 0.63 mmol) in CH_2Cl_2 (5 mL) was added Amberlyst 15 (350 mg) at 0 °C. After the resulting mixture was stirred at the same temperature for 1 h, CH_2Cl_2 was evaporated and the residue was dissolved in 7 N NH_3 in MeOH (2 mL) and stirred for 1 h at 0 °C. Then Amberlyst 15 was filtered, solvent was removed under reduced pressure and column chromatography of the residue on silica gel (1/0–1/1 $CHCl_3$/MeOH) furnished 61 mg (83%) of the title compound as a pale yellow oil: $[\alpha]_D$ +9.3 (c 0.322, MeOH); ^{1}H NMR (500 MHz, CD_3COCD_3) δ 3.38 (m, 1H), 3.58 (m, 1H), 3.72 (m, 1H), 4.20 (tt, J = 5.1, 1.7 Hz, 1H), 5.07 (ddd, J = 10.6, 1.9, 1.5 Hz, 1H), 5.31 (dt, J = 17.3, 1.9 Hz, 1H), 5.94 (ddd, J = 17.2, 10.6, 5.0 Hz, 1H); ^{13}C NMR (150.9 MHz, CD_3COCD_3) δ 63.07, 66.46, 72.27, 114.53, 140.63; IR (CH_3CN) ν 3518, 3398, 3085, 3016, 2982, 2940, 2880, 2606, 1713, 1680, 1642, 1600, 1428, 1038, 998, 931 cm^{-1}; HR-MS (ESI) calcd. for $C_5H_{10}NO_2$ [M+H$^+$] 116,07170 found 116.07140. R_f (1/1 $CHCl_3$/MeOH) = 0.75.

4.3. Cross-metathesis reactions

4.3.1. General procedure for cross-metathesis of alkene 3a with (perfluoroalkyl)propenes **2a–2c**

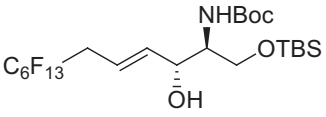
To a mixture of alkene **3a** (202 mg, 0.64 mmol), (perfluoroalkyl)propenes **2a–2c** (397 mg, 461 mg, or 525 mg, 1.3 mmol) and mesitylene (77 mg, 0.64 mmol, as an internal standard) in CH_2Cl_2 (10 mL) was added Hoveyda-Grubbs 2nd generation catalyst (20 mg, 0.032 mmol) under an argon atmosphere. The resulting solution was stirred at 42 °C for 20 min under microwave irradiation (100 W). After that another portion of (perfluoroalkyl)propenes **2a–2c** (198 mg, 230 mg or 262 mg, 0.64 mmol) and Hoveyda-Grubbs 2nd generation catalyst (20 mg, 0.032 mmol) were added and the solution was stirred at 42 °C for 20 min under microwave irradiation (100 W) again. Volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (20/1–10/1 hexane/EtOAc) followed by chromatography on FluoroFlash silica 40 μm, 60 A (2/1 MeOH/H_2O) furnished the corresponding products.

4.3.2. N-*Boc-1-(*O-*TBS)-(*2S,3R*)-4*E*-2-amino-7,7,8,8,9,9,10,10,11,11,11-undecafluoroundec-4-en-3-diol (**8a**)*



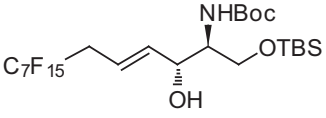
Isolation furnished 150 mg (38%) of the title compound as a pale yellow oil: $[\alpha]_D$ +8.4 (*c* 0.119, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06, 0.07 (s, 2 × 3H), 0.90, 1.45 (s, 2 × 9H), 2.88 (m, 2H), 3.64 (m, 1H), 3.76 (dd, *J* = 10.5, 3.2 Hz, 1H), 3.91 (dd, *J* = 10.5, 2.9 Hz, 1H), 4.31 (m, 1H), 5.25 (bd, *J* = 8.2 Hz, NH), 5.78–5.87 (m, 2H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ −5.82, 18.06, 25.71, 28.32, 34.42 (t, J^{C-F} = 22.8 Hz), 53.99, 63.43, 74.17, 79.76, 118.35, 138.12, 155.87; IR ($CHCl_3$) ν 3612, 3446, 2980, 2901, 1705, 1498, 1472, 1465, 1410, 1393, 1368, 1352, 1277, 1259, 1241, 1170, 1142, 1105, 974, 839, 711, 703, 533 cm^{-1}; HR-MS (ESI) calcd. for $C_{22}H_{34}F_{11}NO_4SiNa$ [M+Na$^+$] 636.1974, found 636.1973. R_f (3/1 hexane/EtOAc) = 0.7.

4.3.3. N-*Boc-1-(*O-*TBS)-(*2S,3R*)-4*E*-2-amino-7,7,8,8,9,9,10,10,11,11,12,12,12-tridecafluorodo-dec-4-en-3-diol (**8b**)*



Isolation furnished 195 mg (46%) of the title compound as a pale yellow oil: $[\alpha]_D$ +4.9 (*c* 0.081, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06, 0.07 (s, 2 × 3H), 0.90, 1.45 (s, 2 × 9H), 2.88 (btd, *J* = 18.1, 5.7 Hz, 2H), 3.65 (m, 1H), 3.69 (m, OH), 3.76 (dd, *J* = 10.5, 2.9 Hz, 1H), 3.91 (dd, *J* = 10.5, 3.0 Hz, 1H), 4.31 (m, 1H), 5.24 (bd, *J* = 8.1 Hz, NH), 5.75–5.90 (m, 2H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ −5.85, −5.81, 18.03, 25.68, 28.28, 34.41 (t, J^{C-F} = 22.5 Hz), 54.08, 63.34, 74.05, 79.70, 118.33 (t, J^{C-F} = 4.4 Hz), 138.12, 155.86; IR ($CHCl_3$) 3616, 3490, 3446, 2980, 2957, 2931, 2904, 2859, 1705, 1499, 1471, 1465, 1458, 1409, 1393, 1368, 1351, 1275, 1260, 1243, 1169, 1145, 1120, 1005, 974, 940, 839, 707, 699, 532 cm^{-1}; HR-MS (ESI) calcd. for $C_{23}H_{34}F_{13}NO_4SiNa$ [M+Na$^+$] 686.1942, found 686.1947. R_f (3/1 hexane/EtOAc) = 0.7.

4.3.4. N-*Boc-1-(*O-*TBS)-(*2S,3R*)-4*E*-2-amino-7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-pentadeca-fluorotridec-4-en-3-diol (**8c**)*

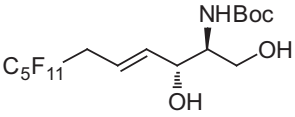


Isolation furnished 213 mg (47%) of the title compound as a pale yellow oil: $[\alpha]_D$ 0 (*c* 0.219, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06, 0.08 (s, 2 × 3H), 0.90, 1.45 (s, 2 × 9H), 2.89 (btd, *J* = 18.3, 5.6 Hz, 2H), 3.65 (m, 1H), 3.76 (m, 1H), 3.91 (m, 1H), 4.31 (m, 1H), 5.25 (bd, *J* = 7.8 Hz, NH), 5.75–5.90 (m, 2H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ −5.84, −5.79, 18.05, 25.69, 28.29, 34.44 (t, J^{C-F} = 22.6 Hz), 54.06, 63.37, 74.08, 79.70, 118.34 (t, J^{C-F} = 4.3 Hz), 138.11, 155.87; IR ($CHCl_3$) 3617, 3446, 2980, 2902, 1706, 1499, 1471, 1465, 1410, 1393, 1368, 1352, 1278, 1259, 1243, 1169, 1150, 1142, 1130, 1098, 975, 839, 709, 701, 531 cm^{-1}; HR-MS (ESI) calcd. for $C_{24}H_{34}F_{15}NO_4$-SiNa [M+Na$^+$] 736.1910, found 736.1909. R_f (3/1 hexane/EtOAc) = 0.7.

*4.3.5. General procedure for cross-metathesis of alkene 3b with (perfluoroalkyl)propenes **2a–2c***

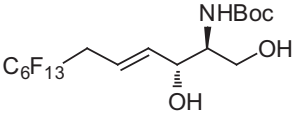
To a mixture of alkene **3b** (139 mg, 0.64 mmol), (perfluoroalkyl)propenes **2a–2c** (397 mg, 461 mg, or 525 mg, 1.3 mmol) and mesitylene (77 mg, 0.64 mmol, as an internal standard) in CH_2Cl_2 (10 mL) was added Hoveyda-Grubbs 2nd generation catalyst (20 mg, 0.032 mmol) under argon atmosphere. The resulting solution was stirred at 42 °C for 20 min under microwave irradiation (100 W). After that another portion of (perfluoroalkyl)propenes **2a–2c** (198 mg, 230 mg or 262 mg, 0.64 mmol) and Hoveyda-Grubbs 2nd generation catalyst (20 mg, 0.032 mmol) were added and the solution was stirred at 42 °C for 20 min under microwave irradiation (100 W) again. Volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (3/1 hexane/EtOAc) followed by chromatography on FluoroFlash silica 40 μm, 60 A (4/3 MeOH/H_2O) furnished the corresponding products.

4.3.6. N-*Boc-(*2S,3R*)-4*E*-2-amino-7,7,8,8,9,9,10,10,11,11,11-undecafluoroundec-4-en-1,3-diol (**10a**)*



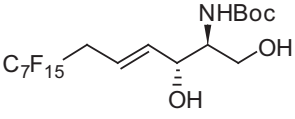
Isolation furnished 107 mg (34%) of the title compound as a pale yellow oil: $[\alpha]_D$ 0 (*c* 0.390, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.89 (m, 2H), 3.65 (bs, 1H), 3.74 (dd, *J* = 11.3, 3.7 Hz, 1H), 3.92 (dd, *J* = 11.3, 3.7 Hz, 1H), 4.42 (m, 1H), 5.31 (bm, NH), 5.78–5.88 (m, 2H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 28.29, 34.42 (t, J^{C-F} = 22.5 Hz), 54.95, 62.44, 73.95, 80.06, 119.14, 137.54; IR ($CHCl_3$) 3617, 3450, 3441, 2982, 2931, 2856, 1704, 1500, 1468, 1456, 1393, 1369, 1351, 1243, 1168, 1150, 1130, 1087, 1057, 976, 708, 701, 531 cm^{-1}; HR-MS (ESI) calcd. for $C_{16}H_{20}F_{11}NO_4Na$ [M+Na$^+$] 522.11089, found 522.11096. R_f (1/1 hexane/EtOAc) = 0.5.

4.3.7. N-*Boc-(*2S,3R*)-4*E*-2-amino-7,7,8,8,9,9,10,10,11,11,12,12,12-tridecafluorododec-4-en-1,3-diol (**10b**)*



Isolation furnished 126 mg (36%) of the title compound as a pale yellow oil: $[\alpha]_D$ 0 (*c* 0.313, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.89 (m, 2H), 3.65 (bs, 1H), 3.74 (dd, *J* = 11.3, 3.7 Hz, 1H), 3.92 (dd, *J* = 11.3, 3.7 Hz, 1H), 4.42 (m, 1H), 5.31 (bm, NH), 5.78–5.88 (m, 2H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 28.29, 34.44 (t, J^{C-F} = 22.7 Hz), 54.95, 62.44, 73.96, 80.07, 119.15, 137.54; IR ($CHCl_3$) 3616, 3450, 3441, 2982, 2931, 2856, 1705, 1500, 1468, 1456, 1393, 1368, 1352, 1241, 1169, 1142, 1130, 1089, 1057, 975, 711, 704, 533 cm^{-1}; HR-MS (ESI) calcd. for $C_{17}H_{20}F_{13}NO_4Na$ [M+Na$^+$] 572.10770, found 572.10778. R_f (1/1 hexane/EtOAc) = 0.5.

4.3.8. N-*Boc-(*2S,3R*)-4*E*-2-amino-7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-pentadecafluorotridec-4-en-1,3-diol (**10c**)*



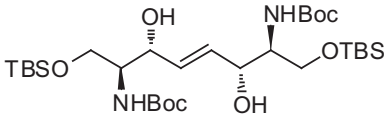
Isolation furnished 124 mg (32%) of the title compound as a pale yellow oil: $[\alpha]_D$ 0 (*c* 0.408, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45

(s, 9H), 2.89 (m, 2H), 3.65 (bs, 1H), 3.74 (dd, J = 11.3, 3.6 Hz, 1H), 3.92 (dd, J = 11.4, 3.7 Hz, 1H), 4.42 (m, 1H), 5.31 (bm, NH), 5.78–5.88 (m, 2H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 28.29, 34.44 (t, J^{C-F} = 22.4 Hz), 54.96, 62.45, 73.95, 80.11, 119.15, 137.54; IR ($CHCl_3$) 3617, 3450, 3441, 2982, 2932, 2856, 1704, 1500, 1468, 1456, 1393, 1369, 1350, 1243, 1168, 1146, 1122, 1091, 1057, 975, 707, 699, 532 cm^{-1}; HR-MS (ESI) calcd. for $C_{18}H_{20}F_{15}NO_4Na$ [M+Na$^+$] 622.10450, found 622.10461. R_f (1/1 hexane/EtOAc) = 0.5.

*4.3.9. General procedure for homometathesis of **3a** and **3b***

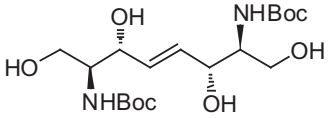
To a mixture of alkene **3a** or **3b** (202 or 139 mg, 0.64 mmol) and mesitylene (77 mg, 0.64 mmol, as an internal standard) in CH_2Cl_2 (10 mL) was added Hoveyda-Grubbs 2nd generation catalyst (20 mg, 0.032 mmol) under argon atmosphere. The resulting solution was stirred at 42 °C for 20 min under microwave irradiation (100 W). After that another portion of Hoveyda-Grubbs 2nd generation catalyst (20 mg, 0.032 mmol) was added and the solution was stirred at 42 °C for 20 min under microwave irradiation (100 W) again. Volatiles were removed under reduced pressure and column chromatography of the residue on silica gel furnished the corresponding products.

*4.3.10. Bis(*N*-Boc)-1,8-bis(*O*-TBS)-(*2R,3S,6R,7S*)-*E*-2,7-amino-oct-4-en-1,3,6,8-tetraol (**9**)*



Column chromatography of the residue (5/1 hexane/EtOAc) furnished 121 mg (30%) of the title compound as a pale yellow oil: $[\alpha]_D$ +15.4 (c 0.182, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07, 0.08 (s, 2 × 3H), 0.90, 1.45 (s, 2 × 18H), 3.62 (m, 2H), 3.78 (m, 2H), 3.92 (dd, J = 10.5, 3.0 Hz, 2H), 4.31 (bs, 2H), 5.27 (bd, J = 7.8 Hz, NH), 5.89 (m, 2H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ −5.64, −5.60, 18.03, 25.76, 28.34, 54.36, 63.33, 73.97, 79.60, 131.32, 155.78; IR ($CHCl_3$) ν 3609, 3490, 3446, 2981, 2956, 2899, 1705, 1498, 1472, 1410, 1393, 1368, 1258, 1240, 1168, 1096, 1063, 1066, 973, 939, 855, 839 cm^{-1}; HR-MS (ESI) calcd. for $C_{30}H_{63}N_2O_8Si_2$ [M+H$^+$] 635.41175, found 635.41191. R_f (3/1 hexane/EtOAc) = 0.25.

*4.3.11. Bis(*N*-Boc)-(*2R,3S,6R,7S*)-*E*-2,7-amino-oct-4-en-1,3,6,8-tetraol (**11**)*



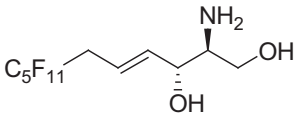
Column chromatography of the residue (EtOAc) furnished 31 mg (12%) of the title compound as a pale yellow oil: $[\alpha]_D$ −1.4 (c 0.218, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 18H), 3.63 (m, 2H), 3.81–3.97 (m, 4H), 4.33 (bs, 2H), 5.61 (bd, J = 7.8 Hz, NH), 5.89 (m, 2H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 28.41, 55.52, 62.31, 72.95, 80.15, 131.31, 156.66; IR ($CHCl_3$) ν 3609, 3490, 3438, 3370, 2981, 1701, 1502, 1393, 1368, 1246, 1168, 1092, 1055, 977, 855 cm^{-1}; HR-MS (ESI) calcd. for $C_{18}H_{34}N_2O_8Na$ [M+Na$^+$] 429.22074, found 429.22058. R_f (1/1 hexane/EtOAc) = 0.3.

4.4. Further transformations

4.4.1. General procedure for the Boc deprotection

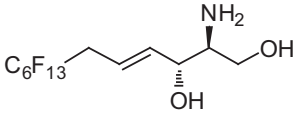
To a solution of Boc protected sphingosine derivatives **10a**–**10c** in CH_2Cl_2 (4 mL) was added TFA (0.1 mL) at 0 °C. After the reaction mixture was stirred at the room temperature for 1 h, solvents were removed under reduced pressure and the residue was dissolved in pyridine (1.5 mL) and stirred for additional 15 min at room temperature. This reaction mixture was then purified by chromatography on silica gel (1/0–1/1 $CHCl_3$/MeOH).

*4.4.2. (2S,3R)-4E-2-Amino-7,7,8,8,9,9,10,10,11,11,11-undecafluoroundec-4-en-1,3-diol (**12a**)*



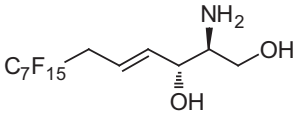
The reaction was carried out with **10a** (43 mg, 0.087 mmol) according to the general procedure. Column chromatography on silica gel furnished 20 mg (58%) of the title compound as a pale yellow oil: $[\alpha]_D$ 0 (c 0.119, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 3.02 (m, 2H), 3.10 (dt, J = 7.9, 4.6 Hz, 1H), 3.61 (dd, J = 11.4, 7.9 Hz, 1H), 3.73 (dd, J = 11.4, 4.3 Hz, 1H), 4.30 (m, 1H), 5.79–5.91 (m, 2H); ^{13}C NMR (150.9 MHz, CD_3OD) δ 35.11 (t, J^{C-F} = 22.5 Hz), 57.97, 61.28, 71.88, 120.84, 138.18; ^{19}F NMR (470.3 MHz, CD_3OD) δ −123.65 (m, 2F), −120.45 (m, 2F), −119.94 (m, 2F), −110.30 (m, 2F), −78.60 (m, 3F); IR (KBr tablet) ν 1238, 1208, 1141, 977, 740, 713, 704, 535 cm^{-1}; HR-MS (ESI) calcd. for $C_{11}H_{13}F_{11}NO_2$ [M+H$^+$] 400.07652, found 400.07652. R_f (1/1 $CHCl_3$/MeOH) = 0.75.

*4.4.3. (2S,3R)-4E-2-Amino-7,7,8,8,9,9,10,10,11,11,12,12,12-tridecafluorododec-4-en-1,3-diol (**12b**)*



The reaction was carried out with **10b** (36 mg, 0.066 mmol) according to the general procedure. Column chromatography on silica gel furnished 20 mg (68%) of the title compound as a pale yellow oil: $[\alpha]_D$ −1.5 (c 0.345, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 3.04 (dt, J = 18.9, 4.2 Hz, 2H), 3.29 (m, 1H), 3.68 (dd, J = 11.6, 8.5 Hz, 1H), 3.78 (dd, J = 11.6, 4.1 Hz, 1H), 4.43 (m, 1H), 5.84–5.92 (m, 2H); ^{13}C NMR (150.9 MHz, CD_3OD) δ 35.03 (t, J^{C-F} = 22.2 Hz), 58.02, 59.08, 70.13, 121.44 (t, J^{C-F} = 4.4 Hz), 137.15; ^{19}F NMR (470.3 MHz, CD_3OD) δ −123.49 (m, 2F), −120.21 (m, 2F), −120.07 (m, 2F), −119.12 (m, 2F), −110.23 (m, 2F), −78.57 (m, 3F); IR (KBr tablet) ν 3235, 3115, 1244, 1210, 1187, 1144, 1070, 1056, 977, 746, 708, 533 cm^{-1}; HR-MS (ESI) calcd. for $C_{12}H_{13}F_{13}NO_2$ [M+H$^+$] 450.07332, found 450.07293. R_f (1/1 $CHCl_3$/MeOH) = 0.75.

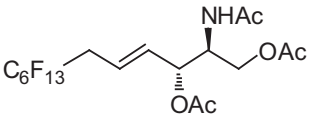
*4.4.4. (2S,3R)-4E-2-Amino-7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-pentadecafluorotridec-4-en-1,3-diol (**12c**)*



The reaction was carried out with **10c** (103 mg, 0.172 mmol) according to the general procedure. Column chromatography on silica gel furnished 75 mg (87%) of the title compound as a pale yellow oil: $[\alpha]_D$ 0 (c 0.202, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 3.03 (dt, J = 18.6, 6.3 Hz, 2H), 3.17 (dt, J = 8.0, 4.4 Hz, 1H), 3.64 (dd, J = 11.5, 8.0 Hz, 1H), 3.75 (dd, J = 11.5, 4.2 Hz, 1H), 4.35 (m, 1H), 5.81–5.92 (m, 2H); ^{13}C NMR (150.9 MHz, CD_3OD) δ 35.10 (t, J^{C-F} = 22.2 Hz), 57.97, 60.44, 71.21, 121.07 (t, J^{C-F} = 4.5 Hz), 137.78; ^{19}F NMR (470.3 MHz, CD_3OD) δ −123.47 (m, 2F), -120.20 (m, 2F), −119.93 (m, 2F), −119.24 (m, 2F), −118.93 (m, 2F), −110.24 (m, 2F), −78.55 (m, 3F); IR (KBr tablet) ν 1681, 1237, 1211, 1148, 1077,

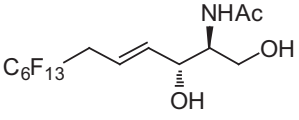
1055, 978, 703, 533 cm^{-1}; HR-MS (ESI) calcd. for $C_{13}H_{13}F_{15}NO_2$ [M+H^+] 500.07013, found 500.07003. R_f (1/1 $CHCl_3$/MeOH) = 0.75.

*4.4.5. (2S,3R)-4E-2-Acetamido-7,7,8,8,9,9,10,10,11,11,12,12,12-tridecafluorododec-4-ene-1,3-diyl diacetate (**12b-perAc**)*



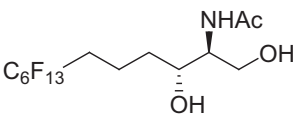
To a solution of **12b** (50 mg, 0.111 mmol) in pyridine (1 mL) was added acetic anhydride (0.25 mL) at room temperature. The mixture was stirred for 6 h then water (0.5 mL) was added. The volatiles were removed under reduced pressure and the residue was subjected to column chromatography on silica gel (2/3 hexane/EtOAc) which furnished 60 mg (94%) of the title compound as a pale yellow oil: $[\alpha]_D$ −4.1 (*c* 0.218, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.97 (s, 3H), 2.09 (s, 6H), 2.78–2.92 (m, 2H), 4.03 (dd, *J* = 11.7, 3.8 Hz, 1H), 4.34 (dd, *J* = 11.7, 5.4 Hz, 1H), 4.48 (m, 1H), 5.33 (t, *J* = 6.5 Hz, 1H), 5.68 (bd, *J* = 9.3 Hz, NH), 5.72–5.82 (m, 2H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 20.75, 20.95, 23.15, 34.46 (t, J^{C-F} = 23.0 Hz), 50.11, 62.48, 72.52, 122.76, 132.94, 169.74, 169.77, 170.89; ^{19}F NMR (470.3 MHz, CD_3OD) δ −122.24 (m, 2F), −119.10 (m, 2F), −119.00 (m, 2F), −118.05 (m, 2F), −109.05 (m, 2F), −76.90 (m, 3F); IR ($CHCl_3$) 3442, 2960, 2928, 2856, 1742, 1681, 1510, 1371, 1350, 1242, 1146, 1122, 1048, 973, 707, 699, 532 cm^{-1}; HR-MS (ESI) calcd. for $C_{18}H_{19}F_{13}NO_5$ [M+H^+] 576.10502, found 576.10520. R_f (1/2 hexane/EtOAc) = 0.4.

*4.4.6. (2S,3R)-4E-2-Acetamido-7,7,8,8,9,9,10,10,11,11,12,12,12-tridecafluorododec-4-ene-1,3-diol (**12b-Ac**)*



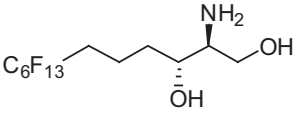
12b-perAc (60 mg, 0.104 mmol) was dissolved in MeOH/MeONa (3 mL) and the resulting mixture was stirred overnight at room temperature. Neutralization of the solution with cation-exchange resin (DOWEX 50), subsequent filtration of the resin and removal of the solvent under reduced pressure furnished 46 mg (87%) of the title compound without further purification as a pale yellow oil: $[\alpha]_D$ −6.0 (*c* 0.252, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ 1.95 (s, 3H), 2.90–3.03 (m, 2H), 3.66–3.73 (m, 2H), 3.90 (dt, *J* = 6.9, 5.2 Hz, 1H), 4.17 (m, 1H), 5.72 (dt, *J* = 15.4, 7.3 Hz, 1H), 5.86 (ddt, *J* = 15.4, 6.5, 1.2 Hz, 1H); ^{13}C NMR (150.9 MHz, CD_3OD) δ 22.69, 35.20 (t, J^{C-F} = 22.3 Hz), 56.68, 61.84, 72.76, 119.87, 139.78, 173.47; ^{19}F NMR (470.3 MHz, CD_3OD) δ −123.49 (m, 2F), −120.19 (m, 2F), −120.06 (m, 2F), −119.13 (m, 2F), −110.29 (m, 2F), −78.58 (m, 3F); IR ($CHCl_3$) 3618, 3436, 3400, 2961, 2929, 2856, 1664, 1511, 1372, 1350, 1243, 1145, 1121, 1088, 1039, 975, 707, 700, 533 cm^{-1}; HR-MS (ESI) calcd. for $C_{14}H_{15}F_{13}NO_3$ [M+H^+] 492.08389, found 492.08385. R_f (6/1 $CHCl_3$/MeOH) = 0.65.

*4.4.7. (2S,3R)-2-Acetamido-7,7,8,8,9,9,10,10,11,11,12,12,12-tridecafluorododec-1,3-diol (**13**)*



To a solution of **10b–Ac** (27 mg, 0.053 mmol) in ethanol (2 mL) was added Pd/C (3 mg, 10 wt%) at room temperature. After the reaction mixture was stirred at the same temperature for 1 day, it was filtered through Celite and volatiles were removed under reduced pressure. Chromatography of the residue on silica gel (1/0–1/1 $CHCl_3$/MeOH) furnished 22 mg (81%) of the title compound as a white solid: $[\alpha]_D$ 0 (*c* 0.236, MeOH); indefinite melting point over 129 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 1.50 (m, 1H), 1.61–1.71 (m, 2H), 1.85 (m, 1H), 1.98 (s, 3H), 2.12–2.26 (m, 2H), 3.63 (ddd, *J* = 9.3, 7.1, 2.7 Hz, 1H), 3.67–3.73 (m, 2H), 3.83 (m, 1H); ^{13}C NMR (150.9 MHz, CD_3OD) δ 17.82, 22.75, 31.66 (t, J^{C-F} = 22.2 Hz), 33.97, 57.00, 62.07, 71.66, 173.44; ^{19}F NMR (470.3 MHz, CD_3OD) δ −123.46 (m, 2F), −120.69 (m, 2F), −120.07 (m, 2F), −119.11 (m, 2F), −111.64 (m, 2F), −78.58 (m, 3F); IR ($CHCl_3$) ν 1651, 1578, 1563, 1523, 1368, 1240, 1209, 1198, 1146, 1085, 1073, 1062, 1042, 732, 700, 528 cm^{-1}; HR-MS (ESI) calcd. for $C_{14}H_{16}F_{13}NO_3Na$ [M+Na^+] 516.08148, found 516.08131, R_f (1/1 $CHCl_3$/MeOH) = 0.75.

*4.4.8. (2S,3R)-2-Amino-7,7,8,8,9,9,10,10,11,11,12,12,12-tridecafluorododec-1,3-diol (**14**)*



To a solution of **12b** (45 mg, 0.1 mmol) in ethanol (2 mL) was added Pd/C (5 mg, 10 wt%) at room temperature. After the reaction mixture was stirred at the same temperature for 2 days, it was filtered through Celite and volatiles were removed under reduced pressure. Chromatography of the residue on silica gel (1/0–1/1 $CHCl_3$/MeOH) furnished 40 mg (88%) of the title compound as a white solid: $[\alpha]_D$ −1.7 (*c* 0.293, MeOH); indefinite melting point over 75 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.52–1.71 (m, 3H), 1.88 (m, 1H), 2.23 (m, 2H), 3.15 (m, 1H), 3.69 (dd, *J* = 11.5, 8.2 Hz, 1H), 3.78 (ddd, *J* = 9.8, 4.2, 3.4 Hz, 1H), 3.83 (dd, *J* = 11.5, 4.2 Hz, 1H); ^{13}C NMR (150.9 MHz, CD_3OD) δ 18.10, 31.48 (t, J^{C-F} = 21.9 Hz), 33.24, 58.40, 59.78, 70.38; ^{19}F NMR (470.3 MHz, CD_3OD) δ −123.50 (m, 2F), −120.71 (m, 2F), −120.08 (m, 2F), −119.11 (m, 2F), −111.62 (m, 2F), −78.58 (m, 3F); IR ($CHCl_3$) ν 1630, 1232, 1213, 1188, 1168, 1148, 1051, 976, 702, 531 cm^{-1}; HR-MS (ESI) calcd. for $C_{12}H_{15}F_{13}NO_2$ [M+H^+] 452.08897, found 452.08876, R_f (1/1 $CHCl_3$/MeOH) = 0.75.

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