39. Synthesis of D-*erythro*- and D-*threo*-Sphingosine Derivatives from L-Serine

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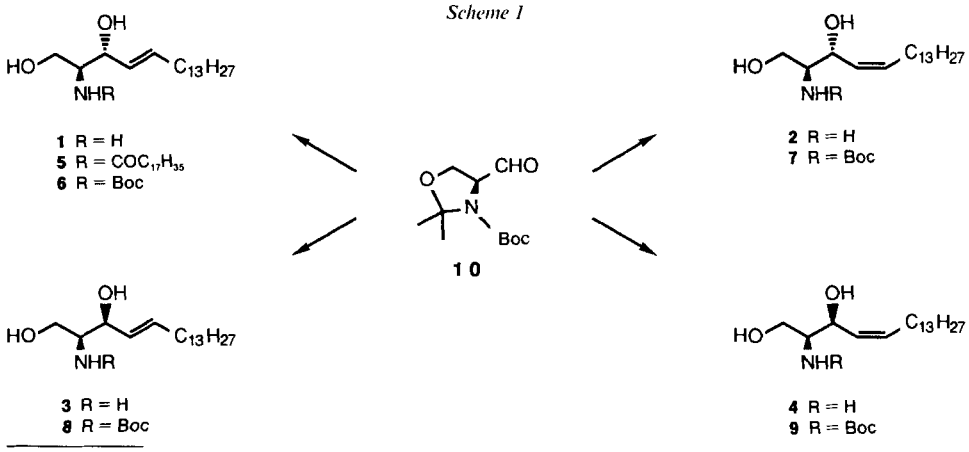
The protected serine aldehyde **10** was converted to the crystalline *N*-Boc-protected sphingosines **6–9** by a three-step reaction sequence. Compound **10** was transformed with high diastereoselectivity (95%) either to the *erythro*- or *threo*-alkynols, **17** and **18**, respectively. The *erythro*-isomer **17** is formed by the addition to **10** of lithium pentadecyne **16** in THF/HMPT at −78°, whereas the corresponding *threo*-isomer **18** is produced in the presence of $ZnBr_2$ in Et_2O. Deprotection of the acetal moiety afforded 1,3-diols **19** and **20**. These diols were selectively reduced with Red-Al to the (*E*)-sphingosines **6** and **8**, or the (*Z*)-isomers **7** and **9** by partial hydrogenation over *Lindlar*'s catalyst. Cleavage of the *N*-Boc group and further transformation to ceramides were readily achieved as demonstrated by the conversion of **6** to *N*-octadecanoyl-D-*erythro*-sphingosine **5**.

Introduction. – Glycosphingolipids are ubiquitious constituents of cell membranes, where they are assumed to participate in various processes based on recognition phenomena [1]. The hydrophilic carbohydrate moiety of the glycosphingolipids varies greatly among the different classes of these substances. Conversely, the lipophilic portion is derived from a common long-chain amino alcohol, sphingosine **1** *(Scheme 1)* [1]. The hydrophilic moiety, located on the external surface of the membrane, determines the specificity of interactions, whereas the lipophilic portion, anchored in the outer-leaflet,

Scheme 1



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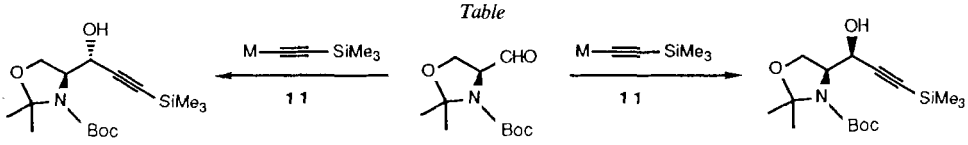
contributes primarily to the structural rigidity of the membrane. To investigate the biological role of glycosphingolipids, syntheses of these compounds have received increasing attention. Efficient syntheses of enantiomerically pure sphingosine **1**, the diastereoisomers **2–4**, having the unnatural configuration, and of the corresponding, structurally related ceramides such as **5** have been reported either starting from carbohydrates [2] and L-serine [3], respectively, or by using an enantioselective approach [4] based on the *Sharpless* asymmetric-epoxidation methodology. However, a versatile enantio- and diastereospecific route, leading to all four diastereoisomers **1–4**, has not been reported. Herein, we describe a highly efficient three-step synthesis of crystalline and stable[2]) *N*-Boc-protected sphingosines **6–9** using the protected serine aldehyde **10** [5] as the common intermediate.

Results. – The protected, configurationally stable serine aldehyde **10** is a potentially useful chiral building block. During the course of our investigations on the synthetic applications of **10**, we discovered that its reactions with metallated ethynyltrimethylsilane (M = H; **11**) produce either the *erythro*- or the *threo*-alkynol, **12** or **13**, respectively, depending on the reaction conditions employed *(Table)*. Considerable *erythro*-selectivity (→**12**, ds 89%) was observed using lithiated **11** (M = Li) in THF at −78° *(Entry 5)*. The addition of cation-complexing agents resulted in a marked increase of *erythro*-selectivity (*Entries 1, 2,* and *4*). HMPT was the most effective agent, producing **12** with 95% diastereoselectivity (ds) *(Entry 1)* [6]. Transmetallation of organometallics with ClTi(i-PrO)$_3$ is usually the method of choice for enhancing *Cram*-selectivity in carbonyl-addition reactions [7]. However, surprisingly, addition of Ti-compound **11** (M = Ti(i-PrO)$_3$)

Table



12 **10** **13**

Entry	M	Additive	Solvent	*Method*[a])	**12**/**13**[b])	ds [%]	**12** + **13** [%][c])
1	Li	HMPT	THF	*A*	20:1	95	85
2	Li	[18-C-6]	THF	*A*	14:1	93	70
3	Li	ClZr(BuO)$_3$	THF	*B*	12:1	92	90
4	Li	TMEDA	THF	*A*	10:1	91	85
5	Li	–	THF	*A*	8:1	89	75
6	MgBr	–	THF	*C*	7:1	87	78
7	Li	ClTi(i-PrO)$_3$	THF	*B*	3:1	75	90
8	MgBr	$ZnBr_2$	THF	*C*	2.5:1	71	90
9	MgBr	$ZnBr_2$	Et_2O	*C*	1:5.5	84	89
10	Li	$ZnBr_2$	Et_2O	*C*	1:11	91	89
11	MgBr	CuI	THF/SMe_2	*D*	1:20	95	86

[a]) *Cf. Exper. Part.*
[b]) Determined by ^{1}H-NMR.
[c]) Isolated yield.

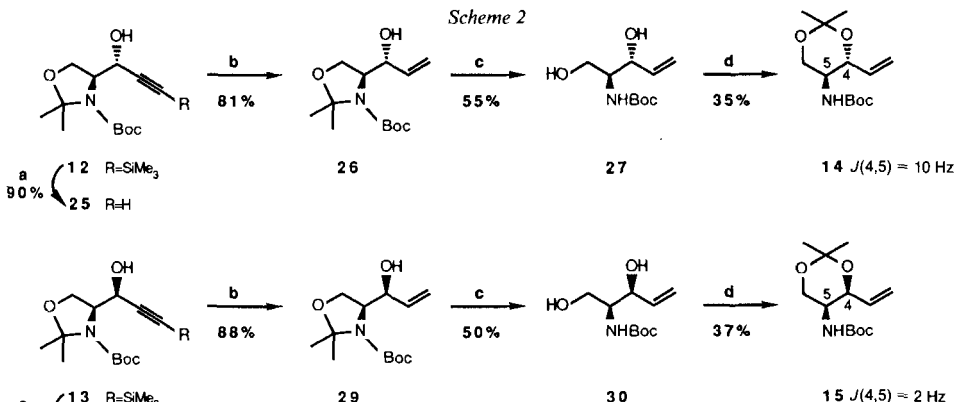
[2]) The free amine bases **1–4** are prone to air-oxidation and are difficult to handle.

to **10** proceeded only with low diastereoselectivity *(Entry 7)*, whereas remarkably high *erythro*-selectivity was observed in the reaction of the corresponding Zr-derivative **11** (M = $Zr(BuO)_3$) [8]. On the other hand, high *threo*-selectivity was observed on addition of **10** to lithiated **11** (M = Li) in the presence of anhydrous $ZnBr_2$ with Et_2O as solvent *(Entry 10)* [9]. As shown, both the solvent and the nature of the organometallic intermediate **11** exhibited a marked influence on diastereoselectivity (*Entries 8* and *9*). The highest *threo*-selectivity (95%) was achieved in the reaction of **10** with the Cu-derivative **11** (M = Cu) *(Entry 11)* [7d] [10]. The experimental results are best explained by assuming a transition state according to the *Cornforth* model [11] for *erythro*-selective reactions, *i.e.* the α-amino moiety and the C=O function are oriented in an antiperiplanar manner. On the other hand, predominant formation of *threo*-adduct **13** may be explained by a chelation-controlled mechanism [9] [10].

The enantiomeric purity of **12** and **13** was determined on the corresponding *Mosher*-derivatives [12]. ^{1}H-NMR analysis of these compounds clearly revealed that all addition reactions of **11** with serine aldehyde **10** had occurred with no detectable racemization. The relative configuration of C(2) and C(3) was established after transformation of ynols **12** and **13** to the acetonides **14** and **15**, respectively *(Scheme 2)*. As expected, the crucial coupling constant $J(4,5)$ was significantly higher (10 Hz) for the *erythro*-diastereoisomer **14** than for its *threo*-counterpart **15** (1 Hz). This finding is consistent with a *trans*-diaxial and an axial-equatorial relationship of H–C(4) and H–C(5), respectively.

Based on the above results, the syntheses of the title compounds **6–9** were investigated *(Scheme 3)*. Diastereoselective addition of 1-pentadecynyllithium (**16**) to **10** afforded the desired alkynols **17** and **18**. As expected, high *erythro*-selectivity (→**17**, ds 95%)[3]) was observed in the reaction of **10** with **16** in THF/HMPT at −78°, whereas predominant formation of the *threo*-isomer **18** (ds 95%) was achieved in the presence of anhydrous $ZnBr_2$ with Et_2O as solvent. Both adducts were formed without racemization[4]). Treat-

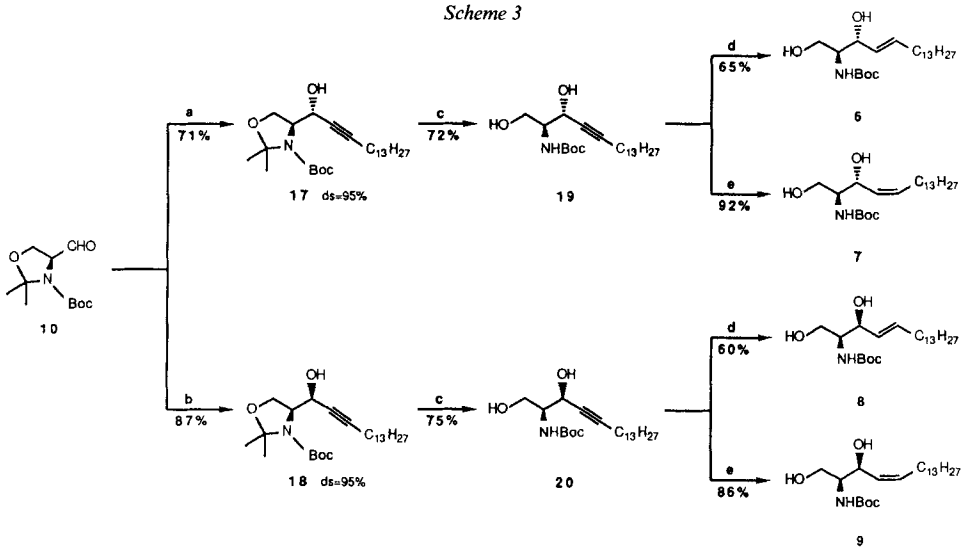
Scheme 2



a) $NH_4F/Bu_4NHSO_4/CH_2Cl_2/H_2O$, r.t. b) H_2/*Lindlar*/AcOEt, r.t.
c) *Amberlyst 15*/CH_3OH, r.t. d) 2,2-Dimethoxypropane/PPTS/CH_2Cl_2, r.t.

[3]) Determined by ^{1}H-NMR.
[4]) Determined *via* the corresponding *Mosher* esters [12].

Scheme 3



a) 1-Pentadecynyllithium (**16**)/THF, −78°. b) **16**/$ZnBr_2$/Et_2O, −78°→r.t. c) *Amberlyst 15*/CH_3OH, r.t. d) Red-Al/Et_2O, 0°→r.t. e) H_2/*Lindlar*/AcOEt, r.t.

ment of **17** and **18** with *Amberlyst 15* in MeOH at r.t. resulted in selective cleavage of the acetal moiety, leading to 1,3-diols **19** and **20**, respectively, which were finally converted to the crystalline, enantiomerically pure *N*-Boc-sphingosines **6**–**9**, respectively, by selective reduction of the C≡C bond with Red-Al in Et_2O [13] (→**6** and **8**) and by partial hydrogenation over *Lindlar*'s catalyst (→**7** and **9**).

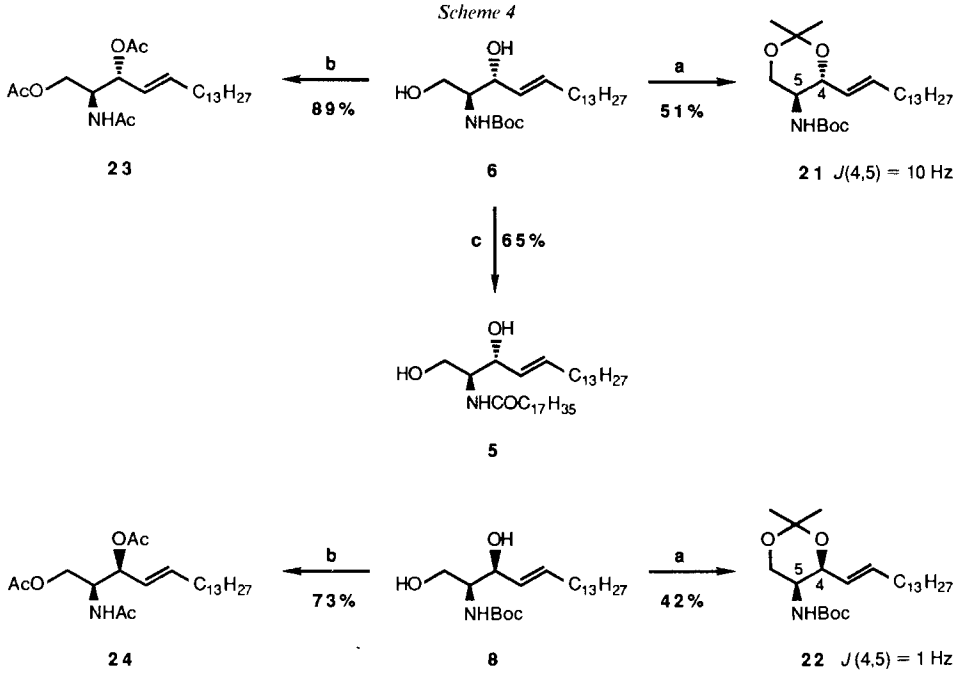
The relative configuration of **6** and **8** was established by ^{1}H-NMR analysis of their corresponding 1,3-acetals **21** ($J(4,5)$ = 10 Hz) and **22** ($J(4,5)$ = 1 Hz), respectively. Further structural proof was obtained by converting **6** and **8** to the known triacetates **23** and **24** *(Scheme 4)*, respectively, whose analytical data *(cf. Exper. Part)* were identical to those described earlier [3d] [4]. As exemplified by the conversion of **6** to **5**, *N*-Boc-protected sphingosines are suitable precursors of ceramides. Cleavage of the carbamate moiety with 1N HCl in dioxane and subsequent reaction of sphingosine **1** with *N*-succinimidyl octadecanoate in THF afforded *N*-octadecanoyl-D-*erythro*-sphingosine **5**, which exhibited the correct spectroscopic and analytical data [4].

Experimental Part

General. H_2O-sensitive reactions were carried out in flame-dried glassware under Ar. THF and Et_2O were distilled over Na/benzophenone just prior to use. Solns. were dried with $MgSO_4$ and evaporated below 50° in a *Büchi* rotary evaporator. TLC: *Merck* precoated silica-gel *60 F-254* plates; detection by UV, $KMnO_4$, or phosphomolybdic acid. Flash chromatography (FC) [14]: silica gel *Merck 60* (40–63 μ). M.p. (uncorrected): *Büchi-510* apparatus. Optical rotations: *Perkin-Elmer-241* polarimeter. ^{1}H-NMR: *Bruker AM-300* and *AM-360*; chemical shifts (δ) are indicated in ppm relative to TMS as internal standard; coupling constants (J) are given in Hz.

Transformations of Table *and* Scheme 2. tert-*Butyl (4S,1'R)- and (4S,1'S)-2,2-Dimethyl-4-[1'-hydroxy-3'-(trimethylsilyl)-2'-propynyl]oxazolidine-3-carboxylate* (**12** and **13**, resp.). *a*) BuLi (*Fluka*; 1.6M in hexane, 2 ml, 3.2 mmol) was added dropwise to a soln. of (1-ethynyl)trimethylsilane (0.49 ml, 3.54 mmol) in abs. THF (17 ml) at

Scheme 4



a) 2,2-Dimethoxypropane/PPTS/CH_2Cl_2, r.t. b) 1. 1N HCl/dioxane, 100°; 2. Ac_2O/pyridine, r.t.
c) 1. 1N HCl/dioxane, 100°; 2. *N*-succinimidyl octadecanoate/THF, r.t.

– 78°. After stirring at –78° for 1 h, HMPT (dist. over CaH_2, 0.77 ml, 4.4 mmol) was added, followed by a soln. of **10** [5] (500 mg, 2.2 mmol) in abs. THF (2 ml). After 2 h at –78°, sat. NH_4Cl (20 ml) was added and the mixture allowed to warm to r.t. After dilution with H_2O and extraction with Et_2O, the org. layer was washed with 0.5N HCl and sat. NaCl, dried, and evaporated *in vacuo*. FC (petroleum ether/AcOEt 6:1) afforded a 20:1 mixture **12**/**13** (612 mg, 85%).

b) A soln. of [(ethynyl)trimethylsilyl]lithium (3.2 mmol) in THF (17 ml), prepared as described above, was added *via* canula to $ClZr(BuO)_3$ (1.3M in Et_2O, 3.4 ml, 4.4 mmol) [8] and abs. THF (5 ml) at –78°. After stirring at –78° for 30 min and at 0° for 1 h, a soln. of **10** (500 mg, 2.2 mmol) in abs. THF (2 ml) was added at –78°. The mixture was allowed to warm to r.t. overnight and worked up as described above, affording a 12:1 mixture **12**/**13** (650 mg, 90%).

c) Anh. $ZnBr_2$ (*Fluka*, 1.0 g, 4.4 mmol) was added to a soln. of [(ethynyl)trimethylsilyl]lithium (3.2 mmol) in abs. Et_2O (20 ml), prepared as described above, at 0°. After stirring at r.t. for 1 h, a soln. of **10** (500 mg, 2.2 mmol) in abs. Et_2O (2 ml) was added at –78°. The heterogenous mixture was allowed to warm to r.t. overnight and worked up as described above, affording a 11:1 mixture **13**/**12** (640 mg, 89%).

d) EtMgBr (*Aldrich*, 3M in Et_2O, 1.1 ml, 3.3 mmol) was added dropwise to a soln. of (ethynyl)trimethylsilane (0.49 ml, 3.54 mmol) in abs. THF (10 ml) at 0°. After stirring under reflux for 1 h, the *Grignard* compound was transferred *via* canula to a soln. of CuI (*Fluka*; 920 mg, 4.83 mmol) in THF (10 ml) and Me_2S (2 ml) at –78°. Stirring was continued at –78° and at –30° for 30 min, then a soln. of **10** (500 mg, 2.2 mmol) in abs. THF (2 ml) was added at –78°. The mixture was allowed to warm to r.t. overnight and worked up as described above, affording a 20:1 mixture **13**/**12** (620 mg, 86%). ^{1}H-NMR ((D_6)DMSO): **12:** 0.13 (*s*, $(CH_3)_3Si$); 1.42 (br., CH_3, *t*-Bu); 1.46 (*s*, CH_3); 3.75–4.08 (*m*, 2 H–C(5), H–C(4)); 4.41–4.50 (*m*, H–C(1')); 5.61 (*d*, *J* = 6, OH). **13:** 0.13 (*s*, $(CH_3)_3Si$); 1.40 (br., CH_3, *t*-Bu); 1.52 (*s*, CH_3); 3.75–4.08 (*m*, 2 H–C(5), H–C(4)); 4.64, 4.70[5]) (2 *dd*, *J* = 6, 5, H–C(1')); 5.74, 5.77[5]) (2 *d*, *J* = 6, OH).

[5]) Doubling of signals due to carbamate rotamers.

tert-*Butyl (4S,1'R)-2,2-Dimethyl-4-(1'-hydroxy-2'-propynyl)oxazolidine-3-carboxylate* (**25**). To a soln. of **12** (3.0 g, 9.16 mmol) and tetrabutylammonium hydrogen sulfate (0.62 g, 1.83 mmol) in CH_2Cl_2 (40 ml) was added NH_4F (45% in H_2O, 20 ml). After vigorous stirring at r.t. for 1 h, the org. layer was separated, washed with H_2O and sat. NaCl, dried, and evaporated *in vacuo*. FC (hexane/AcOEt 3:1) gave pure **25** (2.1 g, 90%) as a colorless oil. $[\alpha]_D^{25} = -57.5°$ (c = 1.1, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO): 1.42 (br., CH_3, *t*-Bu); 1.46 (*s*, CH_3); 3.30, 3.35[5]) (2 *s*, H–C(3')); 3.78–4.02 (*m*, 2 H–C(5), H–C(4)); 4.38, 4.42[5]) (2 br., H–C(1')); 5.63, 5.70[5]) (2 *d*, J = 6.5, OH). Anal. calc. for $C_{13}H_{21}NO_4$ (255.31): C 61.16, H 8.29, N 5.49, O 25.07; found: C 61.20, H 8.21, N 5.55, O 24.94.

tert-*Butyl (4S,1'S)-2,2-Dimethyl-4-(1'-hydroxy-2'-propynyl)oxazolidine-3-carboxylate* (**28**). Following the procedure described above, **13** was converted to **28**. Crystallization ((i-Pr)$_2$O/hexane) yielded pure **28** (84%). M.p. 92.5–93.5°. $[\alpha]_D^{25} = -50.8°$ (c = 1.0, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO): 1.40 (br., CH_3, *t*-Bu); 1.52 (*s*, CH_3); 3.22, 3.40[5]) (2 *s*, H–C(3')); 3.75–4.08 (*m*, 2 H–C(5), H–C(4)); 4.55–4.68 (*m*, H–C(1')); 5.74, 5.77 (*d*, J = 6, OH). Anal. calc. for $C_{13}H_{21}NO_4$ (255.31): C 61.16, H 8.29, N 5.49, O 25.07; found: C 61.12, H 8.28, N 5.62, O 24.92.

tert-*Butyl (4S,1'R)-2,2-Dimethyl-4-(1'-hydroxy-2'-propenyl)oxazolidine-3-carboxylate* (**26**). Compound **25** (6.10 g, 23.9 mmol) was dissolved in AcOEt (120 ml), *Lindlar*'s catalyst (*Fluka*; 3 g) was added, and the mixture was shaken under 1 atm of H_2 for 30 min. The catalyst was removed by filtration through *Celite* and the solvent evaporated *in vacuo*. The residue was purified by bulb-to-bulb distillation, yielding **26** (5.0 g, 81%) as a colorless oil. $[\alpha]_D^{25} = -19.1°$ (c = 0.8, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO): 1.40 (br., CH_3, *t*-Bu); 1.45 (*s*, CH_3); 3.60–4.13 (*m*, 2 H–C(5), H–C(4), H–C(1')); 4.95–5.20 (*m*, H–C(3'), OH); 5.15 (*d*, J = 16, H–C(3')); 5.80 (*ddd*, J = 16, 10, 6, H–C(2')). Anal. calc. for $C_{13}H_{23}NO_4$ (257.33): C 60.68, H 9.01, N 5.44; found: C 60.40, H 9.02, N 5.44.

tert-*Butyl (4S,1'S)-2,2-Dimethyl-4-(1'-hydroxy-2'-propenyl)oxazolidine-3-carboxylate* (**29**). Following the procedure described above, **28** was converted to **29**. Crystallization (hexane) yielded pure **29** (88%). M.p. 82–83°. $[\alpha]_D^{25} = -52.4°$ (c = 1.1, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO): 1.35, 1.37[5]) (2 *s*, CH_3); 1.42 (br., CH_3, *t*-Bu); 3.80–3.97 (*m*, 2 H–C(5), H–C(4)); 4.35 (br., H–C(1')); 5.06–5.22 (*m*, 2 H–C(3'), OH); 5.82 (*ddd*, J = 16, 10, 6, H–C(2')). Anal. calc. for $C_{13}H_{23}NO_4$ (257.33): C 60.68, H 9.01, N 5.44; found: C 60.79, H 9.04, N 5.66.

tert-*Butyl (1S,2R)-N-[2-Hydroxy-1-(hydroxymethyl)-3-butenyl]carbamate* (**27**). Compound **26** (500 mg, 1.94 mmol) was dissolved in MeOH (20 ml), *Amberlyst 15* (*Fluka*; 970 mg) was added, and the heterogenous mixture was stirred at r.t. for 24 h. After filtration through *Celite*, the solvent was evaporated *in vacuo*, yielding a slightly yellow oil. Filtration through a short pad of silica gel, eluting with Et_2O, and bulb-to-bulb distillation afforded pure **27** (232 mg, 55%) as a colorless oil. $[\alpha]_D^{25} = +6.90°$ (c = 0.4, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO): 1.40 (*s*, *t*-Bu); 3.25–3.50 (*m*, 2 H–C(1'), H–C(1)); 3.92 (*ddd*, J = 6, 5, 5, H–C(2)); 4.43 (*t*, J = 5, OH); 4.90 (*d*, J = 5, OH); 5.03 (*d*, J = 10, H–C(4)); 5.15 (*d*, J = 15, H–C(4)); 5.83 (*ddd*, J = 16, 10, 5, H–C(3)); 6.30 (*d*, J = 8, NH). Anal. calc. for $C_{10}H_{19}NO_4$ (217.27): C 55.28, H 8.82, N 6.45; found: C 55.09, H 9.00, N 6.35.

tert-*Butyl (1S,2S)-N-[2-Hydroxy-1-(hydroxymethyl)-3-butenyl]carbamate* (**30**). Following the procedure described above, conversion of **29** yielded **30** (50%) as a colorless oil. $[\alpha]_D^{25} = -23.6°$ (c = 0.55, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO): 1.36 (*s*, *t*-Bu); 3.35–3.50 (*m*, 2 H–C(1'), H–C(1')); 4.10–4.20 (*m*, H–C(2)); 4.60 (*t*, J = 5, OH); 4.80 (*d*, J = 6, OH); 5.05 (*d*, J = 10, H–C(4)); 5.20 (*d*, J = 16, H–C(4)); 5.85 (*ddd*, J = 16, 10, 5, H–C(3)); 6.05 (*d*, J = 8, NH). Anal. calc. for $C_{10}H_{19}NO_4$ (217.27): C 55.28, H 8.82, N 6.45; found: C 54.94, H 9.01, N 6.35.

tert-*Butyl (4R,5S)-N-(2,2-Dimethyl-4-vinyl-1,3-dioxan-5-yl)carbamate* (**14**). Pyridinium *p*-toluenesulfonate (212 mg, 0.84 mmol) was added to a soln. of **27** (183 mg, 0.84 mmol) and 2,2-dimethoxypropane (2 ml, 16.8 mmol) in CH_2Cl_2 (5 ml), and the mixture was stirred at r.t. overnight. Volatiles were evaporated *in vacuo*, and the residue was purified by FC (hexane/AcOEt 3:1) yielding **14** (75 mg, 34.7%) as an oil, which subsequently crystallized. M.p. 70–72°. ^{1}H-NMR ((D_6)DMSO): 1.29 (*s*, CH_3); 1.35 (*s*, *t*-Bu); 1.41 (*s*, CH_3); 3.18–3.32 (*m*, H–C(5)); 3.52–3.67 (*m*, 2 H–C(6)); 4.13 (*dd*, J = 10, 6, H–C(4)); 5.11 (*d*, J = 10, H–C(2')); 5.22 (*d*, J = 17, H–C(2')); 5.70 (*ddd*, J = 17, 10, 6, H–C(1')); 6.42, 6.78[5]) (2 *d*, J = 9.5, NH).

tert-*Butyl (4S,5S)-N-(2,2-Dimethyl-4-vinyl-1,3-dioxan-5-yl)carbamate* (**15**). Following the procedure described above, conversion of **30** gave **15** (37%) as a colorless oil. ^{1}H-NMR ((D_6)DMSO): 1.33 (*s*, CH_3); 1.37 (*s*, *t*-Bu); 1.41 (*s*, CH_3); 3.42–3.50 (*m*, H–C(5)); 3.54 (*dd*, J = 12, 2, H–C(6)); 4.07 (*dd*, J = 12, 2.5, H–C(6)); 4.57 (*dd*, J = 5, 2, H–C(4)); 5.10 (*d*, J = 10, H–C(2')); 5.21 (*d*, J = 17, H–C(2')); 5.72 (*ddd*, J = 17, 10, 5, H–C(1')); 6.16 (*d*, J = 9.5, NH).

Transformations of Scheme 3. tert-*Butyl (4S,1'R)-2,2-Dimethyl-4-(1'-hydroxyhexadec-2'-ynyl)oxazolidine-3-carboxylate* (**17**). BuLi (*Fluka*; 1.6M in hexane, 79 ml, 0.126 mol) was added dropwise to a soln. of 1-pentadecyne (28.72 g, 0.138 mol) in abs. THF (750 ml) at –20°. After stirring at –20° for 2 h, HMPT (distilled over CaH_2, 37 ml, 0.20 mol) was added, followed by a soln. of **10** (24.31 g, 0.106 mol) in abs. THF (60 ml) at –78°. After 1 h at –78°, the mixture was allowed to warm to –20° within 2 h and then quenched by the addition of sat. NH_4Cl (1.2 l). After concentration *in vacuo*, the residue was diluted with H_2O (600 ml) and extracted with Et_2O (3 × 500 ml). The org. layer was washed with 0.5N HCl (2 × 200 ml) and sat. NaCl (2 × 200 ml), dried, and evaporated *in vacuo*. Filtration

through silica gel, first using petroleum ether as the solvent to recover excess 1-pentadecyne, followed by elution with petroleum ether/AcOEt 6:1 yielded a 20:1 mixture of **17**/**18** (32.9 g, 71%) as a colorless oil. For analysis, a sample was purified by FC (petroleum ether/AcOEt 6:1). $[\alpha]_D^{25} = -40.1°$ (c = 1.0, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO): 0.85 (t, J = 7.5, CH_3–C(15')); 1.11–1.50 (m, 37 H); 2.06–2.21 (m, 2 H–C(4')); 3.71–4.06 (m, 2 H–C(5), H–C(4)); 4.41–4.50 (m, H–C(1')); 5.45 (d, J = 6.5, OH). Anal. calc. for $C_{26}H_{47}NO_4$ (437.67): C 71.35, H 10.83, N 3.20, O 14.62; found: C 71.45, H 10.86, N 3.26, O 14.69.

tert-*Butyl (4*S,*1'*S*)-2,2-Dimethyl-4-(1'-hydroxyhexadec-2'-ynyl)oxazolidine-3-carboxylate* (**18**). BuLi (*Fluka*; 1.6M in hexane, 100 ml, 0.16 mol) was added dropwise to a soln. of 1-pentadecyne (36.12 g, 0.173 mol) in abs. Et_2O (900 ml) at –20°. The white suspension was stirred at –20° for 1 h, then anh. $ZnBr_2$ (*Fluka*; 42.0 g, 0.186 mol) was added at 0°. After 1 h at 0° and 1 h at r.t., a soln. of **10** (30.57 g, 0.133 mol) in abs. Et_2O (185 ml) was added dropwise at –78°. The mixture was allowed to warm to r.t. overnight and then quenched by the addition of sat. NH_4Cl (600 ml) at –20°. After dilution with H_2O (750 ml), the aq. layer was separated and extracted with Et_2O (2 × 500 ml). The combined Et_2O extracts were washed with sat. NaCl, dried, and evaporated *in vacuo*. Filtration through silica gel, as described above, afforded a 20:1 mixture of **18**/**17** (48.8 g, 83.6%) as a colorless oil. For analysis, a sample was purified by FC (petroleum ether/AcOEt 6:1). $[\alpha]_D^{25} = -32.4°$ (c = 1.3, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO): 0.85 (t, J = 7.5, CH_3–C(15')); 1.10–1.52 (m, 37 H); 2.13 (t, J = 6, 2 H–C(4')); 3.73–3.85 (m, H–C(4)); 3.88–4.06 (m, 2 H–C(5)); 4.56–4.70 (m, H–C(1')); 5.51, 5.54[5]) (2 d, J = 5.5, OH). Anal. calc. for $C_{26}H_{47}NO_4$ (437.67): C 71.35, H 10.83, N 3.20, O 14.62; found: C 71.20, H 10.85, N 3.18, O 14.71.

tert-*Butyl (1*S,*2*R*)-*N-*[2-Hydroxy-1-(hydroxymethyl)-3-heptadecynyl]carbamate* (**19**). Compound **17** (26.37 g, 0.06 mol) was dissolved in MeOH (600 ml), *Amberlyst 15* (*Fluka*; 31 g) was added, and the heterogenous mixture was stirred at r.t. for 41 h. After filtration through *Celite* and evaporation *in vacuo*, the residue was purified by filtration through silica gel with hexane/AcOEt 1:1: **19** (17.4 g, 72.6%) was isolated as a waxy solid. M.p. 43–44°. $[\alpha]_D^{25} = -8.5°$ (c = 1.0, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO): 0.85 (t, J = 7.5, CH_3–C(16)); 1.15–1.48 (m, 31 H); 2.15 (t, J = 6, 2 H–C(5)); 3.36–3.53 (m, 2 H–C(1'), H–C(1)); 4.15–4.23 (m, H–C(2)); 4.50 (t, J = 5, OH); 5.31 (d, J = 6, OH); 6.18 (d, J = 8, NH). Anal. calc. for $C_{23}H_{43}NO_4$ (397.60): C 69.48, H 10.90, N 3.52, O 16.10; found: C 69.44, H 11.07, N 3.78, O 16.15.

tert-*Butyl (1*S,*2*S*)-*N-*[2-Hydroxy-1-(hydroxymethyl)-3-heptadecynyl]carbamate* (**20**). Following the procedure described above, **18** was converted to **20** (75%), which was isolated as a colorless oil. $[\alpha]_D^{25} = -14.0°$ (c = 0.5, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO): 0.85 (t, J = 7.5, CH_3–C(16)); 1.13–1.50 (m, 31 H); 2.15 (t, J = 6, 2 H–C(5)); 3.26–3.50 (m, 2 H–C(1'), H–C(1)); 4.25–4.36 (m, H–C(2)); 4.60 (t, J = 5, OH); 5.18 (d, J = 7, OH); 6.15 (d, J = 8, NH). Anal. calc. for $C_{23}H_{43}NO_4$ (397.60): C 69.48, H 10.90, N 3.52, O 16.10; found: C 69.65, H 11.03, N 3.73, O 16.24.

tert-*Butyl (3*E,*1*S,*2*R*)-*N-*[2-Hydroxy-1-(hydroxymethyl)-3-heptadecenyl]carbamate* (**6**). A soln. of **19** (5.0 g, 12.6 mmol) in abs. Et_2O (20 ml) was added dropwise to Red-Al (*Aldrich*; 3.5M in toluene, 17.9 ml, 62.9 mmol) and abs. Et_2O (20 ml) at 0°. The clear soln. was stirred at r.t. for 24 h, then MeOH (9 ml) was added dropwise at 0°. After dilution with Et_2O (100 ml) and addition of sat. potassium sodium tartrate (100 ml), the mixture was vigorously stirred at r.t. for 3 h. The aq. layer was separated and extracted with Et_2O (2 × 100 ml). The combined Et_2O extracts were washed with sat. potassium sodium tartrate and sat. NaCl, dried, and evaporated *in vacuo*. Pure **6** (3.26 g, 64.9%) was obtained after FC (hexane/AcOEt 1:1) and crystallization (hexane). M.p. 64–65°. $[\alpha]_D^{25} = -1.4°$ (c = 1.1, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO): 0.85 (t, J = 7.5, CH_3–C(16)); 1.12–1.42 (m, 31 H); 1.75–2.0 (m, 2 H–C(5)); 3.21–3.35 (m, H–C(1)); 3.35–3.51 (m, 2 H–C(1')); 3.83 (td, J = 6.5, 5, H–C(2)); 4.40 (t, J = 5.5, OH); 4.76 (d, J = 5, OH); 5.38 (dd, J = 15, 6.5, H–C(3)); 5.53 (dt, J = 15, 6.5, H–C(4)); 6.20 (d, J = 8.5, NH). Anal. calc. for $C_{23}H_{45}NO_4$ (399.62): C 69.13, H 11.35, N 3.51, O 16.02; found: C 69.37, H 11.48, N 3.67, O 15.84.

tert-*Butyl (3*E,*1*S,*2*S*)-*N-*[2-Hydroxy-1-(hydroxymethyl)-3-heptadecenyl]carbamate* (**8**). Following the procedure described above, **20** was converted to crystalline **8** (60%). M.p. 58–59°. $[\alpha]_D^{25} = -0.4°$ (c = 1.0, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO): 0.85 (t, J = 7.5, CH_3–C(16)); 1.12–1.42 (m, 31 H); 1.75–2.0 (m, 2 H–C(5)); 3.20–3.46 (m, 2 H–C(1'), H–C(1)); 4.04–4.13 (m, H–C(2)); 4.55 (t, J = 5, OH); 4.62 (d, J = 6, OH); 5.40 (dd, J = 15, 5, H–C(3)); 5.55 (dt, J = 15, 6, H–C(4)); 5.95 (d, J = 8.5, NH). Anal. calc. for $C_{23}H_{45}NO_4$ (399.62): C 69.13, H 11.35, N 3.51, O 16.02; found: C 69.17, H 11.32, N 3.57, O 15.96.

tert-*Butyl (3*Z,*1*S,*2*R*)-*N-*[2-Hydroxy-1-(hydroxymethyl)-3-heptadecenyl]carbamate* (**7**). Compound **19** (5.1 g, 12.8 mmol) was dissolved in AcOEt (50 ml), *Lindlar*'s catalyst (*Fluka*; 2.5 g) was added, and the mixture was shaken under 1 atm of H_2 for 1 h. The catalyst was removed by filtration through *Celite* and the solvent evaporated *in vacuo*. Crystallization (hexane) of the residue afforded pure **7** (4.74 g, 92.6%). M.p. 58–59°. $[\alpha]_D^{25} = -14.9$ (c = 1.0, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO): 0.85 (t, J = 7.5, CH_3–C(16)); 1.13–1.41 (m, 31 H); 1.85–2.10 (m, 2 H–C(5)); 3.21–3.38 (m, H–C(1)); 3.38–3.55 (m, 2 H–C(1')); 4.20 (td, J = 7.5, 7, 5, H–C(2)); 4.41 (t, J = 6, OH);

4.71 (*d*, *J* = 5, OH); 5.25–5.40 (*m*, H–C(3), H–C(4)); 6.18 (*d*, *J* = 9, NH). Anal. calc. for $C_{23}H_{45}NO_4$ (399.62): C 69.13, H 11.35, N 3.51, O 16.02; found: C 69.13, H 11.37, N 3.54, O 16.10.

tert-*Butyl (3Z,1S,2S)-*N*-[2-Hydroxy-1-(hydroxymethyl)-3-heptadecenyl]carbamate* (**9**). Following the procedure described above, **20** was converted to crystalline **9** (86%). M.p. 52–53°. $[\alpha]_D^{25} = +29.6°$ (*c* = 0.5, $CHCl_3$). ^{1}H-NMR ((D$_6$)DMSO): 0.85 (*t*, *J* = 7.5, CH_3–C(16)); 1.11–1.28 (*m*, 31 H); 1.78–2.08 (*m*, 2 H–C(5)); 3.20–3.50 (*m*, 2 H–C(1'), H–C(1)); 4.36–4.48 (*ddd*, *J* = 8, 5.5, 3.5, H–C(2)); 4.53 (*t*, *J* = 5.5, OH); 4.63 (*d*, *J* = 5.5, OH); 5.24–5.41 (*m*, H–C(3), H–C(4)); 6.02 (*d*, *J* = 8.5, NH). Anal. calc. for $C_{23}H_{45}NO_4$ (399.62): C 69.13, H 11.35, N 3.51, O 16.02; found: C 69.18, H 11.31, N 3.58, O 16.06.

Transformations of Scheme 4. tert-*Butyl (4R,5S,2'E)-*N*-[2,2-Dimethyl-4-(2'-pentadecenyl)-1,3-dioxan-5-yl]carbamate* (**21**). Pyridinium *p*-toluenesulfonate (357 mg, 1.42 mmol) was added to a soln. of **6** (570 mg, 1.42 mmol) and 2,2-dimethoxypropane (3.5 ml, 28.4 mmol) in CH_2Cl_2 (10 ml), and the mixture was stirred at r.t. overnight. Volatiles were evaporated *in vacuo*, and the residue was purified by FC (hexane/AcOEt 3:1), yielding **21** as a colorless oil, which crystallized upon drying. M.p. 58–60°. ^{1}H-NMR ((D$_6$)DMSO): 0.85 (*t*, *J* = 6.5, CH_3–C(14')); 1.20–1.40 (*m*, 22 H); 1.27 (*s*, CH_3); 1.35 (*s*, *t*-Bu); 1.38 (*s*, CH_3); 1.90–2.0 (*m*, 2 H–C(3')); 3.15–3.30 (*m*, H–C(5)); 3.48–3.65 (*m*, 2 H–C(6)); 4.05 (*dd*, *J* = 10, 7, H–C(4)); 5.25 (*dd*, *J* = 15, 7, H–C(1')); 5.63 (*dt*, *J* = 15, 7, H–C(2')); 6.68 (*d*, *J* = 9, NH).

tert-*Butyl (4S,5S,2'E)-*N*-[2,2-Dimethyl-4-(2'-pentadecenyl)-1,3-dioxan-5-yl]carbamate* (**22**). Following the procedure described above, **8** was converted to **22** (42%), which was isolated as a colorless oil. ^{1}H-NMR ((D$_6$)DMSO): 0.85 (*t*, *J* = 6.5, CH_3–C(14')); 1.20–1.40 (*m*, 22 H); 1.31 (*s*, CH_3); 1.38 (*s*, *t*-Bu); 1.39 (*s*, CH_3); 1.90–2.0 (*m*, 2 H–C(3')); 3.35–3.45 (*m*, H–C(5)); 3.52 (*dd*, *J* = 12, 2, H–C(6)); 4.05 (*dd*, *J* = 12, 2, H–C(6)); 4.49 (*dd*, *J* = 5, 1, H–C(4)); 5.30 (*dd*, *J* = 16, 5, H–C(1')); 5.63 (*dt*, *J* = 16, 7, H–C(2')); 6.12 (*d*, *J* = 9.5, NH).

*1-*O*,2-*N*,3-*O*-Triacetyl-*D-erythro-*sphingosine* (**23**). A soln. of **6** (400 mg, 1 mmol) in dioxane (10 ml) and 1N HCl (5 ml) was stirred at 100° for 30 min. After cooling to r.t., 2N NaOH (5 ml) was added and the mixture extracted with Et_2O (3 × 25 ml). The combined Et_2O extracts were washed with sat. NaCl, dried, and evaporated, yielding crude **1**, which was acetylated with Ac_2O (0.57 ml, 6 mmol) in pyridine (2 ml) at r.t. for 2 h. Dilution with Et_2O, washing with 2N HCl, sat. $NaHCO_3$ and sat. NaCl, drying, and evaporating *in vacuo* afforded crude **23**, which was recrystallized from AcOEt/hexane. Yield: 380 mg (89.3%). M.p. 104.5–105° ([2d]: 105–106°; [2e]: 101–101.5°; [4]: 101–102°). $[\alpha]_D^{25} = -12.9°$ (*c* = 1.0, $CHCl_3$); ([2e]: −11.8°; [4]: −12.8°). ^{1}H-NMR ($CDCl_3$): 0.87 (*t*, *J* = 7, CH_3–C(17)); 1.20–1.40 (*m*, 22 H); 1.97–2.09 (*m*, 2 H–C(6)); 2.00, 2.06, 2.09 (3*s*, 3 $COCH_3$); 4.03 (*dd*, *J* = 11.5, 4, H–C(1)); 4.30 (*dd*, *J* = 11.5, 6, H–C(1)); 4.40–4.50 (*m*, H–C(2)); 5.28 (*dd*, *J* = 7, 6, H–C(3)); 5.39 (*dd*, *J* = 15, 7, H–C(4)); 5.63 (*d*, *J* = 9, NH); 5.80 (*dt*, *J* = 15, 7, H–C(5)). Anal. calc. for $C_{24}H_{43}NO_5$ (425.61): C 67.73, H 10.18, N 3.29, O 18.80; found: C 67.85, H 10.36, N 3.53, O 18.76.

*1-*O*,2-*N*,3-*O*-Triacetyl-*D-threo-*sphingosine* (**24**). Following the procedure described above, **8** was converted to **24**, which was recrystallized from pentane. Yield: 73%. M.p. 44.5–45.5° ([2d]: 43–43.5°). $[\alpha]_D^{25} = +10.4°$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR ((D$_6$)DMSO): 0.87 (*t*, *J* = 7, CH_3–C(17)); 1.20–1.40 (*m*, 22 H); 1.97–2.09 (*m*, 2 H–C(6)); 2.00, 2.06, 2.09 (3*s*, 3 $COCH_3$); 4.02–4.13 (*m*, 2 H–C(1)); 4.35–4.45 (*m*, H–C(2)); 5.37 (*dd*, *J* = 15, 7, H–C(4)); 5.40 (*dd*, *J* = 9, 6, H–C(3)); 5.64 (*d*, *J* = 9, NH); 5.78 (*dt*, *J* = 15, 7, H–C(5)). Anal. calc. for $C_{24}H_{43}NO_5$ (425.61): C 67.73, H 10.18, N 3.29, O 18.80; found: 67, 65, H 10.18, N 3.45, O 18.75.

N-*Octadecanoyl-*D-erythro-*sphingosine* (**5**). A mixture of crude **1** (109 mg, 0.34 mmol), prepared from **6** as described above, and *N*-succinimidyl octadecanoate [4a] (124 mg, 0.32 mmol) in abs. THF (11 ml) was stirred at r.t. for 17 h. After concentration *in vacuo*, FC (CH_2Cl_2/CH_3OH 93:7) and crystallization (EtOH) of the pure fractions (175 mg, 96.6%) yielded **5** (117 mg, 64.6%). M.p. 98.5–100° ([4a]: 97–98°). $[\alpha]_D^{25} = -2.4°$ (*c* = 1.1, $CHCl_3$) ([4a]: −3.1°). ^{1}H-NMR ($CDCl_3$): 0.88 (*t*, *J* = 7, CH_3–C(17), CH_3–C(17')); 1.10–1.45 (*m*, 50 H); 1.55–1.75 (*m*, 2 H); 2.05 (*m*, 2 H–C(6)); 2.24 (*t*, *J* = 7.5, 2 H–C(2')), 2.65 (*d*, $w_{1/2} \approx 15$, 2 OH); 3.71 (*dd*, *J* = 11, 3.5, H–C(1)); 3.85–4.0 (*m*, H–C(1), H–C(2)); 4.33 (*m*, H–C(3)); 5.53 (*dd*, *J* = 15, 6, H–C(4)); 5.78 (*dt*, *J* = 15, 6, H–C(5)); 6.42 (*d*, *J* = 6, NH). Anal. calc. for $C_{36}H_{71}NO_3$ (565.97): C 76.40, H 12.64, N 2.47; found: C 76.77, H 12.62, N 2.42.

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