4,5,6-Trisubstituted Piperidinones as Conformationally Restricted Ceramide Analogues: Synthesis and Evaluation as Inhibitors of Sphingosine and Ceramide Kinases and as NKT Cell-Stimulatory Antigens[1])

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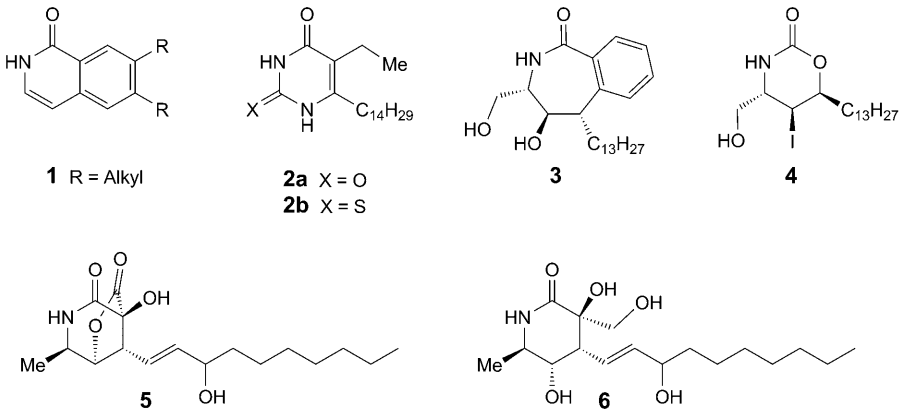
The conformationally based piperidinone sphingosine analogues **7**, **8**, **15**, and **16** were synthesized from allylic alcohol **34** *via* lactams **31** and **32**. The L-*arabino* diol **7** and the L-*ribo* diol **8** were transformed into the amino alcohols **17**–**24**. The L-*gluco* ceramide analogues **43**, **46a**, and **47**, and the L-*altro* ceramide analogues **51a** and **52** were synthesized from either **31** or **32**. The L-*ribo* diols **8** and **16**, and the amino alcohols **19** and **20** inhibit sphingosine kinase 1 (SPHK1), while the L-*arabino* analogues **7**, **15**, **17**, and **18** are inactive. The L-*arabino* and the L-*ribo* dimethylamines **21**–**24**, the L-*gluco* ceramide analogues **43, 46a**, and **47**, and the L-*altro* ceramide analogues **51a** and **52** did not block SPHK1. Neither the L-*arabino* diol **7** nor the L-*ribo* diol **8** inhibited SPHK2 or ceramide kinase. The L-*arabino* diols **7** and **15** stimulate invariant natural killer T (iNKT) cells when presented by living antigen-presenting cells (APC) and also by plate-bound human CD1d, whereas the L-*ribo* diols **8** and **16**, the L-*arabino* amino alcohols **17**–**18**, and the dimethylamines **21**–**22** did not activate iNKT cells. The L-*gluco* ceramide analogues **43**, **46a**, and **47** had strongly stimulatory effects on iNKT cells when presented by living APC and also by plate-bound human CD1d, whereas the L-*altro* ceramide analogue **52** activated only weakly. All activatory compounds induced preferentially the release of pro-inflammatory cytokines, indicating the formation of a stable CD1d–lipid–T-cell receptor complex.

Introduction. – (Glyco)sphingolipids and more specifically ceramides (Cers) adopt a parallel orientation of the lipid chains in the cell membrane, requiring a (*Z*)-configuration of the amide moiety, while the (*E*)-configuration of amides is preferred in solution and in the solid state by a free-energy difference of *ca*. 1.2 kcal/mol [1][2]. There is no *a priori* reason why the amide moiety of a Cer complexed to a receptor should either adopt the (*E*)- or the (*Z*)-configuration. The crystal structure of α-galactosylceramide (αGalCer) bound to the human and the mouse CD1d receptor shows the (*E*)-configuration, *i.e.*, the two alkyl chains diverge from each other [3], suggesting that the configuration of the amide moiety, and not only its H-bond acceptor and donor properties, may be crucial for the interaction with receptors. Yet, only very few compounds have been prepared that may be considered conformationally well-defined ceramide analogues and are biologically active. The isoquinolines **1** were

[1]) Taken in part from the projected Ph.D. Theses of *T. M.* (chemical part) and *M. C.* (biological part).

investigated as conformationally restricted analogues of Cer, and act as ligands of protein phosphatase 2A, a Cer-binding protein that has been implicated in signal transmission [4]. The uracil and thiouracil derivatives **2a** and **2b**, respectively, are further examples which exhibit moderate antitumour activity and toxicity *in vitro* and *in vivo* [5]. Finally, the analogues **3** and **4** [6] inhibit GM-2 synthase. In 2006, *Jang et al.* isolated from the marine fungus *Acremonium sp.* AWA16–1 awajanomycin (**5**) and its derivative **6**, a piperidinone-based cytotoxic agent [7]. Both **5** and **6** inhibit the growth of A549 cells with IC_{50} values of 27.5 and 46.4 μg/ml, respectively.



We were interested in restricting the conformation of the head group of Cer, and in particular of the amide moiety, as they are recognized and modified by sphingosine (Sph)- and Cer-metabolizing enzymes. The conformationally restricted L-*arabino* and the L-*ribo* piperidinones[2]) **7** and **8**, respectively, may be considered analogues of Sph, and the L-*gluco*, L-*manno*, L-*altro*, and L-*allo* piperidinones **9**–**12**, respectively, may be considered Cer analogues mimicking the (*Z*)-configuration of the amide. The piperidinones **9**–**12**, substituted at C(3) and C(6), possess most of the structural features that are required for the biological functions of ceramides, *viz.*, OH groups at C(1) and C(3) [3], the *N*-acylamino substituent at C(2), an (*E*)-C=C bond in the lipid chain of the sphingosine moiety [3][8], and a substituent at C(3) corresponding to the lipid part of the *N*-acyl substituent. As compared to Sphs and Cers, the piperidinones possess one or two additional stereogenic centers, resulting in four diastereoisomeric pairs of enantiomers of the Sph analogues **7** and **8**, and in eight diastereoisomeric pairs of enantiomers of the Cer analogues **9**–**12**. Two and four diastereoisomers possess the same configuration at the corresponding centres as D-*erythro*-sphingosine (**13**) and ceramide (**14**), respectively. Starting the synthesis from D-galactose will result in these two and four diastereoisomers **7**–**12**.

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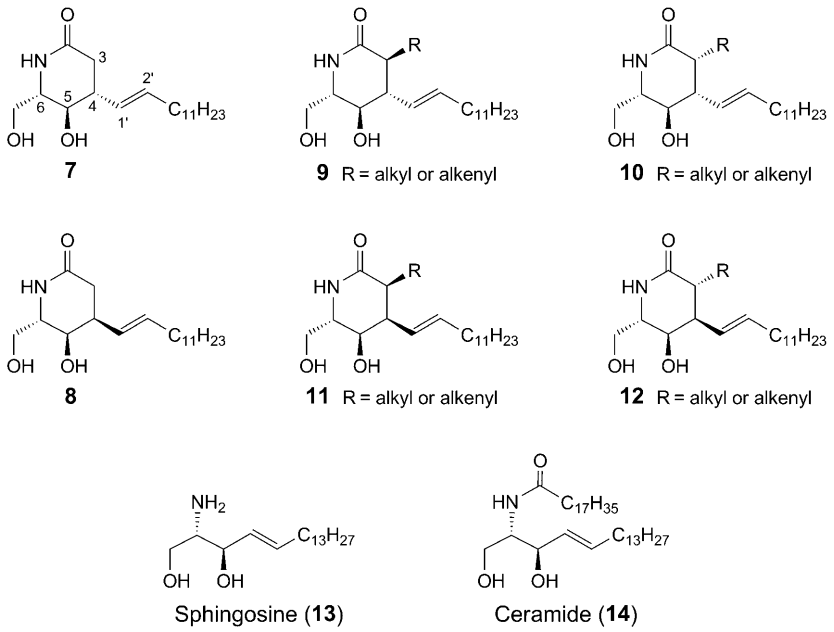
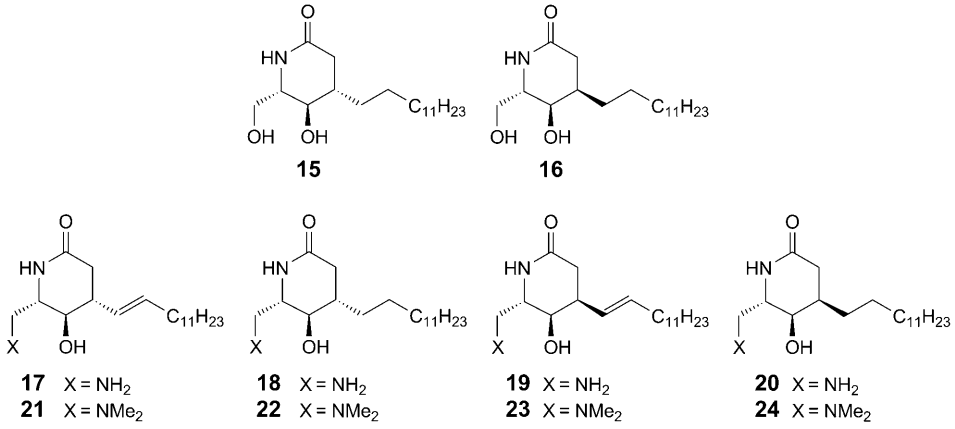
[2]) Piperidinones are also known as hexonolactams. The configuration is specified by the carbohydrate prefix in the *Theoretical Part*, and by the (*R*/*S*)-designation in the *Exper. Part*.



Biological properties for which the piperidinone analogues should be tested include the inhibition of sphingosine [9] and ceramide kinases [10], and the effect on the production of lymphokines [11].

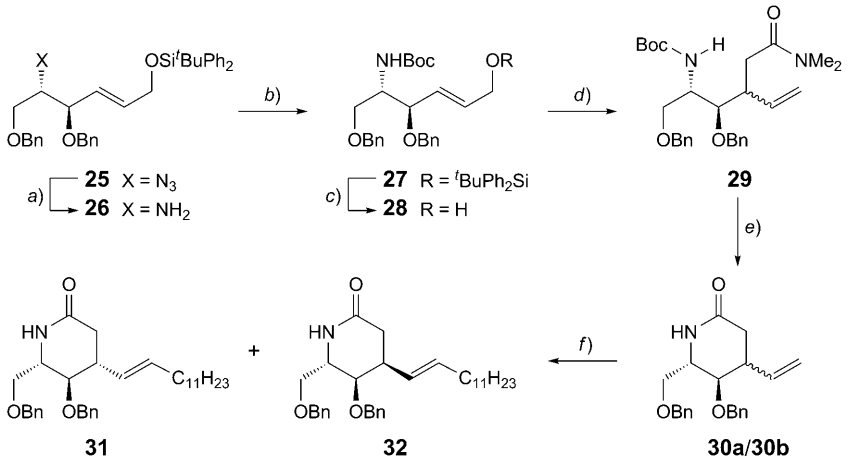
We intended to first synthesize the trisubstituted piperidinones **7** and **8**, their dihydro analogues **15** and **16**, and the unsaturated and saturated amines **17**–**24**, and to then introduce the alkyl chain at C(3) *via* an enolate anion [12][13].



Synthesis. – We planned to prepare the piperidinones **7** and **8** from the known D-galactose-derived azide **25** [14], the *Eschenmoser–Claisen* rearrangement [15] appearing the most promising method for the introduction of the acetamido side chain

(*Schemes 1* and *2*). As the N_3 group interfered with the *Claisen* rearrangement, we reduced **25** to the amine **26** that was protected by (*tert*-butoxy)carbonylation to **27** (*Scheme 1*). Desilylation gave the allylic alcohol **28** that is thus available from D-galactose *via* D-galactal in nine steps and in a *ca.* 50% overall yield [14]. The diastereoisomeric lactams **30** were obtained *via Eschenmoser–Claisen* rearrangement of **28** that led to a 2:1 mixture of the diastereoisomeric amides **29** (85%). Treating a solution of **29** first with CF_3CO_2H in CH_2Cl_2 and then 1M HCl in THF cleaved the *N*-Boc group and effected lactamisation to a 3:1 mixture of the L-*arabino*-configured **30a** and the L-*ribo*-epimer **30b**. Olefin metathesis [16] of **30a**/**30b** 3:1 with undec-1-ene catalyzed by *Grubb*'s second-generation catalyst [16] yielded 70% exclusively of a 3:1 mixture of the (*E*)-alkenyl-substituted pyrimidinones **31** and **32**.

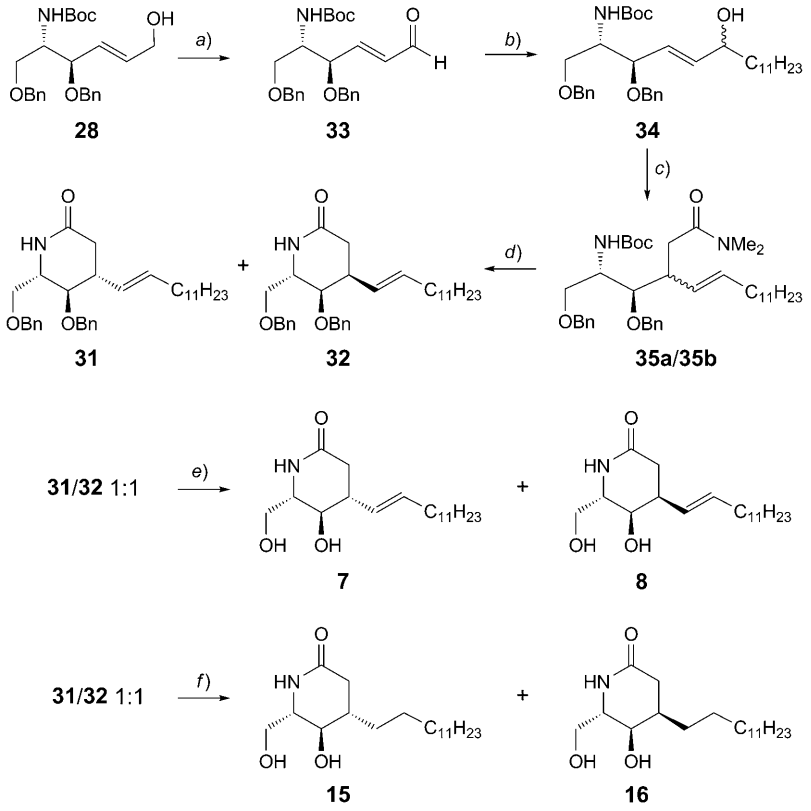
Scheme 1



a) Me_3P, THF/H_2O 4:1. *b*) Boc_2O, β-cyclodextrin, H_2O/acetone/MeOH 4:1:1. *c*) Bu_4NF (TBAF)·3 H_2O, THF; 90% from **25**. *d*) $MeC(OMe)_2NMe_2$, *o*-xylene, 145°; 85%. *e*) 1. CF_3CO_2H, CH_2Cl_2; 2. 1M HCl, THF, reflux; 85%. *f*) Dodec-1-ene, [$(RuCl_2(CHPh)(PCy_3)_2]$], CH_2Cl_2; 70% of **31**/**32** 3:1.

We also introduced the lipid chain before the *Eschenmoser–Claisen* rearrangement, adding $C_{11}H_{23}MgBr$ to the unsaturated aldehyde **33** that was obtained by oxidation of **28** with *Dess–Martin*'s reagent (*Scheme 2*). *Eschenmoser–Claisen* rearrangement of the resulting 11:9 mixture of allylic alcohols **34** led to a 1:1 mixture of the (*E*)-alkenyl amides **35** (74% from **28**). No (*Z*)-isomers were detected. This sequence proved advantageous on account of an easier purification of the products **31** and **32**. The *N*-Boc group of **35** was cleaved, and the resulting amines were transformed into the lactams **31** and **32** (85%), as described above for the transformation of **29** to **30**. A 1:1 mixture of **31** and **32** was debenzylated by treatment with $AlCl_3$ in the presence of anisole to yield 75% of a *ca.* 1:1 mixture **7**/**8**. The isomers were separated by crystallisation ($MeOH/Et_2O$) and/or column chromatography on *Lichoprep* CN silica gel.

Scheme 2



a) *Dess–Martin*'s periodinane, CH_2Cl_2; 95%. *b*) $C_{11}H_{23}MgBr$, Et_2O; 86%. *c*) $MeC(OMe)_2NMe_2$, *o*-xylene, 145°; 90%. *d*) 1. CF_3CO_2H, CH_2Cl_2; 2. 1M HCl, THF, reflux; 85%. *e*) $AlCl_3$, anisole, CH_2Cl_2; 40% of **7** and 35% of **8**. *f*) 10% Pd/C, 6 bar of H_2, AcOH, MeOH; 47% of **15** and 40% of **16**.

The structure of the piperidinones **7** and **8** is evidenced by ^{1}H-NMR spectroscopy, and established by X-ray crystal-structure analysis (*Fig. 1,a*)[3]). Suitable crystals of both isomers were obtained from MeOH/Et_2O.

The crystal structure of **7** shows a $^4H_5$ half-chair conformation with all substituents in a pseudoequatorial orientation (*Fig. 1,b*). The epimer **8** adopts a $^5H_4$ conformation with a pseudoequatorial alkenyl substituent and pseudoaxial CH_2OH and OH groups. *A priori*, one might expect **8** to adopt $^4H_5$ and $^5H_4$ conformations, while the $^5H_4$ conformation is adopted in the solid state and preferred in solution, as evidenced by $J(4,5)=3.3$ and $J(5,6)=4.8$ Hz. The preference for this conformation is attributed to

[3]) The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-720463 for **7**, 720464 for **8**, and 720465 for **15**. Copies of the data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif (or from the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

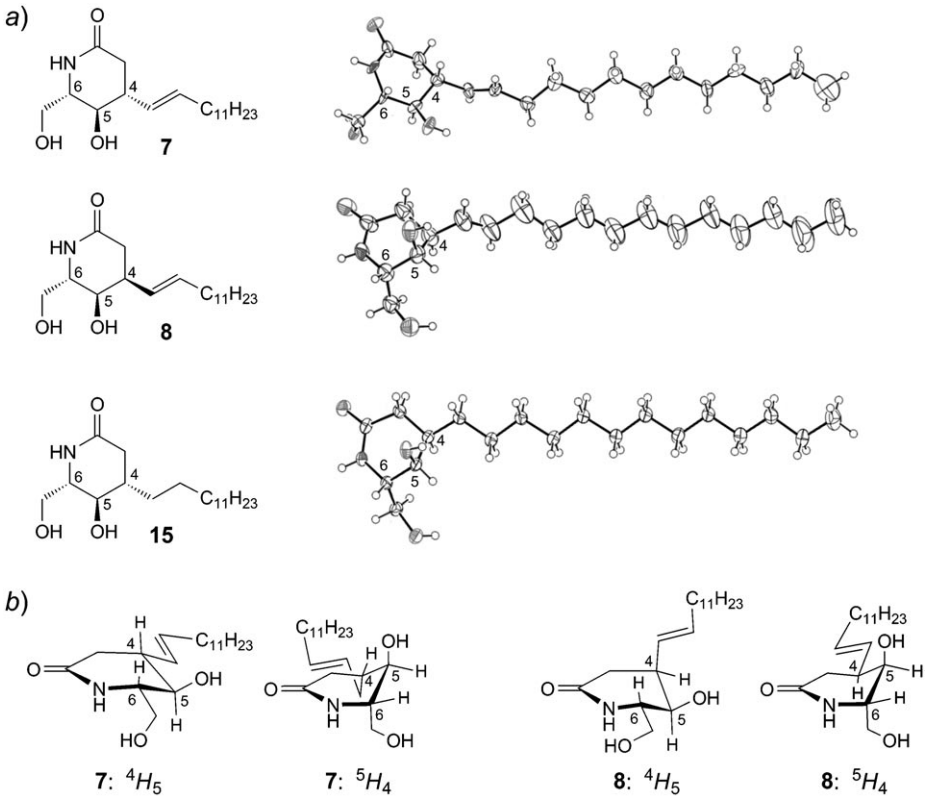


Fig. 1. a) *Crystal structures* (ORTEP diagrams) *of* **7**, **8**, *and* **15**. b) *Half-chair conformations of* **7** *and* **8**.

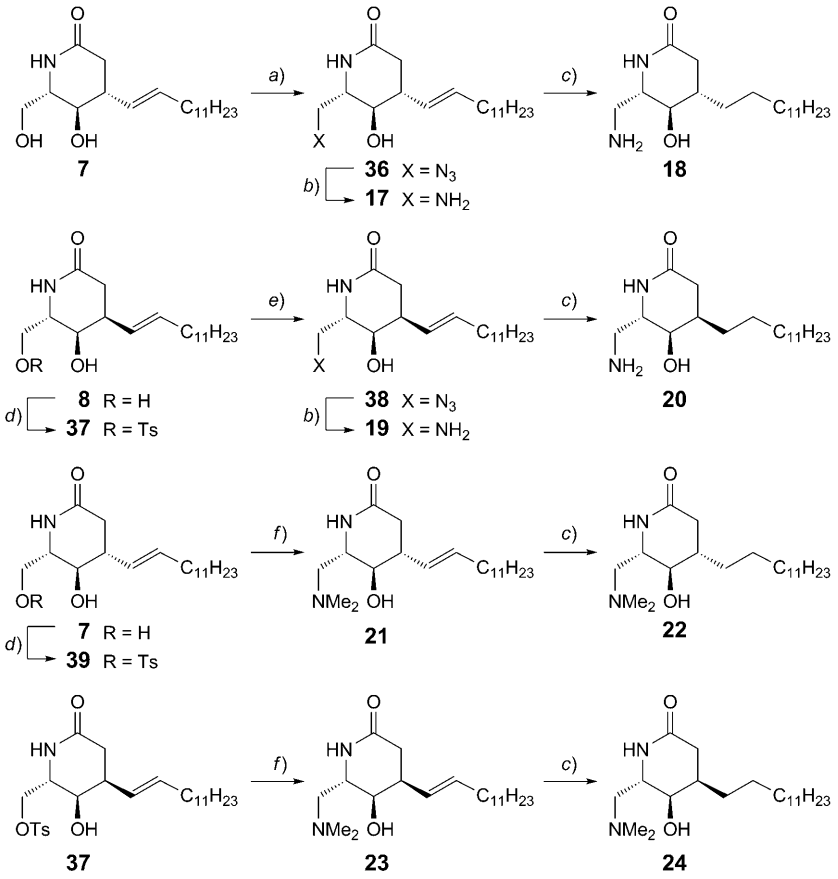
the favourable *gauche*-effect involving the C(2)–N and C(3)–O bonds that overcomes the destabilisation resulting from the pseudoaxial orientation of the CH_2OH and OH groups, while it does not overcome the combined preference of these substituents for a pseudoequatorial orientation, as realized for **7**, and evidenced, in solution, by $J(4,5) = 10.2$ and $J(5,6) = 9.3$ Hz.

For many years, dihydroceramides were regarded as biologically inert [17]. Recent studies [18–21] indicate, however, that these lipids are biologically active, with activities differing from those of Cer. We, therefore, prepared **15** and **16**, the dihydro analogues of **7** and **8**, by catalytic hydrogenation of **31** and **32**, respectively (*Scheme 2*). The structure of **15** is confirmed by X-ray-analysis (*Fig. 1,a*).

We also synthesised the amines **17**–**20** and the *N*,*N*-dimethylamines **21**–**24** (*Scheme 3*), since analogues possessing a basic amino group are expected to be phosphorylated faster by Sph or Cer kinases, and may also inhibit these enzymes.

To introduce the amino group, we subjected the L-*arabino* diol **7** to a *Mitsunobu* reaction with HN_3 (*Scheme 3*). Unfortunately, it proved very difficult to separate the resulting azide **36** from Ph_3PO. A partial purification succeeded when we substituted Ph_3P by [4-(dimethylamino)phenyl](diphenyl)phosphine [22], as most of the resulting

Scheme 3



a) [4-(Dimethylamino)phenyl](diphenyl)phosphine, diethyl azodicarboxylate, HN_3 in toluene, THF; 80%. *b*) 1. Me_3P, THF; 2. 1M NaOH; 90% of **17**; 60% of **19**. *c*) 10% Pd/C, 8 bar of H_2, AcOEt; 95% of **18**; 80% of **20**; 97% of **22**; 94% of **24**. *d*) TsCl, $^iPr_2NEt$, 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2; 82% of **37**; 88% of **39**. *e*) NaN_3, DMF, 100°; 50%. *f*) Me_2NH, THF/H_2O, 85°; 95% of **21**; 92% of **23**.

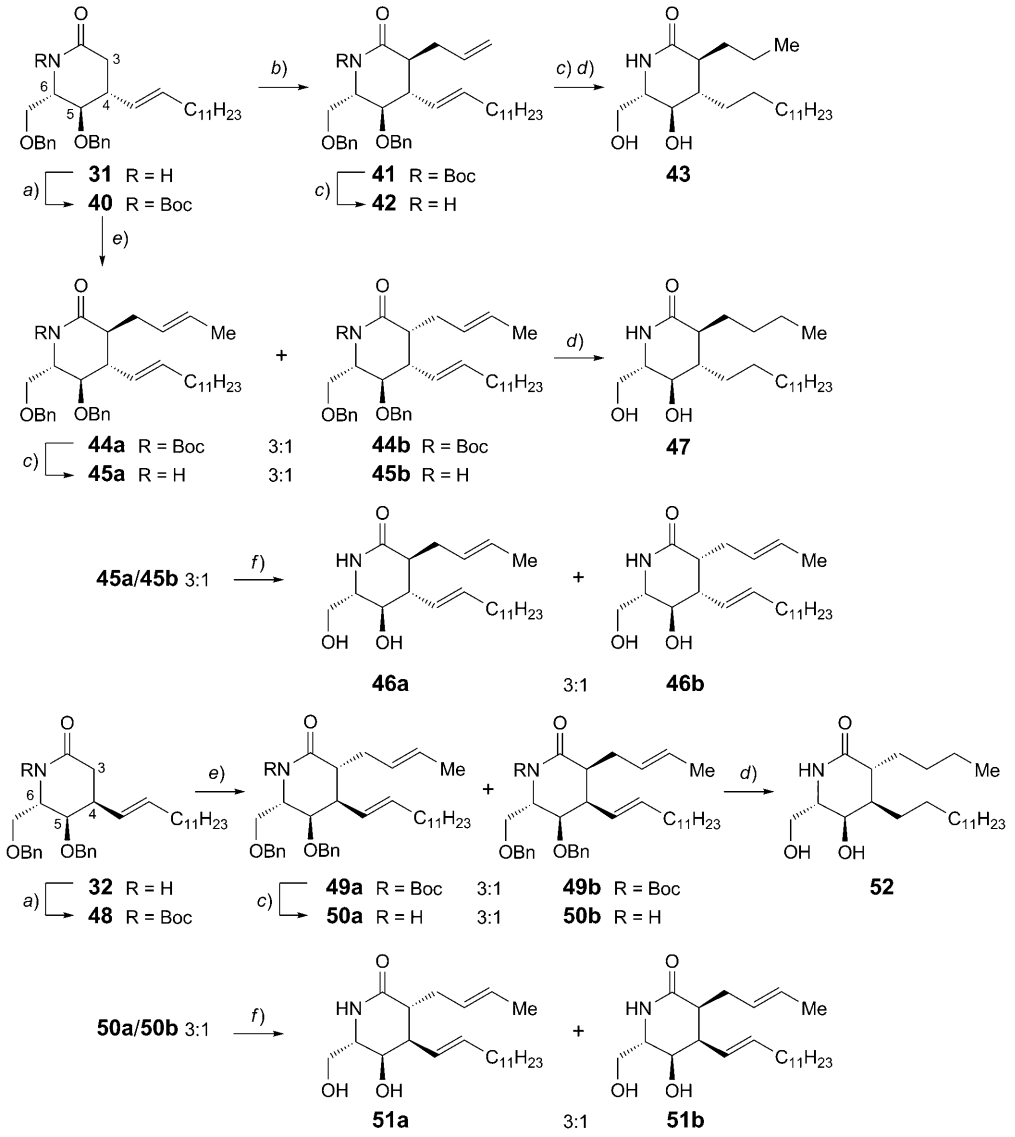
oxide was removed by acidic workup. *Staudinger* reduction [23] of **36** yielded the L-*arabino* amino alcohol **17**, and catalytic hydrogenation gave the dihydro analogue **18**. The analogous procedure failed to provide the NH_2 analogue of the L-*ribo* diol **8**, while tosylation of the primary OH group of **8**, followed by nucleophilic substitution by NaN_3, provided the azido derivative **38**. Catalytic hydrogenation of **38** yielded 80% of the dihydro L-*ribo* amino alcohol **20**, while *Staudinger* reduction of the N_3 group yielded 60% of the L-*ribo* amino alcohol **19**. The dimethylamino derivatives **21** and **23** were obtained by tosylating **7** to **39** and, similarly, **8** to **37**, followed by substitution with $HNMe_2$ to give **21** and **23** in yields of 95 and 92%, respectively. Catalytic hydrogenation of **21** afforded **22** (97%); similarly, **23** gave **24** (94%).

The alkyl chains at C(3) were introduced after *N*-(*tert*-butoxy)carbonylating **31** and **32** to **40** and **48** (80–83% yield), respectively (*Scheme 4*). The *N*-(*tert*-butoxy)carbonylated L-*arabino* lactam **40** was deprotonated with LiHMDS at $-78°$ in the presence of a small amount of HMPA [12][13], and the resulting enolate anion was treated with excess allyl bromide to yield 70% of the L-*gluco* lactam **42** as a single diastereoisomer. It was debocylated and then hydrogenated to yield 68% of the saturated L-*gluco* ceramide analogue **43**. The L-*arabino* lactam **40** was also alkenylated with excess (*E*)-1-bromobut-2-ene to yield 63% of a 3:1 mixture of the tetrasubstituted L-*gluco* and L-*manno* piperidinones **44a** and **44b**, respectively. Similarly, the enolate anion derived from **48** was alkenylated with (*E*)-1-bromobut-2-ene to provide 60% of an inseparable 3:1 mixture of the L-*altro* and L-*allo* diastereoisomers **49a** and **49b**, respectively. Alkenylation in the absence of HMPA resulted in lower yields (< 30%). Removal of the Boc groups in **44a**/**44b** to **45a**/**45b**, followed by debenzylation yielded 67% of a 3:1 mixture of the L-*gluco* and L-*manno* piperidinones **46a** and **46b**, respectively. Similarly, **49a**/**49b** was transformed *via* **50a**/**50b** into a 3:1 mixture of the L-*altro* and L-*allo* isomers **51a** and **51b**, respectively, in 61% yield. Palladium-catalyzed hydrogenation of the 3:1 mixtures **45a**/**45b** and **50a**/**50b** in MeOH/AcOH yielded the saturated L-*gluco* piperidinone **47** and the L-*altro* isomer **52**, respectively, in 74–75% yield as single diastereoisomers. We assume that the Pd-catalyzed migration of the C=C bond, followed by hydrogenation, resulted in the thermodynamically favoured isomer.

The lactam ring of the *N*-unprotected L-*arabino*- and L-*gluco*-configured piperidinones **7**, **15**, **17**, **18**, **30a**, **31**, **36**, **39**, **42**, **43**, **45a**, **46a**, and **47** adopts a $^4H_5$ conformation (see *Fig. 1,b*) with pseudoequatorial substituents evidenced by large J(3ax,4), J(3eq,4), J(4,5), and J(5,6) values ($\geq$8.7 Hz; *Table 1*). This conformation is disfavoured for the *N*-Boc derivatives **40**, **41**, and **44** by the allylic 1,3-strain (see [24] and refs. cit. therein) between the Boc and the $BnOCH_2$ group; a $B_{3,6}$ conformation is evidenced by small J(5,6) (2.1–2.7 Hz) and large J(3ax,4), J(3,4), and J(4,5) values ($\geq$8.1 Hz). The *N*-Boc L-*ribo*- and L-*altro*-configured piperidinones **48** and **49a** adopt a $^5H_4$ conformation (see *Fig. 1,b*) with pseudoequatorial alkenyl and pseudoaxial BnO and $BnOCH_2$ substituents, evidenced by small $J(4,5)=J(5,6)=2.4$ Hz and a large $J(3ax,4)=11.6$ Hz. The *N*-unprotected L-*ribo*- and L-*altro*-configured **8**, **16**, **23**, **24**, **30b**, **32**, **37**, **50a**, **51a**, and **52** ($J(3ax,4)=J(3,4)=6.4–8.9$, $J(4,5)=2.3–3.9$, $J(5,6)=2.9–8.1$ Hz) prefer an equilibrium between $^5H_4$ and $^4H_5$ and/or boat conformations.

Biological Results. – 1. *Sph and Cer Kinase Inhibition.* The L-*ribo* diol **8** inhibited sphingosine kinase 1 (SPHK1) [25] with an IC_{50} value of 11.6 μM and 93% inhibition at the highest test concentration of 100 μM, while the L-*arabino* diol **7** showed only marginal inhibition (14%) at 100 μM, demonstrating the specificity of the enzyme. It is remarkable that the L-*arabino* diol **7** has a conformation similar to that of a sphingoid base, but it is not a good inhibitor for SPHK1; in contradistinction, the L-*ribo* diol **8** with a biased *gauche*-conformation about the C(2)–C(3) bond, as favoured by the *gauche*-effect, is a better inhibitor (*Fig. 1,b*), suggesting that a similar conformation of a sphingoid base is relevant for the binding to SPHK1. Such a conformation may be favoured by protonating Sph leading to a stronger *gauche*-effect. Neither the L-*arabino* **7** nor the L-*ribo*-configured diols **8** inhibited SPHK2 or Cer kinase [26] at

Scheme 4



a) Boc_2O, DMAP, MeCN; 80% of **40**; 83% of **48**. *b*) 1M Lithium hexamethyldisilazide (LiHMDS) in toluene, then hexamethylphosphoric triamide (HMPA) and allyl bromide, THF; 70%. *c*) CF_3CO_2H, anisole, THF; 85% of **42**; 86% of **45a**/**45b**; 80% of **50a**/**50b**. *d*) 10% Pd/C, 8 bar of H_2, AcOH, MeOH; 80% of **43**; 75% of **47**; 74% of **52**. *e*) 1M LiHMDS in toluene, then HMPA and (*E*)-1-bromobut-2-ene, THF; 63% of **44a**/**44b** 3:1; 60% of **49a**/**49b** 3:1. *f*) $AlCl_3$, anisole, 1,2-dichloroethane; 78% of **46a**/**46b** 3:1; 76% of **51a**/**51b** 3:1.

Table 1. *Selected ^{1}H-NMR Coupling Constants* [Hz] *of the Piperidinones in $CDCl_3$ or CD_3OD Listed According to Their Configuration*

Compound	**7**	**15**	**17**	**18**	**21**	**22**	**30a**	**31**	**36**	**39**	**40**
	L-*arabino*										
J(3ax,4)	11.7	11.7	11.8	11.8	[a])	[a])	11.3	11.2	10.8	11.1	12.4
J(3eq,4)	5.1	4.8	5.3	4.9	[a])	[a])	5.4	5.2	5.1	5.4	5.2
J(4,5)	10.2	10.7	10.1	9.9	[a])	[a])	[a])	[a])	[a])	9.6	9.1
J(5,6)	9.3	9.0	8.8	9.9	[a])	[a])	[a])	[a])	[a])	9.0	2.6
Compound	**8**	**16**	**19**	**20**	**23**	**24**	**30b**	**32**	**37**	**38**	**48**
	L-*ribo*										
J(3ax,4)	8.7	[a])	[a])	[a])	[a])	[a])	6.6	6.5	[a])	[a])	11.6
J(3eq,4)	5.7	[a])	[a])	[a])	[a])	[a])	5.4	5.4	[a])	[a])	5.2
J(4,5)	3.3	2.3	[a])	[a])	3.9	3.6	[a])	3.3	3.6	[a])	2.4
J(5,6)	4.8	2.9	[a])	[a])	8.1	7.4	[a])	6.2	3.6	[a])	2.4
Compound	**41**	**44a**	**42**	**43**	**45a**	**46a**	**47**	**49a**	**50a**	**51a**	**52**
	L-*gluco*							L-*altro*			
J(3,4)	9.3	[a])	9.9	9.5	9.6	10.2	9.0	[a])	[a])	8.9	6.4
J(4,5)	8.1	8.5	9.9	9.5	9.6	10.2	10.2	2.4	3.1	2.6	3.2
J(5,6)	2.1	2.7	8.7	8.7	9.0	9.2	8.8	2.4	5.3	3.8	6.0

[a]) Not assigned.

concentrations of up to 100 μM; thus, L-*ribo* **8** is a specific inhibitor of SPHK1 among the lipid kinases tested here. In keeping with these results, the dihydro derivative **16** of L-*ribo* **8** inhibited SPHK1 with an IC_{50} value of 9.8 μM, while the dihydro derivative **15** of L-*arabino* **7** did not inhibit the enzyme. Replacing the $HOCH_2$ group of the L-*ribo* diol **8** and **16** by an NH_2CH_2 group, as in the L-*ribo* amino alcohols **19** and **20**, yielded stronger inhibitors with IC_{50} values of 2.2 and 0.58 μM, respectively, while the L-*arabino* **17** and **18**, and the L-*arabino*- as well as the L-*ribo*-configured dimethylamines **21**–**24** were inactive. The ceramide analogues **43**, **46a**, **47**, **51a**, and **52**, resulting from the introduction of an alkyl moiety at C(3) of the diols **7**, **8**, **15**, and **16** did not block SPHK1.

2. *Activation of Invariant Natural Killer T* (*iNKT*) *Cells.* iNKT Cells recognize a variety of lipid antigens presented by the CD1d molecule. Therefore, we tested whether piperidinones are capable of stimulating this population of human T lymphocytes. The piperidinones were first tested for cytotoxic effects *in vitro*. T Cells were incubated overnight with increasing doses of the sonicated piperidinones, and the next day cell death was assessed by measuring the uptake of propidium iodide or 7-aminoactinomycin D using a *CYAN*™ ADP flow cytometer (*Beckman Coulter*, Fullerton, California, USA). The median lethal concentrations (LC_{50}) were calculated for each compound (*Table 2*).

The piperidinones listed in *Table 2*, with the exception of L-*altro* **51a**, were used to stimulate human iNKT cells presented by THP1 cells transfected with human CD1d gene (THP1-hCD1d; *Fig. 2*). In parallel experiments, plate-bound recombinant soluble human CD1d was loaded with the relevant lipids and used to stimulate iNKT cells. Briefly, THP1-hCD1d cells (2.5×10^4/well) or soluble plate-bound recombinant human CD1d (5 μg/ml) were incubated with the sonicated compounds at the indicated

Table 2. *Median Lethal Concentrations* (LC_{50}) *of Piperidinones*

Compound	Configuration	LC_{50} [μg/ml]	Compound	Configuration	LC_{50} [μg/ml]
7	L-*arabino*	8	**8**	L-*ribo*	n.d.[a])
15	L-*arabino*	9	**16**	L-*ribo*	n.d.
17	L-*arabino*	9	**19**	L-*ribo*	4.5
18	L-*arabino*	4.5	**20**	L-*ribo*	4
21	L-*arabino*	8	**23**	L-*ribo*	9.5
22	L-*arabino*	8	**24**	L-*ribo*	n.d.
43	L-*gluco*	>20	**51a**	L-*altro*	n.d.
46a	L-*gluco*	>20	**52**	L-*altro*	7
47	L-*gluco*	>20			

[a]) n.d.: Not determined.

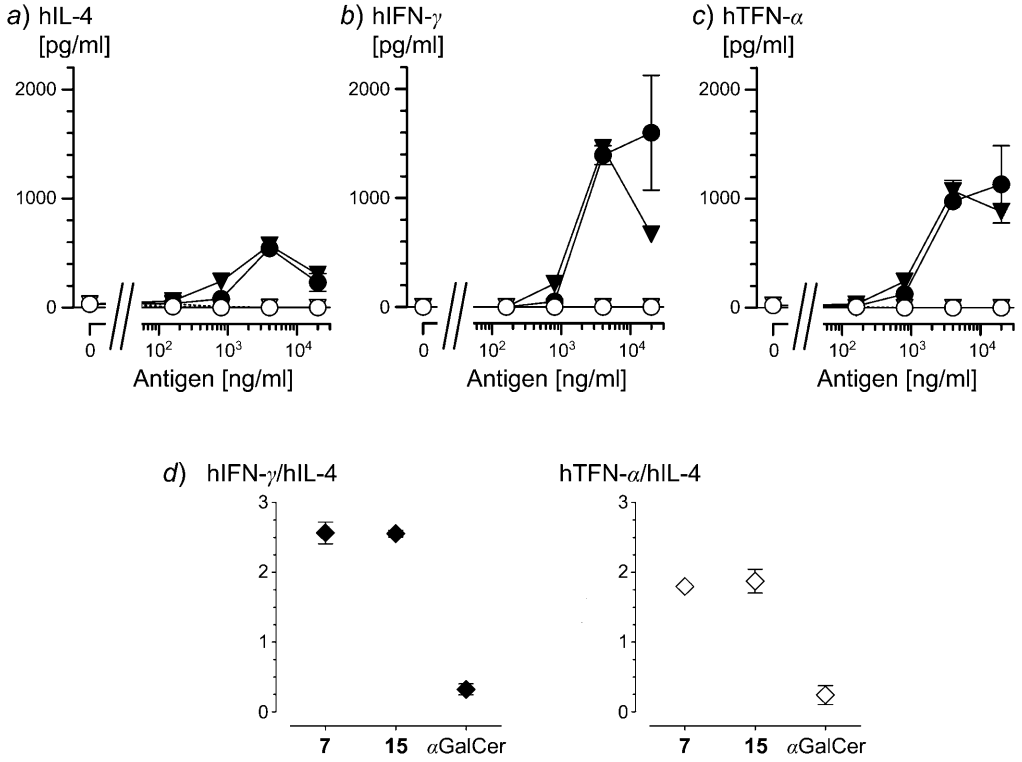


Fig. 2. *Piperidinones with a single lipid tail activate iNKT cells with living antigen-presenting cells* (APC). The L-*arabino* diols **7** and **15** stimulate iNKT cells when presented by THP1-hCD1d APC as measured by release of human *a*) IL-4, *b*) IFN-γ, and *c*) TNF-α (●=**7**, ○=**8**, ▼=**15**, ▽=**16**). *d*) Diols **7** and **15** preferentially induced a T_H1 response, as visualized by the IFN-γ /IL-4 ratio of the stereotype T_H1 *vs.* T_H2 cytokines IFN-γ and by the TNF-α/IL-4 ratio.

concentrations in the presence of T cells (7.5×10^4/well or 1.5×10^5/well, resp.) at 37°. For competition assays, a fixed dose of the piperidinones was given 4.5 h in advance of

titrating αGalCer and addition of T cells. Culture supernatants were collected after 24 h, and iNKT cell released cytokines were measured by ELISA [27][28]. The L-*arabino* diols **7** and **15** activated iNKT cells (*Fig. 2*), although they possess only one lipid tail. This finding was unexpected, since all the iNKT cell-stimulatory compounds so far described in the literature possess two lipid chains. To confirm that the T cell-stimulatory activity is due to formation of complexes with CD1d and not to cellular modifications induced by these piperidinones in APC, T cell-activation was tested using CD1d plate-bound assays. Both L-*arabino* diols **7** and **15** were active also in this type of assay (*Fig. 3*), thus confirming that they form stimulatory complexes with CD1d.

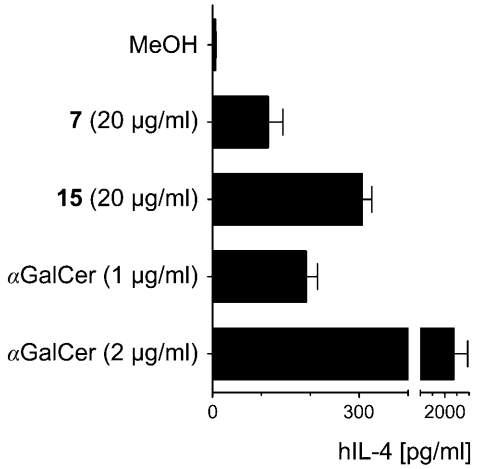


Fig. 3. *Piperidinones with a single lipid tail activate iNKT cells when presented by plate-bound human CD1d.* The L-*arabino* configured diols **7** and **15** induce cytokine production by iNKT cells when presented on recombinant soluble plate-bound human CD1d, as measured by released human IL-4.

The formation of complexes with CD1d is also supported by the finding that only the L-*arabino* diols **7** and **15** possess stimulatory capacity, whereas the L-*ribo* diols **8** and **16** do not (*Fig. 2*).

Importantly, iNKT cells are activated by the L-*arabino* diol **7**, but not by the L-*arabino* amino alcohol **17** and the dimethylamino alcohol **21**, with **7** differing from **17** and **21** only by the $HOCH_2$ group at C(6). A similar activity was observed for the L-*arabino* diol **15** that is active, whereas the L-*arabino* amines **18** and **22** are not. It is tempting to speculate that the primary OH group is important in interacting, presumably *via* H-bonding, with the CD1d molecule, thus determining its position within CD1d. This OH group might also make binding contacts with the TCR of iNKT cells, thus stabilizing the CD1d–lipid–TCR trimolecular complex, as shown for the αGalCer antigen [29–31].

A second important finding is that only the L-*arabino* diols **7** and **15** were active, whereas the L-*ribo* diols **8** and **16** were not, suggesting that binding of the lipid to CD1d, or its positioning within CD1d, is dictated also by this structural element.

Since the presence of a second lipid tail in the lipid antigen might stabilize the CD1d–lipid stimulatory complexes and facilitate T-cell activation, we tested piperidinones with an additional substituent at C(3).

The L-*gluco* ceramide analogues **43**, **46a**, **47** had a strongly stimulatory effect on iNKT cells when presented by living APC and also by plate-bound human CD1d, whereas the L-*altro* ceramide analogue **52** activated only weakly (*Fig. 4*), suggesting that, also in these compounds, the configuration at C(3) and C(4) is important. A similar stimulatory activity was observed in plate-bound assays (*Fig. 5*), confirming that each molecule forms stimulatory complexes with CD1d. The compounds with two lipid tails showed a similar efficacy and potency as **7** and **15**, which have only one lipid tail, indicating that addition of a short alkenyl chain at C(3) does not change this biological activity.

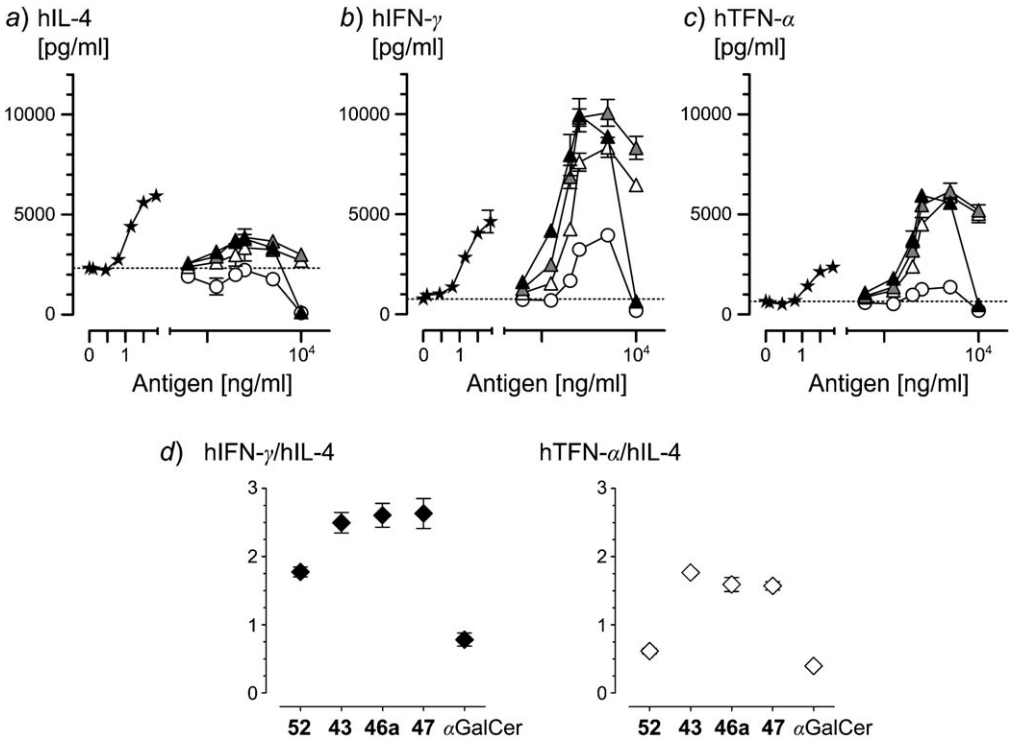


Fig. 4. *Piperidinones with two lipid tails activate iNKT cells with living APC.* The L-*gluco* ceramide analogues **43**, **46a**, and **47**, and the L-*altro* ceramide analogue **52** presented by THP1-hCD1d promote release of human *a*) IL-4, *b*) IFN-γ, and *c*) TNF-α by iNKT cells (★ = αGalCer, △ = **43**, ◬ = **46a**, ▲ = **47**, ○ = **52**). *d*) All active compounds induced more of a T_H1 response, as seen by the ratios IFN-γ and TNF-α to IL-4.

A final unexpected finding was that all tested compounds preferentially induce release of T_H1-like cytokines IFN-γ and TNF-α, whereas the T_H2 cytokine IL-4 is released in low amounts. *Fig. 2*, *d* and *Fig. 4*, *d* show the IFN-γ/IL-4 and TNF-α/IL-4

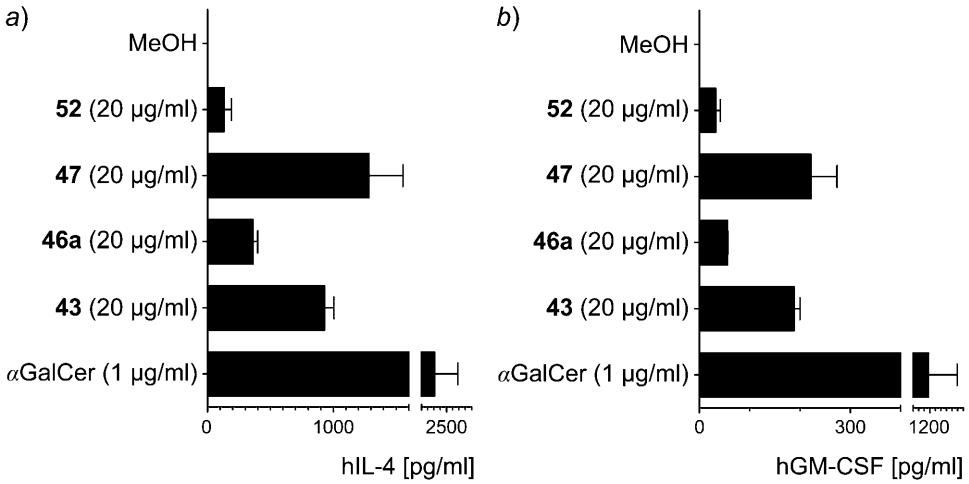


Fig. 5. *Piperidinones with two lipid tails on plate-bound human CD1d activate iNKT cells.* The L-*gluco* ceramide analogues **43**, **46a**, and **47**, and the L-*altro*-configured ceramide analogue **52** are stimulatory for iNKT cells when presented on dimerized plate-bound human CD1d, as human IL-4 (*a*) and GM-CSF (*b*) are released.

ratios with αGalCer, the L-*arabino* diols **7** and **15**, the L-*gluco* ceramide analogues **43**, **46a**, and **47**, and the L-*altro* ceramide analogue **52**, respectively.

Thus, these piperidinones induce preferentially a T_H1 response. As the tested iNKT cells release both classes of cytokines when the αGalCer agonist is used as antigen, the T_H1-biased response has to be ascribed to the type of CD1d–lipid complexes formed by these piperidinones. T_H1 Responses have been associated with strong TCR engagement, whereas T_H2 responses have been ascribed to weak interactions. It is, therefore, tempting to speculate that piperidinones form complexes with CD1d that make high affinity interactions with the TCR of iNKT cells. Future studies will address this point.

In conclusion, fine-tuning the structure of piperidinones may lead to the rational design of new iNKT activatory compounds with unique biological properties. The generation of lipid compounds preferentially inducing T_H1 responses might have applications in novel vaccination and antitumour therapies.

We thank *Novartis AG*, Basel, for a fellowship, the *Swiss National Science Foundation* and ETH Zürich for financial support, Dr. *Bruno Bernet* for numerous contributions to the manuscript, and Dr. *W. Bernd Schweizer* for the X-ray analyses.

Experimental Part

General. See [14].

*(*E*)-2-Amino-1,3-di-*O*-benzyl-6-*O*-[(*tert*-butyl)diphenylsilyl]-2,4,5-trideoxy-*D*-*erythro*-hex-4-enitol* (**26**). An ice-cold soln. of **25** [14] (2.18 g, 3.68 mmol) in THF (30 ml) was treated dropwise with 1M Me_3P in THF (7.4 ml, 7.4 mmol), stirred at 0° for 1 h and at 25° for 5 h, treated with H_2O (7.5 ml), and stirred for 24 h. After evaporation, a soln. of the residue in AcOEt (100 ml) was washed with H_2O (100 ml). The aq. phase was extracted with AcOEt (3 × 100 ml). The combined org. phases were washed with brine,

dried (Na_2SO_4), and evaporated to afford crude **26** (2.1 g, quant.) that was used directly for the next step. A pure sample of **26** was obtained by FC (CH_2Cl_2/MeOH 9:1). Colourless oil. $[\alpha]_D^{25} = -22.6$ ($c = 0.5$, $CHCl_3$). IR (ATR): 3383*w*, 3070*w*, 3029*w*, 2930*w*, 2856*w*, 1471*w*, 1454*w*, 1427*w*, 1380*w*, 1361*w*, 1260*w*, 1205*w*, 1110*s*, 1071*m*, 1028*w*, 975*w*, 822*m*, 738*s*, 699*s*, 633*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.73–7.68 (*m*, 4 arom. H); 7.48–7.27 (*m*, 16 arom. H); 5.86 (*dt*, $J = 15.6$, 4.5, H–C(5)); 5.72 (*ddt*, $J = 15.9$, 8.1, 1.5, H–C(4)); 4.58 (*d*, $J = 11.7$, PhC*H*); 4.55 (*d*, $J = 12.0$, PhC*H*); 4.49 (*d*, $J = 12.0$, PhC*H*); 4.32 (*d*, $J = 11.4$, PhC*H*); 4.30 (br. *dd*, $J = 4.2$, 1.2, 2 H–C(6)); 3.83 (*dd*, $J = 7.8$, 6.6, H–C(3)); 3.63 (*dd*, $J = 9.3$, 4.2, H_a–C(1)); 3.52 (*dd*, $J = 9.0$, 6.9, H_b–C(1)); 3.10 (*td*, $J = 6.6$, 4.2, H–C(2)); 1.51 (br. *s*, NH_2); 1.10 (*s*, *t*-Bu). ^{13}C-NMR ($CDCl_3$, 75 MHz): 138.40, 138.28 (2*s*); 135.42 (*d*, 4 CH); 134.82 (*d*, C(4)); 133.50 (*s*, 2 C); 129.67 (*d*, C(5)); 129.67–127.24 (several *d*); 80.99 (*d*, C(3)); 73.2 (*t*, PhCH_2); 71.79 (*t*, PhCH_2); 70.21 (*t*, C(1)); 63.62 (*t*, C(6)); 54.37 (*d*, C(2)); 26.76 (*q*, *Me*$_3$C); 19.18 (*s*, Me$_3$*C*). HR-MALDI-MS: 566.3082 (100, $[M + H]^+$, $C_{36}H_{44}NO_3Si^+$; calc. 566.3090). Anal. calc. for $C_{36}H_{43}NO_3Si$ (565.83): C 76.42, H 7.66, N 2.48; found: C 76.25, H 7.58, N 2.54.

*(*E*)-1,3-Di*-O-*benzyl-6*-O-*[(*tert*-*butyl)diphenylsilyl]-{[(*tert*-*butoxy)carbonyl]amino}-2,4,5-trideoxy*-D-erythro-*hex-4-enitol* (**27**). A soln. of β-cyclodextrin (180.7 mg, 0.16 mmol) in H_2O (40 ml) was treated with a soln. of crude **26** (2.05 g, 3.63 mmol) in acetone/MeOH 1:1 (15 ml), followed by a soln. of Boc_2O (870.6 mg, 3.99 mmol) in acetone/MeOH 1:1 (5 ml), stirred at 25° for 45 min, diluted with H_2O, and extracted with CH_2Cl_2 (3 × 100 ml). The combined org. phases were washed with brine, dried (Na_2SO_4), and evaporated to afford crude **27** (2.14 g, quant.) that was used directly for the next step. A small amount was subjected to FC (AcOEt/hexane 1:4) to afford pure **27**. Colourless oil. R_f (AcOEt/hexane 1:1) 0.84. $[\alpha]_D^{25} = -22.2$ ($c = 0.75$, $CHCl_3$). IR (ATR): 3450*w*, 2961*w*, 2930*w*, 2857*w*, 1714*m*, 1496*m*, 1472*w*, 1454*w*, 1427*w*, 1390*w*, 1364*w*, 1275*w*, 1259*w*, 1167*m*, 1105*s*, 1063*m*, 1027*m*, 970*w*, 909*w*, 861*w*, 822*w*, 746*s*, 697*s*, 612*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.71–7.69 (*m*, 4 arom. H); 7.47–7.28 (*m*, 16 arom. H); 5.85 (*dt*, $J = 15.3$, 4.2, H–C(5)); 5.73 (*dd*, $J = 15.3$, 7.2, H–C(4)); 4.88 (*d*, $J = 9.0$, NH); 4.58 (*d*, $J = 12.0$, PhC*H*); 4.52 (*d*, $J = 12.0$, PhC*H*); 4.45 (*d*, $J = 12.0$, PhC*H*); 4.32 (*d*, $J = 11.4$, PhC*H*); 4.25 (br. *d*, $J = 3.6$, 2 H–C(6)); 4.01 (*t*, $J = 6.6$, H–C(3)); 3.97–3.87 (br. *s*, H–C(2)); 3.78 (*dd*, $J = 9.6$, 4.5, H_a–C(1)); 3.56 (*dd*, $J = 9.3$, 3.9, H_b–C(1)); 1.42 (*s*, *t*-Bu); 1.10 (*s*, Me$_3$CSi). ^{13}C-NMR ($CDCl_3$, 75 MHz): 155.35 (*s*, C=O); 138.30, 138.15 (2*s*); 135.44 (*d*, 4 CH); 134.22 (*d*, C(4)); 133.57 (*s*, 2 C); 129.63 (*d*, C(5)); 129.63–127.28 (several *d*); 79.19 (*d*, C(3)); 79.19 (*s*, Me$_3$*C*O); 73.14 (*t*, PhCH_2); 70.52 (*t*, PhCH_2); 68.85 (*t*, C(1)); 63.91 (*t*, C(6)); 53.36 (*d*, C(2)); 28.51 (*q*, *Me*$_3$CO); 26.76 (*q*, *Me*$_3$CSi); 19.18 (*s*, Me$_3$*C*Si). HR-MALDI-MS: 688.3430 (100, $[M + Na]^+$, $C_{41}H_{51}NNaO_5Si^+$; calc. 688.3434). Anal. calc. for $C_{41}H_{51}NO_5Si$ (665.94): C 73.95, H 7.72, N 2.10; found: C 73.46, H 8.01, N 2.12.

*(*E*)-1,3-Di*-O-*benzyl-2*-N-*{[(*tert*-*butoxy)carbonyl]amino}-2,4,5-trideoxy*-D-erythro-*hex-4-enitol* (**28**). An ice-cold soln. of crude **27** (2.125 g, 3.19 mmol) in THF (50 ml) was treated with Bu_4NF (TBAF)·3 H_2O (2.04 g, 6.38 mmol), and stirred at 0° for 10 min and then at 25° for 13 h. The mixture was diluted with AcOEt (100 ml), H_2O (100 ml), and brine (5 ml). After separation of the layers, the aq. phase was extracted with AcOEt (3 × 100 ml). The combined org. phases were washed with brine, dried (Na_2SO_4), and evaporated to afford crude **28** that was filtered through a short pad of silica gel (AcOEt/pentane 1:4 → 1:1) to afford **28** (1.23 g, 90% from **25**). Pale yellow oil. R_f (AcOEt/hexane 1:1) 0.51. $[\alpha]_D^{25} = -35.6$ ($c = 1.3$, $CHCl_3$). IR (ATR): 3441*w* (br.), 3346*w*, 3030*w*, 2976*w*, 2929*w*, 2866*w*, 1694*s*, 1497*s*, 1453*m*, 1391*w*, 1365*s*, 1247*w*, 1204*w*, 1165*m*, 1091*s*, 1065*s*, 1026*s*, 974*m*, 911*w*, 860*w*, 778*w*, 735*s*, 697*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.34–7.27 (*m*, 10 arom. H); 5.89 (*dt*, $J = 15.9$, 5.4, H–C(5)); 5.70 (*dd*, $J = 15.9$, 7.8, H–C(4)); 5.02 (*d*, $J = 8.7$, NH); 4.60 (*d*, $J = 12.0$, PhC*H*); 4.51 (*d*, $J = 11.7$, PhC*H*); 4.44 (*d*, $J = 12.0$, PhC*H*); 4.34 (*d*, $J = 11.7$, PhC*H*); 4.19–4.08 (*m*, 2 H–C(6)); 3.96 (*t*, $J = 7.5$, H–C(3)); 3.91–3.78 (*m*, H_a–C(1), H–C(2)); 3.55 (*dd*, $J = 8.7$, 3.0, H_b–C(1)); 2.36 (br. *s*, OH); 1.42 (*s*, *t*-Bu). ^{13}C-NMR ($CDCl_3$, 75 MHz): 155.53 (*s*, C=O); 138.20, 138.01 (2*s*); 134.02 (*d*, C(4)); 128.87 (*d*, C(5)); 128.28–127.47 (several *d*); 79.23 (*s*, Me$_3$*C*); 79.03 (*d*, C(3)); 73.07 (*t*, PhCH_2); 70.54 (*t*, PhCH_2); 68.59 (*t*, C(1)); 62.54 (*t*, C(6)); 53.23 (*d*, C(2)); 28.29 (*q*, *Me*$_3$C). HR-MALDI-MS: 450.2255 (100, $[M + Na]^+$, $C_{25}H_{33}NNaO_5^+$; calc. 450.2256). Anal. calc. for $C_{25}H_{33}NO_5 \cdot 0.3\ H_2O$ (432.9378): C 69.31, H 7.82, N 3.24; found: C 69.31, H 8.03, N 3.24.

4,6-Di-O-*benzyl-5-{[(*tert*-*butoxy)carbonyl]amino}-2,3,5-trideoxy*-N,N-*dimethyl-3*-C-*vinyl*-L-arabino- *and* -L-ribo-*hexonamide* (**29**). A soln. of **28** (120 mg, 0.28 mmol) in *o*-xylene (3 ml) was treated with *N*,*N*-dimethylacetamide dimethyl acetal (0.1 ml, 0.56 mmol), stirred at 145° for 5 h, cooled to 25°, diluted with AcOEt (50 ml), and washed with H_2O (50 ml). The aq. phase was extracted with AcOEt (3 ×

50 ml). The combined org. phases were washed with brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/pentane 3:7→1:1) gave **29** (2:1 mixture of diastereoisomers; 118 mg, 85%). Colourless gum. R_f (AcOEt/hexane 2:3) 0.43. ^{1}H-NMR ($CDCl_3$, 300 MHz, 2:1 mixture of diastereoisomers): 7.38–7.22 (*m*, 10 arom. H); 5.90 (br. *dt*, *J* = 17.5, 9.5, 0.33 H), 5.87 (br. *dt*, *J* = 17.5, 9.5, 0.67 H) (H–C(1′)); 5.13–5.05 (*m*, 2 H–C(2′)); 4.95 (*d*, *J* = 9.0, NH); 4.66–4.52 (*m*, 2 PhC*H*$_2$); 4.00–3.88 (*m*, H–C(5)); 3.78–3.65 (*m*, H–C(4), H_a–C(6)); 3.55 (*td*, *J* = 9.5, 4.5, H_b–C(6)); 3.05 (br. *q*, *J* ≈ 7.5, H–C(3)); 2.93 (*s*, 1 H), 2.90 (*s*, 3 H), 2.84 (*s*, 2 H) (Me_2N); 2.65 (br. *dd*, *J* ≈ 14.5, 4.0, 0.33 H); 2.50–2.30 (*m*, 1.67 H) (2 H–C(2)); 1.45 (br. *s*, *t*-Bu). ^{13}C-NMR ($CDCl_3$, 75 MHz; 2:1 mixture of diastereoisomers): signals of the major diastereoisomer: 171.44 (*s*, C(1)); 155.04 (*s*, OC=O); 138.49, 137.98 (2*s*); 137.34 (*d*, C(1′)); 128.23–127.47 (several *d*); 117.06 (*t*, C(2′)); 79.67 (*d*, C(4)); 79.05 (*s*, Me_3C); 73.51 (*t*, PhC*H*$_2$); 73.17 (*t*, PhC*H*$_2$); 69.57 (*t*, C(6)); 51.94 (*d*, C(5)); 41.68 (*t*, C(2)); 37.25, 35.42 (2*q*, Me_2N); 34.61 (*d*, C(3)); 28.48 (*q*, *Me*$_3$C); signals of the minor diastereoisomer: 171.53 (*s*, C(1)); 155.31 (*s*, OC=O); 138.84 (*d*, C(1′)); 138.32, 137.90 (2*s*); 128.23–127.47 (several *d*); 116.35 (*d*, C(2′)); 81.31 (*d*, C(4)); 79.32 (*s*, Me_3C); 74.37 (*t*, PhC*H*$_2$); 73.01 (*t*, PhC*H*$_2$); 68.81 (*t*, C(6)); 51.74 (*d*, C(5)); 42.17 (*t*, C(2)); 37.37, 35.47 (2*q*, Me_2N); 33.56 (*d*, C(3)); 28.48 (*q*, *Me*$_3$C). HR-MALDI-MS: 519.2835 (65, $[M + Na]^+$, $C_{40}H_{62}N_2NaO_3^+$; calc. 519.2828), 397.2998 (100, $[M - Boc + H]^+$, $C_{24}H_{33}N_2O_3^+$; calc. 397.2491).

*(4*R,5R,6S*)- and (4*S,5R,6S*)-5-(Benzyloxy)-6-[(benzyloxy)methyl]-4-ethenylpiperidin-2-one* (**30a** and **30b**, resp.). An ice-cold soln. of **29** (2:1 mixture of diastereoisomers; 110 mg, 0.22 mmol) in CH_2Cl_2 (2 ml) was treated with CF_3CO_2H (0.5 ml), stirred at 25° for 8 h, and evaporated. A soln. of the residue in THF (3 ml) was treated with 1M HCl (3 ml), stirred at 25° for 15 h, and kept at reflux for 5 h. The mixture was diluted with AcOEt (100 ml) and washed with $NaHCO_3$ soln. (100 ml). The aq. phase was extracted with AcOEt (3 × 100 ml). The combined org. phases were washed with brine, dried (Na_2SO_4), and evaporated. FC (AcOEt) gave **30a**/**30b** 3:1 (66 mg, 85%). Colourless gum. R_f (AcOEt) 0.35. ^{1}H-NMR ($CDCl_3$, 300 MHz; **30a**/**30b** 6:1): signals of **30a**: 7.39–7.21 (*m*, 10 arom. H); 5.99 (br. *s*, NH); 5.83 (*ddd*, *J* = 17.4, 10.1, 7.4, H–C(1′)); 5.23 (*dt*, *J* = 17.4, 1.2, H_a–C(2′)); 5.18 (*dt*, *J* = 10.2, 1.2, H_b–C(2′)); 4.67, 4.39 (2*d*, *J* = 10.9, PhC*H*$_2$); 4.48 (br. *s*, PhC*H*$_2$); 3.66–3.56 (*m*, H–C(6), CH_a–C(6)); 3.37–3.26 (*m*, H–C(5), CH_b–C(6)); 2.87–2.73 (*m*, H–C(4)); 2.54 (br. *dd*, *J* = 17.7, 5.4, H_a–C(3)); 2.31 (*dd*, *J* = 17.7, 11.3, H_b–C(3)); signals of **30b**: 5.98 (*ddd*, *J* = 17.4, 10.5, 6.3, H–C(1′)); 5.92 (br. *s*, NH); 5.21 (*dt*, *J* = 10.2, 1.2, H_a–C(2′)); 5.16 (*dt*, *J* = 17.1, 1.2, H_b–C(2′)); 4.63, 4.51 (2*d*, *J* = 11.7, PhC*H*$_2$); 4.50, 4.46 (2*d*, *J* ≈ 11.5, PhC*H*$_2$); 3.75–3.66 (*m*, H–C(6), CH_a–C(6)); 2.62 (*dd*, *J* = 17.4, 6.6, H_a–C(3)); 2.40 (*dd*, *J* = 17.4, 5.4, H_b–C(3)). HR-MALDI-MS: 352.1907 (100, $[M + H]^+$, $C_{22}H_{26}NO_3^+$; calc. 352.1913).

Transformation of **30** *into* **31**/**32**. Under N_2 in a 25-ml flame-dried *Schlenk* flask, a soln. of **30a**/**30b** 3:1 (63 mg, 0.18 mmol) in dry CH_2Cl_2 (2 ml) was treated with dodec-1-ene (60 µl, 0.27 mmol) and a soln. of [($RuCl_2$(CHPh)(PCy_3)$_2$] (7.6 mg, 9 µmol) in CH_2Cl_2 (1.6 ml), and stirred for 7 h at reflux. The mixture was cooled to 25°, treated with DMSO (0.5 ml), stirred for 15 h, and evaporated. FC (AcOEt/pentane 1:1→1:0) gave **31**/**32** 3:1 (63 mg, 70%).

*(*E*)-4,6-Di-*O*-benzyl-5-*N*-{[(*tert*-butoxy)carbonyl]amino}-2,3,5-trideoxy-*L*-*erythro*-hex-2-enose* (**33**). A soln. of **28** (1.146 g, 2.68 mmol) in CH_2Cl_2 (15 ml) was treated with *Dess–Martin* periodinane (15% in CH_2Cl_2, 9.1 ml, 3.22 mmol), stirred at 25° for 1.5 h, diluted with Et_2O (200 ml), and filtered through *Celite* (removal of the precipitated iodinane). The filtrate was washed with a 7:1 mixture 10% aq. $Na_2S_2O_3$/sat. aq. $NaHCO_3$ (2 × 100 ml) and brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/pentane 1:9→1:4) gave **33** (1.11 g, 95%). Colourless oil. R_f (Et_2O/pentane 2:3) 0.46. $[\alpha]_D^{25} = -14.75$ (*c* = 1.0, $CHCl_3$). IR (ATR): 3452*w*, 3357*w*, 3062*w*, 3030*w*, 2976*w*, 2929*w*, 2867*w*, 1712*m*, 1689*s*, 1496*s*, 1454*m*, 1391*w*, 1365*m*, 1318*w*, 1246*w*, 1163*s*, 1095*s*, 1065*s*, 1026*m*, 977*m*, 861*w*, 778*w*, 736*s*, 697*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 9.55 (*d*, *J* = 8.1, H–C(1)); 7.38–7.24 (*m*, 10 arom. H); 6.82 (*dd*, *J* = 15.9, 7.2, H–C(3)); 6.26 (*dd*, *J* = 15.9, 8.1, H–C(2)); 5.01 (*d*, *J* = 9.0, NH); 4.58 (*d*, *J* = 11.7, PhC*H*); 4.50 (*d*, *J* = 11.7, PhC*H*); 4.43 (*d*, *J* = 11.7, PhC*H*); 4.37 (*d*, *J* = 11.7, PhC*H*); 4.21 (*t*, *J* = 7.5, H–C(4)); 3.97–3.92 (*m*, H–C(5)); 3.86 (br. *dd*, *J* = 9.3, 3.0, H_a–C(6)); 3.53 (*dd*, *J* = 9.3, 3.9, H_b–C(6)); 1.39 (*s*, *t*-Bu). ^{13}C-NMR ($CDCl_3$, 75 MHz): 193.13 (*d*, C(1)); 155.18 (*s*, C=O); 154.57 (*d*, C(3)); 137.62, 137.24 (2*s*); 134.12 (*d*, C(2)); 128.41–127.75 (several *d*); 79.75 (*s*, Me_3C); 78.23 (*d*, C(4)); 73.35 (*t*, PhCH_2); 71.96 (*t*, PhCH_2); 68.31 (*t*, C(6)); 52.96 (*d*, C(5)); 28.43 (*q*, *Me*$_3$C). HR-MALDI-MS: 448.2097 (100, $[M + Na]^+$, $C_{25}H_{31}NNaO_5^+$; calc. 448.2100). Anal. calc. for $C_{25}H_{31}NO_5$ (425.52): C 70.57, H 7.34, N 3.29; found: C 70.76, H 7.48, N 3.27.

*(4*E,*6*R/S*)-1,3-Di*-O-*benzyl-{[(*tert-*butoxy)carbonyl]amino}-2,4,5-trideoxy-6*-C-*undecyl*-D-erythro-*hex-4-enitol* (**34**). An ice-cold soln. of **33** (904 mg, 2.12 mmol) in Et_2O (10 ml) was treated dropwise with $C_{11}H_{23}MgBr$ in Et_2O (freshly prepared from 0.71 ml of $C_{11}H_{23}Br$ (3.17 mmol) and 128.5 mg of Mg (5.29 mmol) in 5 ml of Et_2O), and stirred at 0° for 10 min and at 25° for 15 h. The mixture was cooled to 0°, treated dropwise with sat. aq. NH_4Cl soln., and diluted with H_2O (20 ml) and Et_2O (100 ml). After separation of the layers, the aq. phase was extracted with Et_2O (3 × 50 ml). The combined org. phases were washed with brine, dried (Na_2SO_4), and evaporated. FC (Et_2O/pentane 1:4 → 3:7 → 1:3) gave **34** (1.06 g, 86%) as a 11:9 mixture of diastereoisomers that was used directly for the next step. Colourless gum. R_f (AcOEt/hexane 1:4) 0.28. $[\alpha]_D^{25} = -25.9$ ($c = 1.0$, $CHCl_3$). IR (ATR): 3446 (br.), 3062*w*, 3030*w*, 2923*s*, 2853*m*, 1712*s*, 1698*s*, 1497*s*, 1465*m*, 1454*m*, 1390*w*, 1365*m*, 1247*w*, 1206*w*, 1166*s*, 1091*s*, 1064*s*, 1027*s*, 973*m*, 911*w*, 861*w*, 776*w*, 733*s*, 696*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz; 11:9 mixture of diastereoisomers): 7.37–7.23 (*m*, 10 arom. H); 5.766 (*dd*, *J* = 15.6, 5.9, 0.45 H), 5.746 (*dd*, *J* = 15.6, 5.9, 0.55 H), 5.63 (br. *d*, *J* = 15.7, 1 H) (CH=CH); 5.02–4.09 (br. *s*, NH); 4.54, 4.44 (2*d*, *J* = 11.8, PhCH_2); 4.58, 4.35 (2*d*, *J* = 11.9, 0.9 H), 4.57, 4.32 (2*d*, *J* = 11.8, 1.1 H) (PhCH_2); 4.15–4.07 (*m*, H–C(2)); 3.94 (br. *t*, *J* = 7.3, H–C(3)); 3.88–3.82 (*m*, 2 H–C(1)); 3.55 (br. *q*, *J* = 5.7, H–C(6)); 1.84 (br. *s*, OH); 1.55–1.48 (*m*, 2 H–C(7)); 1.43, 1.42 (2*s*, *Me*$_3$C); 1.34–1.25 (*m*, 18 H); 0.89 (*t*, *J* = 6.7, Me). ^{13}C-NMR ($CDCl_3$, 75 MHz; 11:9 mixture of diastereoisomers): 155.42 (*s*, C=O); 138.26, 138.02 (2*s*); 128.27–127.59 (several *d*); 128.23 (*d*, C(4)); 127.49 (*d*, C(5)); 79.34 (*s*, Me$_3$*C*); 79.18 (*d*, C(3)); 73.17 (br. *t*, Ph*C*H$_2$); 70.67, 70.61 (2*t*, Ph*C*H$_2$); 72.18, 72.05 (2*d*, C(6)); 68.74 (br. *t*, C(1)); 53.41 (*d*, C(2)); 37.16 (*t*, C(7)); 32.04 (*t*); 29.75–29.49 (several *t*); 28.55, 28.52 (2*q*, *Me*$_3$C); 25.64, 25.56 (2*t*); 22.83 (br. *t*); 14.29 (*q*, Me). HR-MALDI-MS: 450.2255 (100, $[M + Na]^+$, $C_{25}H_{33}NNaO_5^+$; calc. 450.2256). Anal. calc. for $C_{25}H_{33}NO_5 \cdot 0.3\ H_2O$ (432.94): C 69.31, H 7.82, N 3.24; found: C 69.31, H 8.03, N 3.24.

Eschenmoser–Claisen *Rearrangement of* **34** *with* N,N-*Dimethylacetamide Dimethyl Acetal*. A soln. of **34** (11:9 mixture of diastereoisomers; 870 mg, 1.5 mmol) in *o*-xylene (15 ml) was treated with *N,N*-dimethylacetamide dimethyl acetal (0.54 ml, 4.5 mmol), stirred at 145° for 15 h, cooled to 25°, diluted with AcOEt (100 ml), and washed with H_2O (50 ml). The aq. phase was extracted with AcOEt (3 × 100 ml). The combined org. phases were washed with brine, dried (Na_2SO_4), and evaporated. FC (Et_2O/pentane 1:1 → 9:1) afforded **35a**/**35b** 1:1 (878 mg, 90%). Slow FC (AcOEt/hexane 2:3) of a small amount gave pure samples of **35a** and **35b**.

4,6-Di-O-*benzyl-5-{[(*tert-*butoxy)carbonyl]amino}-2,3,5-trideoxy*-N,N-*dimethyl-3*-C-*[(*E*)-tridec-1-enyl]*-L-arabino-*hexonamide* (**35a**). Colourless gum. R_f (AcOEt/hexane 2:3) 0.40. $[\alpha]_D^{25} = +8.5$ ($c = 0.3$, $CHCl_3$). IR (ATR): 3448*w* (br.), 3302*w* (br.), 3034*w*, 2923*s*, 2853*m*, 1710*s*, 1638*s*, 1496*s*, 1463*m*, 1454*m*, 1391*m*, 1364*s*, 1314*w*, 1248*m*, 1168*s*, 1095*s*, 1057*s*, 1027*s*, 971*m*, 911*w*, 861*w*, 772*w*, 733*s*, 696*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.36–7.23 (*m*, 10 arom. H); 5.54–5.38 (*m*, H–C(1′), H–C(2′)); 5.00 (*d*, *J* = 8.8, NH); 4.62, 4.57 (2*d*, *J* = 11.4, PhCH_2); 4.49, 4.46 (2*d*, *J* = 11.9, PhCH_2); 3.96–3.94 (*m*, H–C(5)); 3.70–3.67 (*m*, H–C(4), H_a–C(6)); 3.58 (*dd*, *J* = 9.7, 3.8, H_b–C(6)); 2.91–2.84 (*m*, H–C(3)); 2.92, 2.87 (2*s*, Me_2N); 2.61 (*dd*, *J* = 14.6, 4.0, H_a–C(2)); 2.39 (*dd*, *J* = 14.8, 9.3, H_b–C(2)); 1.97 (*q*, *J* = 6.3, 2 H–C(3′)); 1.43 (*s*, *t*-Bu); 1.36–1.18 (*m*, 18 H); 0.88 (*t*, *J* = 6.7, Me). ^{13}C-NMR ($CDCl_3$, 75 MHz): 171.91 (*s*, Me_2N*C*=O); 155.41 (*s*, OC=O); 138.46, 137.99 (2*s*); 132.68 (*d*, C(1′)); 129.72 (*d*, C(2′)); 128.25–127.45 (several *d*); 81.58 (*d*, C(4)); 79.12 (*s*, Me$_3$*C*); 74.29, 72.86 (2*t*, 2 Ph*C*H$_2$); 68.63 (*t*, C(6)); 51.62 (*d*, C(5)); 41.40 (*t*, C(2)); 37.31, 37.29 (2*q*, Me_2N); 35.30 (*t*); 34.06 (*d*, C(3)); 31.82, 32.55 (2*t*); 29.61–29.12 (several *t*); 28.31 (*q*, *Me*$_3$C); 22.59 (*t*); 14.04 (*q*, Me). HR-MALDI-MS: 673.4543 (28, $[M + Na]^+$, $C_{40}H_{62}N_2NaO_3^+$; calc. 673.4556); 551.4192 (100, $[M - Boc + 2\ H]^+$, $C_{35}H_{55}N_2O_3^+$; calc. 551.4213). Anal. calc. for $C_{40}H_{62}N_2O_5 \cdot 0.5\ H_2O$ (659.54): C 73.81, H 9.62, N 4.24; found: C 73.87, H 9.43, N 4.25.

4,6-Di-O-*benzyl-5-{[(*tert-*butoxy)carbonyl]amino}-2,3,5-trideoxy*-N,N-*dimethyl-3*-C-*[(*E*)-tridec-1-enyl]*-L-ribo-*hexonamide* (**35b**). Colourless gum. R_f (AcOEt/hexane 2:3) 0.38. $[\alpha]_D^{25} = -8.4$ ($c = 1.94$, $CHCl_3$). IR (ATR): 3440*w* (br.), 3306*w* (br.), 3034*w*, 2923*s*, 2853*m*, 1713*s*, 1644*s*, 1497*s*, 1463*m*, 1454*s*, 1391*m*, 1364*s*, 1246*m*, 1221*m*, 1168*s*, 1107*s*, 1092*s*, 1056*s*, 1027*s*, 973*m*, 913*w*, 863*w*, 772*s*, 734*s*, 697*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.36–7.25 (*m*, 10 arom. H); 5.54–5.39 (*m*, H–C(1′), H–C(2′)); 4.95 (*d*, *J* = 9.7, NH); 4.62, 4.47 (2*d*, *J* = 11.6, PhCH_2); 4.53, 4.48 (2*d*, *J* = 12.0, PhCH_2); 3.97 (*m*, H–C(5)); 3.73–3.65 (*m*, H–C(4), H_a–C(6)); 3.55 (*dd*, *J* = 9.4, 3.8, H_b–C(6)); 2.97 (*q*, *J* = 6.4, H–C(3)); 2.87, 2.84 (2*s*, Me_2N); 2.42–2.27 (*m*, 2 H–C(2)); 2.06–1.89 (*m*, 2 H–C(3′)); 1.43 (*s*, *t*-Bu); 1.36–1.18 (*m*, 18 H); 0.88 (*t*, *J* = 6.7, Me). ^{13}C-NMR ($CDCl_3$, 75 MHz): 171.72 (*s*, Me_2N*C*=O); 155.03 (*s*, OC=O); 138.55, 138.04 (2*s*); 133.52

(*d*, C(1′)); 128.34 (*d*, C(2′)); 128.19–127.40 (several *d*); 79.79 (*s*, Me_3C); 79.77 (*d*, C(4)); 73.25, 73.12 (2*t*, 2 PhCH_2); 69.66 (*t*, C(6)); 51.79 (*d*, C(5)); 41.15 (*t*, C(2)); 37.38, 37.35 (2*q*, Me_2N); 35.43, 31.99 (2*t*); 32.80 (*d*, C(3)); 29.78–29.10 (several *t*); 28.48 (*q*, Me_3C); 22.79 (*t*); 14.24 (*q*, Me). HR-MALDI-MS: 673.4552 (28, $[M+Na]^+$, $C_{40}H_{62}N_2NaO_3^+$; calc. 673.4556); 551.4194 (100, $[M-Boc+2H]^+$, $C_{35}H_{55}N_2O_3^+$; calc. 551.4213). Anal. calc. for $C_{40}H_{62}N_2O_5$ (650.94): C 73.81, H 9.60, N 4.30; found: C 73.87, H 9.43, N 4.25.

Transformation of **35a/35b** *into the Lactams* **31** *and* **32**. An ice-cold soln. of **35a/35b** 1:1 (803 mg, 1.23 mmol) in CH_2Cl_2 (6.0 ml) was treated with CF_3CO_2H (0.91 ml, 12.3 mmol), stirred at 25° for 15 h, treated with H_2O (3 ml), and stirred again for 1 h. The mixture was diluted with CH_2Cl_2 (50 ml) and washed with H_2O (2 × 50 ml). The combined aq. phases were extracted with CH_2Cl_2 (3 × 50 ml). The combined org. phases were washed with H_2O and brine, dried (Na_2SO_4), and evaporated. A soln. of the residue in THF (10 ml) was treated with 1M HCl (2 ml) and stirred at reflux for 24 h. The mixture was cooled to 25° and worked up as described above. FC (AcOEt/pentane 1:1 → 1:0) gave **31/32** 1:1 (528 mg, 85%), which were separated by slow FC (AcOEt/hexane 1:1).

*(4*R*,5*R*,6*S*)-5-(Benzyloxy)-6-[(benzyloxy)methyl]-4-[(*E*)-tridec-1-enyl)]piperidin-2-one* (**31**). Colourless gum. R_f (AcOEt/hexane 1:1) 0.29. $[\alpha]_D^{25} = -20.2$ ($c = 1.0$, $CHCl_3$). IR (ATR): 3208*w*, 3062*w*, 3030*w*, 2922*s*, 2852*m*, 1667*s*, 1496*w*, 1466*w*, 1453*m*, 1401*w*, 1363*w*, 1317*m*, 1219*s*, 1097*s*, 1073*s*, 1028*w*, 968*w*, 911*w*, 772*s*, 732*s*, 695*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.39–7.21 (*m*, 10 arom. H); 6.06 (br. *s*, NH); 5.62 (*dtd*, $J = 15.3, 7.1, 0.7$, H–C(2′)); 5.34 (*ddt*, $J = 15.3, 3.7, 1.3$, H–C(1′)); 4.66, 4.39 (2*d*, $J = 11.0$, PhCH_2); 4.50, 4.46 (2*d*, $J = 12.3$, PhCH_2); 3.65–3.56 (*m*, H–C(6), CH_a–C(6)); 3.34–3.23 (*m*, H–C(5), CH_b–C(6)); 2.77–2.66 (*m*, H–C(4)); 2.51 (*dd*, $J = 17.5, 5.2$, H_a–C(3)); 2.26 (*dd*, $J = 17.6, 11.2$, H_b–C(3)); 2.03 (*q*, $J = 6.7$, 2 H–C(3′)); 1.37–1.25 (*m*, 18 H); 0.88 (*t*, $J = 6.7$, Me). ^{13}C-NMR ($CDCl_3$, 75 MHz): 170.55 (*s*, C=O); 137.56, 137.43 (2*s*); 133.52 (*d*, C(1′)); 128.87 (*d*, C(2′)); 128.55–127.86 (several *d*); 77.67 (*d*, C(5)); 73.76, 73.35 (2*t*, 2 PhCH_2); 71.00 (*t*, CH_2–C(6)); 56.69 (*d*, C(6)); 42.32 (*d*, C(4)); 35.60 (*t*, C(3)); 32.68, 31.94 (2*t*); 29.71–29.25 (several *t*); 22.71 (*t*); 14.14 (*q*, Me). HR-MALDI-MS: 506.3638 (100, $[M+H]^+$, $C_{33}H_{48}NO_3^+$; calc. 506.3634). Anal. calc. for $C_{33}H_{47}NO_3$ (505.74): C 78.37, H 9.37, N 2.77; found: C 78.20, H 9.28, N 2.75.

*(4*S*,5*R*,6*S*)-5-(Benzyloxy)-6-[(benzyloxy)methyl]-4-[(*E*)-tridec-1-enyl)]piperidin-2-one* (**32**). Colourless gum. R_f (AcOEt/hexane 1:1) 0.24. $[\alpha]_D^{25} = -50.0$ ($c = 1.05$, $CHCl_3$). IR (ATR): 3208*w*, 3062*w*, 3031*w*, 2922*s*, 2852*m*, 1665*s*, 1495*w*, 1465*w*, 1454*m*, 1406*w*, 1362*w*, 1330*m*, 1304*w*, 1253*w*, 1219*w*, 1090*s*, 1071*m*, 1027*w*, 968*w*, 934*w*, 772*s*, 732*s*, 695*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.39–7.26 (*m*, 10 arom. H); 6.10 (br. *s*, NH); 5.60–5.48 (*m*, H–C(1′), H–C(2′)); 4.61, 4.50 (2*d*, $J = 11.7$, PhCH_2); 4.50 (*s*, PhCH_2); 3.74–3.67 (*m*, H–C(6)); 3.61 (*dd*, $J = 9.0, 4.2$, CH_a–C(6)); 3.54 (*dd*, $J = 6.2, 3.3$, H–C(5)); 3.34 (*t*, $J \approx 8.6$, CH_b–C(6)); 2.82–2.78 (*m*, H–C(4)); 2.58 (*dd*, $J = 17.5, 6.5$, H_a–C(3)); 2.37 (*dd*, $J = 17.5, 5.4$, H_b–C(3)); 2.05–1.99 (*m*, 2 H–C(3′)); 1.34–1.16 (*m*, 18 H); 0.89 (*t*, $J = 6.7$, Me). ^{13}C-NMR ($CDCl_3$, 75 MHz): 170.71 (*s*, C=O); 137.58, 137.39 (2*s*); 133.23 (*d*, C(1′)); 128.39–127.64 (several *d*); 126.90 (*d*, C(2′)); 74.99 (*d*, C(5)); 73.32, 71.60 (2*t*, 2 PhCH_2); 71.06 (*t*, CH_2–C(6)); 53.66 (*d*, C(6)); 36.01 (*d*, C(4)); 33.57 (*t*, C(3)); 32.65, 31.83 (2*t*); 29.60–29.09 (several *t*); 22.60 (*t*); 14.04 (*q*, Me). HR-MALDI-MS: 506.3635 (100, $[M+H]^+$, $C_{33}H_{48}NO_3^+$; calc. 506.3634). Anal. calc. for $C_{33}H_{47}NO_3$ (505.74): C 78.37, H 9.37, N 2.77; found: C 78.29, H 9.45, N 2.80.

Debenzylation of **31/32**. An ice-cold soln. of **31/32** 1:1 (440 mg, 0.87 mmol) in CH_2Cl_2 (20 ml) was treated with anisole (0.57 ml, 5.23 mmol) and $AlCl_3$ (465 mg, 3.49 mmol), stirred at 0° for 4 h, and treated dropwise with 1M HCl (5 ml). After separation of the layers, the aq. phase was extracted with AcOEt (3 × 100 ml). The combined org. phases were washed with H_2O and brine, dried (Na_2SO_4), and evaporated. FC (*Lichoprep* CN phase, CH_2Cl_2/MeOH 1:0 → 49:1 → 97:3) gave **7** (113.5 mg, 40%) and **8** (99.3 mg, 35%).

*(4*R*,5*R*,6*S*)-5-Hydroxy-6-(hydroxymethyl)-4-[(*E*)-tridec-1-enyl)]piperidin-2-one* (**7**). Colourless crystals. R_f (CH_2Cl_2/MeOH 9:1) 0.30. M.p. 112.8°. $[\alpha]_D^{25} = +10.1$ ($c = 0.5$, $CHCl_3$). IR (ATR): 3272*w* (br.), 2961*w*, 2917*s*, 2849*m*, 1649*s*, 1490*w*, 1463*w*, 1415*m*, 1366*w*, 1317*m*, 1269*w*, 1170*w*, 1097*w*, 1075*m*, 1065*s*, 1032*m*, 960*s*, 905*w*, 758*m*, 731*m*, 646*m*. ^{1}H-NMR (CD_3OD, 300 MHz): 5.48 (*dt*, $J = 14.7, 6.3$, H–C(2′)); 5.36 (br. *dd*, $J = 15.3, 7.5$, H–C(1′)); 3.81 (*dd*, $J = 11.1, 3.0$, CH_a–C(6)); 3.58 (*dd*, $J = 11.7, 6.3$, CH_b–C(6)); 3.41 (*dd*, $J = 10.2, 9.3$, H–C(5)); 3.22 (*ddd*, $J = 9.0, 6.0, 3.3$, H–C(6)); 2.54–2.45 (*m*, H–C(4)); 2.37 (*dd*, $J = 17.4, 5.1$, H_a–C(3)); 2.21 (*dd*, $J = 17.4, 11.7$, H_b–C(3)); 2.05 (*q*, $J = 6.9$, 2 H–C(3′)); 1.33–1.24 (*m*, 2 H–C(4′)); 1.24–1.20 (*m*, 16 H); 0.81 (*t*, $J \approx 6.7$, Me). ^{13}C-NMR (CD_3OD,

75 MHz): 173.48 (*s*, C=O); 133.79 (*d*, C(1′)); 130.29 (*d*, C(2′)); 69.37 (*d*, C(5)); 62.92 (*t*, *C*H$_2$–C(6)); 60.96 (*d*, C(6)); 43.67 (*d*, C(4)); 36.42 (*t*, C(3)); 33.49, 32.82 (2*t*); 30.51–30.03 (several *t*); 23.50 (*t*); 14.23 (*q*, Me). HR-MALDI-MS: 326.2688 (100, $[M+H]^+$, $C_{19}H_{36}NO_3^+$; calc. 326.2695). Anal. calc. for $C_{19}H_{35}NO_3$ (325.49): C 70.11, H 10.84, N 4.30; found: C 70.24, H 10.74, N 4.37.

*(4*S*,5*R*,6*S*)-5-Hydroxy-6-(hydroxymethyl)-4-[(*E*)-tridec-1-enyl)]piperidin-2-one* (**8**). Colourless crystals. R_f (CH_2Cl_2/MeOH 9:1) 0.27. M.p. 114.9°. $[\alpha]_D^{25} = -24.6$ ($c = 1.0$, THF). IR (ATR): 3243*m*, 3112*w*, 2954*w*, 2919*s*, 2850*m*, 1638*s*, 1485*m*, 1467*m*, 1419*w*, 1399*m*, 1344*w*, 1318*m*, 1254*w*, 1144*w*, 1086*w*, 1051*m*, 1033*w*, 1004*w*, 964*m*, 948*m*, 891*w*, 765*m*, 749*m*, 720*w*, 682*w*, 658*w*. ^{1}H-NMR (CD_3OD, 300 MHz): 5.64–5.51 (*m*, H–C(1′), H–C(2′)); 3.90 (*dd*, $J = 4.8$, 3.3, H–C(5)); 3.59 (*dd*, $J = 11.1$, 6.0, CH_a–C(6)); 3.55 (*dd*, $J = 11.4$, 5.7, CH_b–C(6)); 3.35 (*td*, $J = 5.7$, 4.5, H–C(6)); 2.70–2.65 (*m*, H–C(4)); 2.42 (*dd*, $J = 17.7$, 8.7, H_a–C(3)); 2.30 (*dd*, $J = 17.4$, 5.7, H_b–C(3)); 2.05 (*q*, $J = 6.9$, 2 H–C(3′)); 1.40–1.20 (*m*, 18 H); 0.90 (*t*, $J \approx 6.8$, Me). ^{13}C-NMR (CD_3OD, 75 MHz): 173.83 (*s*, C=O); 133.25 (*d*, C(1′)); 129.28 (*d*, C(2′)); 67.65 (*d*, C(5)); 63.62 (*t*, *C*H$_2$–C(6)); 60.02 (*d*, C(6)); 38.96 (*d*, C(4)); 33.53 (*t*, C(3)); 32.80 (*t*); 30.48–30.00 (several *t*); 23.48 (*t*); 14.21 (*q*, Me). HR-MALDI-MS: 326.2690 (100, $[M+H]^+$, $C_{19}H_{36}NO_3^+$; calc. 326.2695). Anal. calc. for $C_{19}H_{35}NO_3$ (325.49): C 70.11, H 10.84, N 4.30; found: C 70.14, H 10.70, N 4.35.

X-Ray Analysis of **7**. In a 5-ml round-bottomed flask, a soln. of **7** (*ca.* 20 mg) in MeOH (5 ml) was treated dropwise with H_2O until the turbidity persisted for *ca.* 1 min, and treated with MeOH (2 ml) to obtain a clear soln. The flask was closed with a perforated Al foil, and kept undisturbed. The plate-like crystals formed within 2 d were suitable for X-ray analysis. Dimensions: $0.3 \times 0.08 \times 0.005$ mm. Colourless crystals: $C_{19}H_{35}NO_3$ (325.493), orthorhombic $P2_12_12_1$; $a = 4.9903(3)$, $b = 9.7480(6)$, $c = 39.811(3)$ Å, $V = 1936.6(2)$ Å^3, $Z = 4$, $D_{calc} = 1.116$ Mg/m^3. All reflections were measured using a *Bruker Nonius-Kappa CCD* diffractometer (MoK_α radiation, $\lambda = 0.71073$) at 22 K. 6904 Measured reflections, 2448 independent reflections, 1459 observed reflections. Refinement of F^2: full-matrix least-squares refinement, R(all) = 0.2050, R(gt) = 0.1305, wR(ref) = 0.2749, wR(gt) = 0.2473. All diagrams and calculations were performed using maXus (*Bruker Nonius*, *Delft & MacScience*, Japan). Programme used to solve structure: SIR97. Programme used to refine structure: SHELXL-97

X-Ray Analysis of **8**. In a 5-ml round-bottomed flask, a soln. of **8** (*ca.* 20 mg) in MeOH (5 ml) was treated dropwise with H_2O until the turbidity persisted for *ca.* 1 min, and treated with MeOH (2 ml) to obtain a clear soln. The flask was closed with a perforated Al foil, and kept undisturbed. The plate-like crystals formed within 2 d were suitable for X-ray analysis. Dimensions: $0.36 \times 0.18 \times 0.1$ mm. Colourless crystals: $C_{19}H_{35}NO_3$ (325.493), monoclinic $P2_1$; $a = 5.4658(3)$, $b = 6.5116(4)$, $c = 27.989(2)$ Å, $V = 993.05$ (10) Å^3, $Z = 2$, $D_{calc} = 1.089$ Mg/m^3. All reflections were measured using a *Bruker Nonius-Kappa CCD* diffractometer (MoK_α radiation, $\lambda = 0.71073$) at 223 K. 3900 Measured reflections, 2364 independent reflections, 2055 observed reflections. Refinement of F^2: full-matrix least-squares refinement, R(all) = 0.0919, R(gt) = 0.0792, wR(ref) = 0.2307, wR(gt) = 0.2179. All diagrams and calculations were performed using maXus (*Bruker Nonius*, *Delft & MacScience*, Japan). Programme used to solve structure: SIR97. Programme used to refine structure: SHELXL-97.

Hydrogenation of **31/32**. A soln. of **31/32** 1:1 (200 mg, 0.4 mmol) in MeOH (5 ml) was treated with 10% Pd/C (40 mg) and AcOH (0.5 ml), stirred at 25° under 6 bar of H_2 for 20 h, and filtered through *Celite* (washing with MeOH). The combined filtrate and washings were evaporated. A soln. of the residue in MeOH was adsorbed on silica gel and submitted to a FC (CH_2Cl_2/MeOH 1:0 → 95:5 → 9:1) affording **15** (61.5 mg, 47%) and **16** (52.4 mg, 40%).

*(4*R*,5*R*,6*S*)-5-Hydroxy-6-(hydroxymethyl)-4-(tridecyl)piperidin-2-one* (**15**). Colourless crystals. R_f (CH_2Cl_2/MeOH 9:1) 0.40. M.p. 103.2°. $[\alpha]_D^{25} = +23.8$ ($c = 0.25$, MeOH). IR (ATR): 3423*w* (br.), 3253*w*, 3185*w*, 3063*w*, 2954*w*, 2918*m*, 2849*m*, 1620*m*, 1488*w*, 1470*m*, 1415*w*, 1373*w*, 1283*w*, 1258*w*, 1219*m*, 1138*w*, 1071*m*, 1044*m*, 810*w*, 772*s*, 719*w*, 673*w*. ^{1}H-NMR (CD_3OD, 300 MHz): 3.82 (*dd*, $J = 11.1$, 3.0, CH_a–C(6)); 3.57 (*dd*, $J = 11.4$, 6.3, CH_b–C(6)); 3.33 (*dd*, $J = 10.2$, 9.0, H–C(5)); 3.19 (*ddd*, $J = 9.0$, 5.7, 3.0, H–C(6)); 2.47 (*dd*, $J = 17.7$, 4.8, H_a–C(3)); 1.99 (*dd*, $J = 17.1$, 11.7, H_b–C(3)); 1.89–1.74 (*m*, H–C(4)); 1.29–1.08 (*m*, 24 H); 0.89 (*t*, $J \approx 6.3$, Me). ^{13}C-NMR (CD_3OD, 75 MHz): 174.44 (*s*, C=O); 66.10 (*d*, C(5)); 63.91 (*t*, *C*H$_2$–C(6)); 60.88 (*d*, C(6)); 34.75 (*d*, C(4)); 33.21 (*t*, C(3)); 32.64, 31.26 (2*t*); 30.45–30.04 (several *t*); 27.46, 23.30 (2*t*); 14.23 (*q*, Me). HR-MALDI-MS: 328.2849 (100, $[M+H]^+$, $C_{19}H_{38}NO_3^+$; calc. 328.2852). Anal. calc. for $C_{19}H_{37}NO_3$ (327.51): C 69.68, H 11.39, N 4.28; found: C 69.40, H 11.53, N 4.33.

(4S,5R,6S)-5-Hydroxy-6-(hydroxymethyl)-4-(tridecyl)piperidin-2-one (**16**). Colourless crystals. R_f (CH_2Cl_2/MeOH 9:1) 0.37. M.p. 145.3°. IR (ATR): 3350*w* (br.), 3277*w* (br.), 3237*w* (br.), 2949*w*, 2918*m*, 2848*m*, 1642*m*, 1486*w*, 1467*w*, 1421*w*, 1402*w*, 1320*w*, 1113*w*, 1071*w*, 1019*s*, 1004*w*, 960*m*, 721*w*. ^{1}H-NMR (CD_3OD, 300 MHz): 3.93 (br. *t*, *J* = 2.6, H−C(5)); 3.52 (*m*, CH_2−C(6)); 3.41 (*ddd*, *J* = 6.8, 5.7, 2.9, H−C(6)); 2.24–2.20 (*m*, 2 H−C(3)); 2.00–1.89 (*m*, H−C(4)); 1.58–1.49 (*m*, 2 H−C(1′)); 1.33–1.29 (*m*, 22 H); 0.90 (*t*, *J* = 6.8, Me). ^{13}C-NMR (CD_3OD, 75 MHz): 174.44 (*s*, C=O); 66.10 (*d*, C(5)); 63.91 (*d*, C(6)); 60.88 (*t*, CH_2−C(6)); 34.75 (*d*, C(4)); 33.21 (*t*, C(3)); 32.64, 31.26 (2*t*); 30.45–30.04 (several *t*); 27.46, 23.30 (2*t*); 13.99 (*q*, Me). HR-MALDI-MS: 328.2850 (100, $[M + H]^+$, $C_{19}H_{38}NO_3^+$; calc. 328.2852). Anal. calc. for $C_{19}H_{37}NO_3$ (327.51): C 69.68, H 11.39, N 4.28; found: C 69.59, H 11.42, N 4.37.

X-Ray Analysis of **15**. In a 5-ml round-bottomed flask, a soln. of **15** (*ca.* 20 mg) in hot MeOH (5 ml) was closed with a perforated Al foil, and kept undisturbed for 7 d at r.t. affording plate-like crystals suitable for X-ray analysis. Dimensions: 0.4 × 0.2 × 0.005 mm. Colourless crystals: $C_{19}H_{37}NO_3$ (327.509), monoclinic $P2_1$; *a* = 5.4911 (2), *b* = 6.8227 (3), *c* = 26.3831 (12) Å, β = 92.015 (2), *V* = 987.81 (7) Å^3, *Z* = 2, D_{calc} = 1.101 Mg/m^3. All reflections were measured using a *Bruker Nonius-Kappa CCD* diffractometer (MoK_α radiation, λ = 0.71073) at 173 K. 5363 Measured reflections, 3077 independent reflections, 2246 observed reflections. Refinement of F^2: full-matrix least-squares refinement, *R*(all) = 0.0842, *R*(gt) = 0.0516, *wR*(ref) = 0.1464, *wR*(gt) = 0.1226. All diagrams and calculations were performed using maXus (*Bruker Nonius*, *Delft & MacScience*, Japan). Programme used to solve structure: SIR97. Programme used to refine structure: SHELXL-97.

(4R,5R,6S)-6-(Azidomethyl)-5-hydroxy-4-[(E)-tridec-1-enyl)]piperidin-2-one (**36**). An ice-cold soln. of [4-(dimethylamino)phenyl](diphenyl)phosphine (48.4 mg, 0.16 mmol) in THF (1 ml) was treated dropwise with diethyl azodicarboxylate (40% in toluene; 0.7 µl, 0.16 mmol), keeping the mixture colourless. The mixture was stirred at 0° for 15 min, when the initially formed colourless precipitate was dissolved completely. The soln. was treated dropwise with a soln. of **7** (25.8 mg, 0.08 mmol) in THF (1 ml). The clear homogeneous soln. was treated with freshly prepared 0.8M HN_3 soln. in toluene (0.3 ml, 0.24 mmol), and stirred at 0° for 1 h, and at 25° for 2 h. After dilution with AcOEt (50 ml), the mixture was washed with 1M HCl (2 × 25 ml). The combined aq. phases were extracted with AcOEt (3 × 50 ml). The combined org. phases were washed with sat. aq. $NaHCO_3$ soln., H_2O, and brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/pentane 1:1 → 3:2) gave **36** (22 mg, 80%). Colourless crystals. R_f (CH_2Cl_2/MeOH 9:1) 0.32. M.p. 76.9°. $[\alpha]_D^{25} = -15.8$ (*c* = 0.75, $CHCl_3$). IR (ATR): 3288*w* (br.), 3221*w* (br.), 2957*w*, 2921*s*, 2852*s*, 2103*s*, 1652*s*, 1463*m*, 1445*m*, 1405*m*, 1347*w*, 1311*m*, 1279*m*, 1178*w*, 1105*w*, 1064*m*, 965*m*, 865*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.65 (*s*, NH); 5.69 (*dt*, *J* = 15.2, 6.8, H−C(2′)); 5.16 (br. *dd*, *J* = 15.3, 8.4, H−C(1′)); 3.83–3.76 (*m*, H−C(5)); 3.44–3.10 (*m*, CH_2−C(6), H−C(6)); 2.52 (*dd*, *J* = 16.5, 5.1, H_a−C(3)); 2.48–2.39 (*m*, H−C(4)); 2.37 (*d*, *J* = 2.0, OH); 2.22 (*dd*, *J* = 16.2, 10.8, H_b−C(3)); 2.05 (*q*, *J* ≈ 6.7, 2 H−C(3′)); 1.41–1.21 (*m*, 18 H); 0.87 (*t*, *J* = 6.7, Me). ^{13}C-NMR (CD_3OD, 75 MHz): 170.77 (*s*, C=O); 136.81 (*d*, C(1′)); 127.67 (*d*, C(2′)); 60.08 (*d*, C(5)); 57.31 (*d*, C(6)); 53.49 (*t*, CH_2−C(6)); 43.85 (*d*, C(4)); 35.75 (*t*, C(3)); 32.66, 32.01 (2*t*); 29.76–29.29 (several *t*); 22.81 (*t*); 14.26 (*q*, Me). HR-MALDI-MS: 351.2755 (100, $[M + H]^+$, $C_{19}H_{35}N_4O_2^+$; calc. 351.2760). Anal. calc. for $C_{19}H_{34}N_4O_2$ (350.50): C 65.11, H 9.78, N 15.98; found: C 65.35, H 9.74, N 15.84.

(4R,5R,6S)-6-(Aminomethyl)-5-hydroxy-4-[(E)-tridec-1-enyl)]piperidin-2-one (**17**). An ice-cold soln. of **36** (18 mg, 0.05 mmol) in THF (2 ml) was treated dropwise with 1M Me_3P in THF (0.1 ml, 0.1 mmol), stirred at 0° for 5 h, treated with 1M NaOH (0.5 ml), and stirred at 25° for 15 h. After dilution with AcOEt (20 ml), the mixture was washed with H_2O (25 ml). The aq. phase was extracted with AcOEt (3 × 20 ml). The combined org. phases were washed with H_2O and brine, dried (Na_2SO_4), and evaporated. A suspension of residue in pentane was cooled to 5°, and the supernatant was decanted. This process was repeated 5 times, until TLC showed absence of pentane-soluble impurities. The precipitate was dried *in vacuo* to afford **17** (15 mg, 90%). Colourless syrup. R_f (NH_2 phase silica gel; CH_2Cl_2/MeOH 9:1) 0.32. $[\alpha]_D^{25} = +9.8$ (*c* = 0.15, $CHCl_3$). IR (ATR): 3440*w* (sh), 3352*w*, 3281*w* (br.), 2957*w*, 2920*s*, 2850*s*, 1646*s*, 1466*w*, 1416*w*, 1326*w*, 1270*w*, 1154*w*, 1058*m*, 1022*w*, 965*w*, 865*w*, 721*w*. ^{1}H-NMR (CD_3OD, 300 MHz): 5.58 (*dtd*, *J* = 15.3, 6.6, 0.6, H−C(2′)); 5.36 (*ddt*, *J* = 15.3, 7.5, 1.2, H−C(1′)); 3.36 (*dd*, *J* = 10.1, 8.8, H−C(5)); 3.19–3.13 (*m*, H−C(6)); 2.96 (*dd*, *J* = 13.5, 3.9, CH_a−C(6)); 2.78 (*dd*, *J* = 13.5, 5.5, CH_b−C(6)); 2.53–2.43 (*m*, H−C(4)); 2.37 (*dd*, *J* = 17.6, 5.3, H_a−C(3)); 2.23 (*dd*, *J* = 17.5, 11.8, H_b−C(3)); 2.05 (*q*, *J* = 6.7, 2 H−C(3′)); 1.43–1.23 (*m*, 18 H); 0.90 (*t*, *J* = 6.8, Me). ^{13}C-NMR (CD_3OD,

75 MHz): 173.05 (*s*, C=O); 134.20 (*d*, C(1′)); 130.87 (*d*, C(2′)); 71.30 (*d*, C(5)); 63.56 (*d*, C(6)); 40.01 (*t*, *C*H_2–C(6)); 38.72 (*t*, C(3)); 35.90 (*d*, C(4)); 33.00, 32.58 (2*t*); 29.65–29.21 (several *t*); 22.74 (*t*); 14.40 (*q*, Me). HR-MALDI-MS: 325.2849 (100, $[M+H]^+$, $C_{19}H_{37}N_2O_2^+$; calc. 325.2855).

*(4*R*,5*R*,6*S*)-6-(Aminomethyl)-5-hydroxy-4-(tridecyl)piperidin-2-one* (**18**). A soln. of **36** (20 mg, 0.06 mmol) in MeOH (3 ml) was treated with 10% Pd/C (10 mg, 50 wt-%) stirred at 25° under 8 bar of H_2 for 20 h, and filtered through *Celite* (washings with MeOH). Evaporation of the combined filtrate and washings, and FC (CH_2Cl_2/MeOH 9:1) gave **18** (17.7 mg, 95%). Colourless syrup solidifying upon standing at 5°. R_f (NH_2 phase; CH_2Cl_2/MeOH 9:1) 0.27. $[\alpha]_D^{25} = +33.6$ ($c = 0.21$, $CHCl_3$). IR (ATR): 3387*w* (sh), 3282*w* (br.), 2953*w*, 2918*s*, 2850*s*, 1629*s*, 1470*w*, 1408*w*, 1320*w*, 1261*w*, 1080*m*, 845*w*, 772*w*, 718*w*. ^{1}H-NMR (CD_3OD, 300 MHz): 3.28 (*t*, $J = 9.9$, H–C(5)); 3.16–3.10 (*m*, H–C(6)); 2.97 (*dd*, $J =$ 13.4, 3.9, CH_a–C(6)); 2.78 (*dd*, $J = 13.4$, 5.5, CH_b–C(6)); 2.47 (*dd*, $J = 17.5$, 4.9, H_a–C(3)); 2.00 (*dd*, $J =$ 17.6, 11.8, H_b–C(3)); 1.89–1.74 (*m*, H–C(4)); 1.42–1.22 (*m*, 20 H); 0.90 (*t*, $J = 6.7$, Me). ^{13}C-NMR (CD_3OD, 75 MHz): 174.26 (*s*, C=O); 70.19 (*d*, C(5)); 63.25 (*d*, C(6)); 61.33 (*t*, *C*H_2–C(6)); 39.72 (*t*, C(3)); 35.93 (*d*, C(4)); 33.07, 32.53 (2*t*); 30.97–30.48 (several *t*); 27.02, 23.74 (2*t*); 14.47 (*q*, Me). HR-MALDI-MS: 327.3010 (100, $[M+H]^+$, $C_{19}H_{39}N_2O_2^+$; calc. 327.3012).

*(4*S*,5*R*,6*S*)-5-Hydroxy-6-{[(4-methylphenyl)sulfonyl]oxy}methyl)-4-[(*E*)-tridec-1-enyl)]piperidin-2-one* (**37**). A soln. of **8** (20 mg, 0.061 mmol) in CH_2Cl_2 (10 ml) was treated with ^{i}Pr_2NEt (101 µl, 0.6 mmol), TsCl (17.6 mg, 0.092 mmol), and 4-(dimethylamino)pyridine (0.8 mg, 0.006 mmol), and stirred at 25° for 22 h. After dilution with CH_2Cl_2 and H_2O, the aq. layer was separated and extracted with CH_2Cl_2 (3 × 20 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. The residue was filtered through a short pad of silica gel (AcOEt/pentane 1:1 → 4:1) to afford crude **37** (24 mg, 82%), which was used directly for the next step. Colourless syrup. R_f (CH_2Cl_2/MeOH 9:1) 0.48. IR (ATR): 3541*w* (sh), 3350*w* (br.), 2953*w*, 2923*s*, 2853*m*, 1652*s*, 1599*w*, 1463*m*, 1403*m*, 1361*s*, 1308*w*, 1189*m*, 1176*s*, 1096*m*, 1067*w*, 974*m*, 947*m*, 911*w*, 830*w*, 813*m*, 786*m*, 733*w*, 665*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.80–7.78 (*m*, 2 arom. H); 7.37–7.35 (*m*, 2 arom. H); 5.77 (*s*, NH); 5.65 (*dt*, $J = 15.6$, 6.8, H–C(2′)); 5.40 (br. *dd*, $J =$ 15.5, 7.8, H–C(1′)); 4.24 (*dd*, $J = 10.1$, 3.8, CH_a–C(6)); 3.98 (*dd*, $J = 10.2$, 7.4, CH_b–C(6)); 3.74 (*td*, $J = 7.1$, 3.6, H–C(5)); 3.58–3.51 (*m*, H–C(6)); 2.70–2.62 (*m*, H–C(4)); 2.48–2.46 (*m*, 2 H–C(3)); 2.46 (*s*, *Me*C_6H_4); 2.05 (*q*, $J = 6.5$, 2 H–C(3′)); 1.86 (*d*, $J = 7.1$, OH); 1.41–1.26 (*m*, 18 H); 0.88 (*t*, $J = 6.6$, Me). ^{13}C-NMR ($CDCl_3$, 100 MHz): 170.34 (*s*, C=O); 145.47 (*s*); 136.66 (*d*, C(1′)); 132.36 (*s*); 130.11 (*d*, 2 CH); 127.98 (*d*, 2 CH); 125.37 (*d*, C(2′)); 70.26 (*t*, *C*H_2–C(6)); 66.80 (*d*, C(5)); 55.34 (*d*, C(6)); 39.45 (*d*, C(4)); 33.55 (*t*, C(3)); 32.71, 31.91 (2*t*); 29.65–29.19 (several *t*); 22.67 (*t*); 21.68 (*q*, *Me*C_6H_4); 14.09 (*q*, Me). HR-MALDI-MS: 480.2781 (100, $[M+H]^+$, $C_{26}H_{42}NO_5S^+$; calc. 480.2784).

*(4*S*,5*R*,6*S*)-6-(Azidomethyl)-5-hydroxy-4-[(*E*)-tridec-1-enyl)]piperidin-2-one* (**38**). A soln. of crude **37** (15 mg, 0.032 mmol) in DMF (1.5 ml) was treated with NaN_3 (20.4 mg, 0.21 mmol) and kept at 100° for 15 h. The mixture was cooled to r.t., poured into H_2O (15 ml), and extracted with AcOEt (3 × 30 ml). The combined org. layers were washed with brine (50 ml), dried (Na_2SO_4), and evaporated. FC (AcOEt/pentane 2:4 → 1:0) gave **38** (5.6 mg, 50%). Colourless gum. R_f (AcOEt) 0.52. IR (ATR): 3288*w* (br.), 2923*w*, 2853*s*, 2104*s*, 1649*s*, 1463*m*, 1445*m*, 1347*w*, 1311*w*, 1279*w*, 1178*w*, 1105*w*, 1064*m*, 965*w*, 825*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 5.89 (*s*, NH); 5.69 (*dt*, $J = 15.6$, 6.8, H–C(2′)); 5.45 (br. *dd*, $J = 15.5$, 7.8, H–C(1′)); 3.76–3.65 (*m*, H–C(5), CH_a–C(6)); 3.41–3.33 (*m*, H–C(6), CH_b–C(6)); 2.73–2.67 (*m*, H–C(4)); 2.52–2.50 (*m*, 2 H–C(3)); 2.07 (*q*, $J = 6.5$, 2 H–C(3′)); 1.61 (br. *s*, OH); 1.39–1.19 (*m*, 18 H); 0.88 (*t*, $J = 6.6$, Me). HR-MALDI-MS: 351.2754 (52, $[M+H]^+$, $C_{19}H_{35}N_4O_2^+$; calc. 351.2760).

*(4*S*,5*R*,6*S*)-6-(Aminomethyl)-5-hydroxy-4-[(*E*)-tridec-1-enyl)]piperidin-2-one* (**19**). Analogously to the preparation of **17**, **38** (2.5 mg, 7.1 µmol) was transformed into **19** (1.4 mg, 60%). Colourless syrup. R_f (NH_2-phase silica gel; CH_2Cl_2/MeOH 9:1) 0.20. IR (ATR): 3440*w* (sh), 3351*w*, 3281*w* (br.), 2955*w*, 2918*s*, 2852*s*, 1652*s*, 1468*w*, 1411*w*, 1273*w*, 1160*w*, 1021*w*, 960*w*, 867*w*, 722*w*. ^{1}H-NMR (CD_3OD, 300 MHz): 5.61 (*dt*, $J = 15.6$, 6.8, H–C(2′)); 5.45 (br. *dd*, $J = 15.5$, 7.8, H–C(1′)); 3.81–3.73 (*m*, H–C(5), H–C(6)); 3.14–3.05 (*m*, CH_2–C(6)); 2.69–2.65 (*m*, H–C(4)); 2.49–2.45 (*m*, 2 H–C(3)); 2.05 (*q*, $J = 6.5$, 2 H–C(3′)); 1.31–1.20 (*m*, 18 H); 0.85 (*t*, $J = 6.6$, Me). HR-MALDI-MS: 325.2841 (68, $[M+H]^+$, $C_{19}H_{37}N_2O_2^+$; calc. 325.2855).

*(4*S*,5*R*,6*S*)-6-(Aminomethyl)-5-hydroxy-4-(tridecyl)piperidin-2-one* (**20**). Analogously to the preparation of **18**, **38** (1.5 mg, 4.3 µmol) was transformed into **20** (1.1 mg, 80%). Colourless gum. R_f (NH_2 phase; CH_2Cl_2/MeOH 9:1) 0.20. IR (ATR): 3381*w* (sh), 3286*w* (br.), 2953*w*, 2920*s*, 1632*s*, 1475*w*, 1408*w*,

1320*w*, 1266*w*, 1084*m*, 846*w*, 772*w*, 724*w*. ^{1}H-NMR (CD_3OD, 300 MHz): 3.53–3.41 (*m*, H–C(5), H–C(6)); 3.10–3.01 (*m*, CH_2–C(6)); 2.23–2.31 (*m*, 2 H–C(3)); 2.25–2.20 (*m*, H–C(4)); 1.39–1.20 (*m*, 20 H); 0.87 (*t*, *J* = 6.6, Me). HR-MALDI-MS: 327.3013 (100, $[M+H]^+$, $C_{19}H_{39}N_2O_2^+$; calc. 327.3012).

*(4*R*,5*R*,6*S*)-5-Hydroxy-6-({[(4-methylphenyl)sulfonyl]oxy}methyl)-4-[(*E*)-tridec-1-enyl)]piperidin-2-one* (**39**). Analogously to the preparation of **37**, **7** (40 mg, 0.123 mmol) was transformed into **39**. The residue was filtered through a short pad of silica gel (AcOEt/pentane 1:1 → 4:1) to afford crude **39** (52 mg, 88%), which was used directly for the next step. Colourless syrup. R_f (CH_2Cl_2/MeOH 9:1) 0.64. IR (ATR): 3541*w* (br.), 3345*w* (br.), 3221*w* (sh), 2922*s*, 2852*m*, 1653*s*, 1598*w*, 1456*m*, 1403*m*, 1358*s*, 1324*m*, 1189*m*, 1174*s*, 1096*m*, 1019*w*, 968*s*, 920*m*, 878*w*, 812*s*, 789*m*, 706*m*, 667*s*. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.81–7.78 (*m*, 2 arom. H); 7.38–7.35 (*m*, 2 arom. H); 5.85 (*s*, NH); 5.85 (*dt*, *J* = 15.2, 6.8, H–C(2′)); 5.12 (br. *dd*, *J* = 15.2, 8.4, H–C(1′)); 4.36 (*dd*, *J* = 10.2, 2.6, CH_a–C(6)); 4.03 (*dd*, *J* = 10.2, 7.5, CH_b–C(6)); 3.51 (*td*, *J* ≈ 8.2, 2.4, H–C(6)); 3.30 (*td*, *J* = 9.6, 2.1, irrad. at 3.51 → br. *d*, *J* = 9.6, H–C(5)); 2.51 (*dd*, *J* = 16.2, 5.4, H_a–C(3)); 2.58–2.39 (*m*, H–C(4)); 2.46 (*s*, *Me*C_6H_4); 2.22 (*dd*, *J* = 16.5, 11.1, H_b–C(3)); 2.16 (*d*, *J* = 2.1, OH); 2.04 (*q*, *J* = 6.9, 2 H–C(3′)); 1.42–1.18 (*m*, 18 H); 0.88 (*t*, *J* = 6.7, Me). ^{13}C-NMR ($CDCl_3$, 75 MHz): 169.93 (*s*, C=O); 145.31 (*s*); 137.19 (*d*, C(1′)); 132.22 (*s*); 130.00 (*d*, 2 CH); 127.89 (*d*, 2 CH); 127.31 (*d*, C(2′)); 70.08 (*t*, *C*H_2–C(6)); 67.95 (*d*, C(5)); 56.76 (*d*, C(6)); 43.73 (*d*, C(4)); 35.41 (*t*, C(3)); 32.42, 31.81 (2*t*); 29.51–29.05 (several *t*); 22.58 (*t*); 21.59 (*q*, *Me*C_6H_4); 14.02 (*q*, Me). HR-MALDI-MS: 480.2775 (100, $[M+H]^+$, $C_{26}H_{42}NO_5S^+$; calc. 480.2784).

*(4*R*,5*R*,6*S*)-6-[(Dimethylamino)methyl]-5-hydroxy-4-[(*E*)-tridec-1-enyl)]piperidin-2-one* (**21**). A soln. of crude **39** (47.9 mg, 0.1 mmol) in THF (2 ml) was treated with 40% Me_2NH in H_2O (1 ml) and stirred at 85° for 18 h. After cooling to 25°, the mixture was diluted with H_2O and extracted with AcOEt (4 × 30 ml). The combined org. phases were washed with H_2O (2 × 50 ml), dried (Na_2SO_4), and evaporated. FC (CH_2Cl_2/MeOH 9:1) gave **21** (33.5 mg, 95%). R_f (CH_2Cl_2/MeOH 9:1) 0.38. $[\alpha]_D^{25} = +13.2$ (*c* = 0.26, $CHCl_3$). IR (ATR): 3456*w*, 3180*w*, 3016*m*, 2970*m*, 2949*s*, 2919*s*, 2850*m*, 2779*w*, 1663*s*, 1540*m* (br.), 1435*m*, 1403*m*, 1365*s*, 1228*s*, 1216*s*, 1091*w*, 1029*w*, 957*w*, 894*w*, 749*w*, 721*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.02 (*s*, NH); 5.64 (*dt*, *J* = 15.1, 6.8, H–C(2′)); 5.26 (*dd*, *J* = 15.2, 7.7, H–C(1′)); 4.32 (br. *s*, OH); 3.35–3.28 (*m*, H–C(5), H–C(6)); 2.64 (*dd*, *J* = 12.0, 6.4, CH_a–C(6)); 2.55–2.47 (*m*, H_a–C(3), H–C(4)); 2.37–2.16 (*m*, H_b–C(3), CH_b–C(6)); 2.28 (*s*, Me_2N); 2.06 (*q*, *J* = 6.7, 2 H–C(3′)); 1.43–1.19 (*m*, 18 H); 0.88 (*t*, *J* = 6.6, Me). ^{13}C-NMR ($CDCl_3$, 75 MHz): 170.58 (*s*, C=O); 135.06 (*d*, C(1′)); 128.41 (*d*, C(2′)); 73.50 (*d*, C(5)); 63.90 (*t*, *C*H_2–C(6)); 53.61 (*d*, C(6)); 45.73 (*q*, Me_2N); 43.65 (*d*, C(4)); 35.67 (*t*, C(3)); 32.60, 31.94 (2*t*); 29.63–29.20 (several *t*); 22.71 (*t*); 14.14 (*q*, Me). HR-MALDI-MS: 353.3162 (100, $[M+H]^+$, $C_{21}H_{41}N_2O_2^+$; calc. 353.3168).

*(4*R*,5*R*,6*S*)-6-[(Dimethylamino)methyl]-5-hydroxy-4-(tridecyl)piperidin-2-one* (**22**). A soln. of **21** (15 mg, 0.043 mmol) in AcOEt (3 ml) was treated with 10% Pd/C (3 mg, 20 wt%), stirred at 25° under 8 bar of H_2 for 24 h, and filtered through *Celite* (washing with AcOEt). Evaporation of the combined filtrate and washings, and FC (CH_2Cl_2/MeOH 9:1) yielded **22** (14.5 mg, 97%). Colourless syrup. R_f (CH_2Cl_2/MeOH 9:1) 0.28. $[\alpha]_D^{25} = +44.1$ (*c* = 0.56, $CHCl_3$). IR (ATR): 3363*w*, 3290*w*, 3183*w*, 3066*w*, 2954*w*, 2919*s*, 2850*m*, 2829*w*, 2784*w*, 1661*s*, 1468*m*, 1403*w*, 1306*w*, 1265*w*, 1183*w*, 1082*m*, 1043*w*, 1024*w*, 885*w*, 840*w*, 824*w*, 747*m*, 719*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.15, 5.85 (2*s*, NH, OH); 3.38–3.25 (*m*, H–C(5), H–C(6)); 2.66–2.52 (*m*, H_a–C(3), CH_a–C(6)); 2.40 (*dd*, *J* = 12.1, 4.1, CH_b–C(6)); 2.32 (*s*, Me_2N); 2.04–1.81 (*m*, H_b–C(3), H–C(4)); 1.39–1.07 (*m*, 24 H); 0.88 (*t*, *J* = 6.6, Me). ^{13}C-NMR ($CDCl_3$, 75 MHz): 171.98 (*s*, C=O); 75.99 (*d*, C(5)); 64.98 (*t*, *C*H_2–C(6)); 53.38 (*d*, C(6)); 45.95 (*q*, Me_2N); 38.64 (*d*, C(4)); 35.13 (*t*, C(3)); 31.94, 31.11 (2*t*); 29.79–29.37 (several *t*); 25.83, 22.70 (2*t*); 14.13 (*q*, Me). HR-MALDI-MS: 355.3321 (100, $[M+H]^+$, $C_{21}H_{43}N_2O_2^+$; calc. 355.3325).

*(4*S*,5*R*,6*S*)-6-[(Dimethylamino)methyl]-5-hydroxy-4-[(*E*)-tridec-1-enyl)]piperidin-2-one* (**23**). Analogously to the preparation of **21**, **37** (23.7 mg, 0.05 mmol) was transformed into **23** (16.2 mg, 92%). Colourless gum. R_f (CH_2Cl_2/MeOH 9:1) 0.30. $[\alpha]_D^{25} = -25.6$ (*c* = 0.45, $CHCl_3$). IR (ATR): 3301*w* (br.), 3103*w* (sh), 2961*m*, 2922*s*, 2852*m*, 2774*w*, 1645*s*, 1459*m*, 1409*w*, 1320*w*, 1260*s*, 1182*w*, 1090*s*, 1021*s*, 971*m*, 848*w*, 799*s*, 721*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 5.94 (*s*, NH); 5.67–5.54 (*m*, H–C(1′), H–C(2′)); 4.19 (br. *s*, OH); 3.72 (*dd*, *J* = 8.1, 3.9, H–C(5)); 3.31 (*q*, *J* ≈ 7.5, H–C(6)); 2.74–2.71 (*m*, H–C(4)); 2.59 (*dd*, *J* = 12.0, 7.7, CH_a–C(6)); 2.55–2.45 (*m*, 2 H–C(3)); 2.34 (*dd*, *J* = 12.1, 6.8, CH_b–C(6)); 2.28 (*s*, Me_2N); 2.10–2.04 (*m*, 2 H–C(3′)); 1.38–1.32 (*m*, 2 H–C(4′)); 1.32–1.25 (*m*, 16 H); 0.88 (*t*, *J* = 6.7, Me). ^{13}C-NMR ($CDCl_3$, 75 MHz): 170.88 (*s*, C=O); 134.59 (*d*, C(1′)); 126.42 (*d*, C(2′)); 72.49 (*d*, C(5)); 64.29

(*t*, *C*H$_2$–C(6)); 50.56 (*d*, C(6)); 45.89 (*q*, Me$_2$N); 39.55 (*d*, C(4)); 34.17 (*t*, C(3)); 32.82, 31.93 (2*t*); 29.66–29.20 (several *t*); 22.70 (*t*); 14.13 (*q*, Me). HR-MALDI-MS: 353.3164 (100, $[M+H]^+$, $C_{21}H_{41}N_2O_2^+$; calc. 353.3168).

*(4*S*,5*R*,6*S*)-6-[(Dimethylamino)methyl]-5-hydroxy-4-(tridecyl)piperidin-2-one* (**24**). Analogously to the preparation of **22**, **23** (13 mg, 0.037 mmol) was transformed into **24** (12.3 mg, 94%). Colourless gum. R_f (CH_2Cl_2/MeOH 9:1) 0.22. $[\alpha]_D^{25} = -10.8$ ($c = 0.18$, $CHCl_3$). IR (ATR): 3360*w*, 3285*w*, 3180*w*, 3069*w*, 2953*w*, 2920*s*, 2852*m*, 2830*w*, 1658*s*, 1468*m*, 1401*w*, 1306*w*, 1260*w*, 1183*w*, 1088*m*, 1043*w*, 1024*m*, 885*w*, 840*w*, 720*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 5.69 (*s*, NH); 3.79 (*dd*, $J = 7.4$, 3.6, H–C(5)); 3.39 (*q*, $J \approx 6.9$, H–C(6)); 2.54 (*dd*, $J = 12.0$, 8.7, CH_a–C(6)); 2.47–2.35 (*m*, 2 H–C(3)); 2.36 (*dd*, $J = 11.3$, 5.5, CH_b–C(6)); 2.30 (*s*, Me$_2$N); 1.93 (*m*, H–C(4)); 1.49–1.37 (*m*, 2 H–C(1′)); 1.39–1.19 (*m*, 22 H); 0.88 (*t*, $J = 6.7$, Me). ^{13}C-NMR ($CDCl_3$, 75 MHz): 171.15 (*s*, C=O); 72.91 (*d*, C(5)); 65.00 (*t*, *C*H$_2$–C(6)); 50.89 (*d*, C(6)); 46.00 (*q*, Me$_2$N); 36.60 (*d*, C(4)); 33.89 (*t*, C(3)); 31.92 (*t*); 29.85–29.34 (several *t*); 27.46, 27.35, 22.70 (3*t*); 14.17 (*q*, Me). HR-MALDI-MS: 355.3320 (100, $[M+H]^+$, $C_{21}H_{43}N_2O_2^+$; calc. 355.3325).

*(4*R*,5*R*,6*S*)-5-(Benzyloxy)-6-[(benzyloxy)methyl]-1-[(*tert*-butoxy)carbonyl]-4-[(*E*)-tridec-1-enyl]-piperidin-2-one* (**40**). A soln. of **31** (400 mg, 0.79 mmol) in MeCN (15 ml) was treated with Boc_2O (431.5 mg, 1.98 mmol) and 4-(dimethylamino)pyridine (145 mg, 1.19 mmol), stirred at 25° for 24 h, treated with Boc_2O (259 mg, 1.19 mmol) and 4-(dimethylamino)pyridine (48.3 mg, 0.4 mmol), and stirred for 5 h. After evaporation of the solvent, FC (Et_2O/hexane 5:95 → 3:7) gave **40** (383 mg, 80%). Colourless gum. R_f (Et_2O/hexane 3:7) 0.22. $[\alpha]_D^{25} = +73.5$ ($c = 1.08$, $CHCl_3$). IR (ATR): 3034*w*, 2954*w*, 2923*s*, 2853*m*, 1774*m*, 1722*s*, 1454*m*, 1390*w*, 1367*m*, 1294*s*, 1253*m*, 1219*m*, 1154*s*, 1097*s*, 1028*w*, 967*w*, 852*w*, 772*w*, 734*m*, 697*m*. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.28–7.17 (*m*, 10 arom. H); 5.47 (*dt*, $J = 14.9$, 7.2, H–C(2′)); 5.24 (*dd*, $J = 15.4$, 7.4, H–C(1′)); 4.49, 4.45 (2*d*, $J = 11.6$, PhCH_2); 4.41, 4.37 (2*d*, $J = 12.0$, PhCH_2); 4.36 (*dt*, $J = 5.3$, 2.9, H–C(6)); 3.57 (*dd*, $J = 9.1$, 2.6, H–C(5)); 3.47 (*dd*, $J = 9.6$, 5.5, CH_a–C(6)); 3.41 (*dd*, $J = 9.6$, 3.5, CH_b–C(6)); 2.57–2.49 (*m*, H–C(4)); 2.36 (*dd*, $J = 17.2$, 5.2, H$_a$–C(3)); 2.29 (*dd*, $J = 17.2$, 12.4, H$_b$–C(3)); 1.93 (*q*, $J = 6.9$, 2 H–C(3′)); 1.42 (*s*, *t*-Bu); 1.29–1.18 (*m*, 18 H); 0.81 (*t*, $J = 6.8$, Me). ^{13}C-NMR ($CDCl_3$, 75 MHz): 172.04 (*s*, C(2)); 152.48 (*s*, C=O); 137.92, 137.66 (2*s*); 132.78 (*d*, C(1′)); 129.36 (*d*, C(2′)); 128.45–127.67 (several *d*); 83.10 (*d*, C(5)); 79.42 (*s*, Me$_3$*C*); 73.35, 72.08 (2*t*, 2 Ph*C*H$_2$); 71.30 (*t*, *C*H$_2$–C(6)); 60.28 (*d*, C(6)); 40.85 (*d*, C(4)); 37.60 (*t*, C(3)); 32.60, 31.93 (2*t*); 29.70–29.21 (several *t*); 28.03 (*q*, *Me*$_3$C); 22.68 (*t*); 14.11 (*q*, Me). HR-MALDI-MS: 628.3982 (45, $[M+Na]^+$, $C_{38}H_{55}NNaO_5^+$; calc. 628.3978), 506.3633 (100, $[M-Boc+2H]^+$, $C_{33}H_{48}NO_3^+$; calc. 506.3634). Anal. calc. for $C_{38}H_{55}NO_5$ (605.86): C 75.33, H 9.15, N 2.31; found: C 75.28, H 9.16, N 2.41.

*(3*S*,4*S*,5*R*,6*S*)-3-Allyl-5-(benzyloxy)-6-[(benzyloxy)methyl)]-1-[(*tert*-butoxy)carbonyl]-4-[(*E*)-tridec-1-enyl]piperidin-2-one* (**41**). A soln. of **40** (60 mg, 0.1 mmol) in THF (2 ml) was treated at −78° with 1M LiHMDS in toluene (130 µl, 0.13 mmol), allowed to warm to 0° within 4.5 h, and stirred at 25° for 30 min. The mixture was treated with HMPA (40 µl), cooled to −78°, treated with a soln. of allyl bromide (130 µl, 1.5 mmol) in THF (0.1 ml), warmed to 0° within 3.5 h, and stirred at 25° for 1 h. The mixture was treated dropwise with sat. aq. NH_4Cl soln. After dilution with CH_2Cl_2, the aq. phase was separated and extracted with CH_2Cl_2 (3 × 50 ml). The combined org. phases were washed with brine, dried (Na_2SO_4), and evaporated. FC (Et_2O/pentane 1:9) gave **41** (45 mg, 70%). Colourless gum. R_f (AcOEt/pentane 1:9) 0.16. IR (ATR): 3070*w*, 3030*w*, 2975*w*, 2953*w*, 2923*s*, 2853*m*, 1770*w*, 1716*s*, 1639*w*, 1496*w*, 1454*m*, 1389*w*, 1367*s*, 1291*s*, 1254*s*, 1205*m*, 1153*s*, 1095*s*, 1068*s*, 1028*w*, 999*m*, 969*m*, 913*m*, 852*w*, 771*w*, 734*s*, 696*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz; assignments based on a DQFCOSY spectrum): 7.35–7.24 (*m*, 10 arom. H); 5.82–5.72 (*m*, CH_2=C*H*CH$_2$–C(3)); 5.58 (*dt*, $J = 15.0$, 6.9, H–C(2′)); 5.11 (*ddt*, $J = 15.2$, 9.0, 1.3, H–C(1′)); 5.03–4.98 (*m*, C*H*$_2$=CHCH$_2$–C(3)); 4.52 (*s*, PhCH_2); 4.49 (*d*, $J \approx 12.4$, PhC*H*); 4.45 (*d*, $J \approx 12.0$, PhC*H*); 4.44–4.33 (*m*, H–C(6)); 3.67 (*dd*, $J = 8.1$, 2.1, H–C(5)); 3.58 (*dd*, $J = 9.6$, 5.5, CH$_a$–C(6)); 3.53–3.45 (*dd* of CH$_b$–C(6) hidden by the solvent signal); 2.65–2.57 (*m*, CH$_2$=CHC*H*$_a$–C(3)); 2.49 (*q*, $J \approx 9.3$, H–C(4)); 2.35–2.28 (*m*, H–C(3), CH$_2$CHC*H*$_b$–C(3)); 2.04 (br. *q*, $J \approx 7.1$, 2 H–C(3′)); 1.49 (*s*, *t*-Bu); 1.38–1.24 (*m*, 18 H); 0.89 (*t*, $J = 7.1$, Me). ^{13}C-NMR ($CDCl_3$, 100 MHz; assignments based on a HSQC spectrum): 173.71 (*s*, C(2)); 152.76 (*s*, C=O); 138.02, 137.73 (2*s*); 135.16 (*d*, C(1′)); 134.76 (*d*, C*H*=CH$_2$); 129.97 (*d*, C(2′)); 128.42–127.68 (several *d*); 117.21 (*t*, CH=*C*H$_2$); 82.85 (*s*, Me$_3$*C*); 78.62 (*d*, C(5)); 73.31, 71.98 (2*t*, 2 Ph*C*H$_2$); 70.69 (*t*, *C*H$_2$–C(6)); 59.43 (*d*, C(6)); 45.68 (*d*, C(4)); 44.32 (*d*, C(3)); 32.65 (*t*); 32.16 (*t*, *C*H$_2$CH=CH$_2$); 31.91 (*t*); 29.68–29.29 (several *t*); 28.02 (*q*, *Me*$_3$C); 22.67, 22.32 (2*t*);

14.03 (*q*, Me). HR-MALDI-MS: 668.4283 (21, $[M+Na]^+$, $C_{41}H_{59}NNaO_5^+$; calc. 668.4291), 546.3940 (100, $[M-Boc+2H]^+$, $C_{36}H_{52}NO_3^+$; calc. 546.3947).

*(3S,4S,5R,6S)-3-Allyl-5-(benzyloxy)-6-[(benzyloxy)methyl]-4-[(*E*)-tridec-1-enyl]piperidin-2-one* (**42**). An ice-cold soln. of **41** (30 mg, 0.046 mmol) in THF (1.5 ml) was treated with anisole (0.15 ml) and CF_3CO_2H (0.3 ml), stirred at 25° for 15 h, and evaporated. A soln. of the residue in CH_2Cl_2 was washed with sat. aq. $NaHCO_3$ soln. (2 × 50 ml), dried (Na_2SO_4), and evaporated. The residue was filtered through a short pad of silica gel (AcOEt/hexane 4:6) to afford **42** (21.4 mg, 85%) that was used directly for the next step. Colourless gum. R_f (AcOEt/hexane 3.5:6.5) 0.27. IR (ATR): 3200*w* (br.), 3066*w*, 3030*w*, 2954*w*, 2923*s*, 2853*m*, 1666*s*, 1496*w*, 1454*w*, 1391*w*, 1364*w*, 1322*w*, 1208*w*, 1112*m*, 1073*m*, 1026*w*, 974*w*, 912*w*, 816*w*, 734*m*, 697*m*. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.39–7.18 (*m*, 10 arom. H); 6.07 (*s*, NH); 5.77–5.59 (*m*, H–C(2′), CH_2=C*H*CH_2–C(3)); 5.17 (*dd*, *J* = 15.2, 9.1, H–C(1′)); 5.08–5.02 (*m*, CH=CH_2); 4.64, 4.34 (2*d*, *J* = 10.7, PhCH_2); 4.49, 4.47 (2*d*, *J* = 12.0, PhCH_2); 3.67 (*dd*, *J* = 9.0, 2.8, CH_a–C(6)); 3.54 (*td*, *J* = 8.7, 2.7, H–C(6)); 3.33–3.24 (*m*, CH_b–C(6), H–C(5)); 2.80 (*td*, *J* = 10.0, 4.3, H–C(3)); 2.60 (*q*, *J* = 9.9, H–C(4)); 2.32–2.22 (*m*, CH_2–C(3)); 2.07 (*q*, *J* = 6.8, 2 H–C(3′)); 1.42–1.19 (*m*, 18 H); 0.88 (*t*, *J* = 6.7, Me). ^{13}C-NMR ($CDCl_3$, 75 MHz): 171.74 (*s*, C(2)); 137.44, 137.24 (2*s*); 135.44 (*d*, C*H*=CH_2); 134.36 (*d*, C(1′)); 128.50 (*d*, C(2′)); 128.42–127.76 (several *d*); 117.92 (*t*, CH=CH_2); 76.91 (*d*, C(5)); 73.85, 73.22 (2*t*, 2 PhCH_2); 70.65 (*t*, CH_2–C(6)); 56.01 (*d*, C(6)); 46.43 (*d*, C(4)); 43.71 (*d*, C(3)); 32.66 (*t*); 32.16 (*t*, CH_2CH=CH_2); 31.81 (*t*); 29.57–29.23 (several *t*); 22.59 (*t*); 14.03 (*q*, Me). HR-MALDI-MS: 546.3935 (100, $[M+H]^+$, $C_{36}H_{52}NO_3^+$; calc. 546.3947).

(3S,4S,5R,6S)-5-Hydroxy-6-(hydroxymethyl)-3-propyl-4-(tridecyl)piperidin-2-one (**43**). An ice-cold soln. of **42** (10 mg, 0.027 mmol) in MeOH (2.5 ml) was treated with AcOH (0.25 ml) and 10% Pd/C (20 mg), and stirred under 8 bar of H_2 for 24 h. The mixture was filtered through *Celite* (washing with MeOH). The combined filtrate and washings were evaporated. FC (CH_2Cl_2/MeOH 1:0 → 9:1) gave **43** (7.9 mg, 80%). Colourless gum. R_f (CH_2Cl_2/MeOH 9:1) 0.32. $[\alpha]_D^{25} = -19.7$ (*c* = 0.21, $CHCl_3$). IR (ATR): 3326*w*, 3287*w* (br.), 3160*w* (br.), 2956*m*, 2920*s*, 2851*s*, 1634*s*, 1484*w*, 1456*w*, 1436*w*, 1378*w*, 1356*w*, 1325*w*, 1304*w*, 1263*w*, 1235*w*, 1223*w*, 1149*w*, 1087*m*, 1069*m*, 1037*w*, 964*w*, 894*w*, 771*m*, 736*m*, 721*w*, 674*w*. ^{1}H-NMR ($CDCl_3$, 600 MHz): 7.03 (*s*, NH); 3.81 (br. *s*, OH); 3.75–3.70 (*m*, CH_2–C(6)); 3.43 (*t*, *J* = 9.5, H–C(5)); 3.16 (*dt*, *J* = 8.7, 4.2, H–C(6)); 2.86 (*s*, OH); 2.13 (*dt*, *J* = 9.1, 4.7, H–C(3)); 1.79–1.73 (*m*, H_a–C(1′)); 1.67 (*tt*, *J* = 9.5, 4.7, H–C(4)); 1.61–1.56 (*m*, H_a–C(2′)); 1.54–1.49 (*m*, H_b–C(1′)); 1.48–1.45 (*m*, 2 H–C(1″)); 1.36–1.29 (*m*, H_b–C(2′)); 1.25–1.17 (*m*, 24 H); 0.85 (*t*, *J* = 7.3, Me); 0.80 (*t*, *J* = 7.0, Me). ^{13}C-NMR ($CDCl_3$, 150 MHz): 174.89 (*s*, C(2)); 68.59 (*d*, C(5)); 61.36 (*d*, C(6)); 57.76 (*t*, CH_2–C(6)); 43.05 (*d*, C(3)); 41.16 (*d*, C(4)); 31.68, 30.92 (2*t*, C(1′), C(1″)); 29.24–28.68 (several *t*); 24.10, 21.68 (2*t*); 18.08 (*t*); 13.29, 13.09 (2*q*, 2 Me). HR-MALDI-MS: 370.3316 (100, $[M+H]^+$, $C_{22}H_{44}NO_3^+$; calc. 370.3321).

*(3S/R,4S,5R,6S)-5-(Benzyloxy)-6-[(benzyloxy)methyl]-3-[(*E*)-but-2-enyl]-1-[(*tert*-butoxy)carbonyl]-4-[(*E*)-tridec-1-enyl]piperidin-2-one* (**44a**/**44b**). A soln. of **40** (80 mg, 0.13 mmol) in THF (2 ml) was treated at −78° with 1M LiHMDS in toluene (170 µl, 0.17 mmol), allowed to warm to 0° within 4.5 h, and stirred at 0° for 30. The mixture was treated with HMPA (50 µl), cooled to −78°, treated with a soln. of (*E*)-1-bromobut-2-ene (267 µl, 2.6 mmol) in THF (0.2 ml), warmed to 0° within 3.5 h, and stirred at 25° for 1 h. The mixture was treated dropwise with sat. aq. NH_4Cl soln., and diluted with CH_2Cl_2. The phases were separated, and the aq. phase was extracted with CH_2Cl_2 (3 × 50 ml). The combined org. phases were washed with brine, dried (Na_2SO_4), and evaporated. FC (Et_2O/hexane 17:3) gave **44a**/**44b** 3:1 (55 mg, 63%). Colourless gum. R_f (Et_2O/hexane 17:3) 0.19. $[\alpha]_D^{25} = +61.2$ (*c* = 1.0, $CHCl_3$). IR (ATR): 3030*w*, 2954*w*, 2923*s*, 2853*m*, 1773*w*, 1715*s*, 1496*w*, 1454*m*, 1391*w*, 1367*m*, 1291*s*, 1255*m*, 1205*m*, 1154*s*, 1097*s*, 1069*s*, 1028*w*, 967*m*, 947*w*, 854*w*, 771*w*, 734*s*, 696*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz; **44a**/**44b** 3:1): signals of **44a**: 7.36–7.25 (*m*, 10 arom. H); 5.57 (*dt*, *J* = 14.7, 7.2, H–C(2′)); 5.49–5.30 (*m*, C*H*=C*H*Me); 5.11 (*dd*, *J* = 15.4, 8.8, H–C(1′)); 4.52–4.47 (*m*, 2 PhCH_2); 4.43–4.38 (*m*, H–C(6)); 3.66 (*dd*, *J* = 8.5, 2.7, H–C(5)); 3.58 (*dd*, *J* = 9.6, 5.5, CH_a–C(6)); 3.50 (*dd*, *J* = 9.6, 3.5, CH_b–C(6)); 2.59–2.19 (*m*, H–C(3), H–C(4), CH_2–C(3)); 2.04 (*q*, *J* = 6.4, 2 H–C(3′)); 1.61 (*d*, *J* = 4.6, CH=CH*Me*); 1.50 (*s*, *t*-Bu); 1.37–1.26 (*m*, 18 H); 0.88 (*t*, *J* = 6.5, Me); signals of **44b**: 1.56 (*d*, *J* = 6.5, CH=CH*Me*). ^{13}C-NMR ($CDCl_3$, 100 MHz; **44a**/**44b** 3:1): signals of **44a**: 173.98 (*s*, C(2)); 152.81 (*s*, C=O); 138.06, 137.78 (2*s*); 134.53 (*d*, C(1′)); 129.12 (*d*, C(2′)); 127.91, 127.82 (2*d*, MeC*H*=C*H*CH$_2$–C(3)); 127.72–127.33 (several *d*); 82.70 (Me_3C); 78.61 (*d*, C(5)); 73.30, 72.03 (2*t*, 2 PhCH_2); 70.68 (*t*, CH_2–C(6)); 59.44 (*d*, C(6)); 45.51 (*d*, C(4));

44.68 (*d*, C(3)); 32.67, 31.92 (2*t*); 29.69–29.29 (several *t*); 28.04 (*q*, *Me*$_3$C); 22.68 (*t*); 18.02 (*q*, CH=CH*Me*); 14.10 (*q*, Me); signals of **44b**: 173.87 (*s*, C(2)); 152.77 (*s*, C=O); 137.75 (*s*); 129.20 (*d*, C(2′)); 125.40 (*d*, CH=*C*HMe); 82.79 (Me$_3$*C*); 78.65 (*d*, C(5)); 71.94 (*t*, Ph*C*H$_2$); 70.66 (*t*, *C*H$_2$–C(6)); 59.36 (*d*, C(6)); 46.09 (*d*, C(4)); 44.78 (*d*, C(3)); 32.70, 31.00 (2*t*); 25.63 (*t*); 13.10 (*q*, Me). HR-MALDI-MS: 682.4456 (26, $[M+Na]^+$, $C_{42}H_{61}NNaO_5^+$; calc. 682.4447), 560.4109 (100, $[M-Boc+2H]^+$, $C_{37}H_{54}NO_3^+$; calc. 560.4104).

*(3*S*/*R*,4*S*,5*R*,6*S*)-5-(Benzyloxy)-6-[(benzyloxy)methyl]-3-[(*E*)-but-2-enyl]-4-[(*E*)-tridec-1-enyl]piperidin-2-one* (**45a**/**45b**). An ice-cold soln. of **44a**/**44b** 3:1 (60 mg, 0.09 mmol) in THF (4 ml) was treated with anisole (0.25 ml, 2.3 mmol) and CF_3CO_2H (1 ml, 13.5 mmol), stirred at 25° for 24 h, and evaporated. A soln. of the residue in CH_2Cl_2 was washed with sat. aq. $NaHCO_3$ soln. (2 × 50 ml), dried (Na_2SO_4), and evaporated. The residue was filtered through a short pad of silica gel (AcOEt/hexane 7:13) to afford crude **45a**/**45b** 3:1 (44 mg, 86%) that was used directly for the next step. Colourless gum. R_f (AcOEt/hexane 1:1) 0.29. IR (ATR): 3245*w* (br.), 3030*w*, 2923*s*, 2853*m*, 1663*s*, 1496*w*, 1454*m*, 1403*w*, 1363*w*, 1319*w*, 1208*s*, 1162*s*, 1095*s*, 1028*m*, 967*s*, 911*w*, 819*w*, 786*w*, 732*s*, 695*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz; **45a**/**45b** 3:1): signals of **45a**: 7.57 (*s*, NH); 7.39–7.19 (*m*, 10 arom. H); 5.66 (*dt*, *J* = 15.1, 6.9, H–C(2′)); 5.48 (*dt*, *J* = 14.6, 7.0, C*H*=CHMe); 5.31–5.24 (*m*, CH=C*H*Me); 5.16 (br. *dd*, *J* = 15.2, 9.1, H–C(1′)); 4.65 (*d*, *J* = 10.6, PhC*H*); 4.55–4.47 (*m*, PhC*H*$_2$); 4.36 (*d*, *J* = 10.7, PhC*H*); 3.670 (*dd*, *J* = 9.3, 2.4, CH$_a$–C(6)); 3.53 (*ddd*, *J* = 9.0, 6.9, 2.4, H–C(6)); 3.43 (*dd*, *J* = 9.3, 6.9, CH$_b$–C(6)); 3.37 (*dd*, *J* = 9.6, 9.0, H–C(5)); 2.73–2.66 (*m*, H–C(3)); 2.60 (*q*, *J* = 9.6, H–C(4)); 2.45–2.18 (*m*, C*H*$_2$CH=CHMe); 2.08 (br. *q*, *J* = 6.8, 2 H–C(3′)); 1.65 (*d*, *J* = 6.3, CH=CH*Me*); 1.44–1.20 (*m*, 18 H); 0.89 (*t*, *J* = 6.7, Me); signals of **45b**: 3.663 (*dd*, *J* = 9.3, 2.4, CH$_a$–C(6)); 3.35 (*dd*, *J* ≈ 9.3, 1.8, H–C(5)); 2.60 (*q*, *J* = 9.3, H–C(4)); 1.60 (*d*, *J* = 6.8, CH=CH*Me*). ^{13}C-NMR ($CDCl_3$, 75 MHz; **45a**/**45b** 3:1): signals of **45a**: 174.60 (*s*, C(2)); 137.33, 137.17 (2*s*); 133.73 (*d*, C(1′)); 129.25 (*d*, C(2′)); 128.39, 128.34 (2*d*); 128.25 (*d*, MeCH=*C*HCH$_2$–C(3)); 128.02–127.90 (several *d*); 125.79 (*d*, CH=C*H*Me); 76.07 (*d*, C(5)); 74.12, 73.41 (2*t*, 2 Ph*C*H$_2$); 69.49 (*t*, *C*H$_2$–C(6)); 56.46 (*d*, C(6)); 45.97 (*d*, C(4)); 43.89 (*d*, C(3)); 32.66, 31.82 (2*t*); 29.58–29.20 (several *t*); 22.59 (*t*); 17.97 (*q*, CH=CH*Me*); 14.13 (*q*, Me); signals of **45b**: 174.73 (*s*, C(2)); 127.06 (*d*, *C*H=CHMe); 125.21 (*d*, CH=*C*HMe); 74.08 (*t*, Ph*C*H$_2$); 69.44 (*t*, *C*H$_2$–C(6)); 46.50 (*d*, C(4)); 44.10 (*d*, C(3)); 32.69, 31.79 (2*t*); 25.43 (*t*); 13.15 (*q*, Me). HR-MALDI-MS: 560.4105 (100, $[M+H]^+$, $C_{39}H_{60}NO_3^+$; calc. 560.4104).

*(3*S*/*R*,4*S*,5*R*,6*S*)-3-[(*E*)-But-2-enyl]-5-hydroxy-6-(hydroxymethyl)-4-[(*E*)-tridec-1-enyl]piperidin-2-one* (**46a**/**46b**). An ice-cold soln. of **45a**/**45b** 3:1 (23 mg, 0.04 mmol) in 1,2-dichloroethane (1 ml) was treated with anisole (88.8 mg, 0.82 mmol) and $AlCl_3$ (54.8 mg, 0.41 mmol), stirred at 25° for 2 h, treated dropwise with 1M HCl, and extracted with AcOEt (3 × 50 ml). The combined org. phases were washed with brine, dried (Na_2SO_4), and evaporated. FC (CH_2Cl_2/MeOH 9:1) afforded **46a**/**46b** 3:1 (12 mg, 78%). Complete removal of the minor isomer **46b** was achieved by slow FC (CH_2Cl_2/MeOH 1:0 → 9:1).

Data of **46a**. Colourless gum. R_f (CH_2Cl_2/MeOH 9:1) 0.42. $[\alpha]_D^{25} = -18.3$ (*c* = 0.16, $CHCl_3$). IR (ATR): 3298*w* (br.), 3254*w*, 3131*w*, 2957*w*, 2920*s*, 2852*m*, 1644*s*, 1492*w*, 1465*w*, 1431*m*, 1376*w*, 1311*w*, 1267*w*, 1103*w*, 1062*m*, 1033*w*, 967*w*, 954*w*, 790*w*, 747*m*. ^{1}H-NMR ($CDCl_3$ + 1 drop of CD_3OD, 300 MHz): 5.63 (*dt*, *J* = 15.2, 6.8, H–C(2′)); 5.44 (*dq*, *J* = 14.4, 6.9, CH=C*H*Me); 5.30–5.22 (*m*, C*H*=CHMe); 5.03 (*ddt*, *J* = 15.2, 9.1, 1.3, H–C(1′); 3.83 (*dd*, *J* = 11.5, 3.3, CH$_a$–C(6)); 3.54 (*dd*, *J* = 11.5, 6.3, CH$_b$–C(6)); 3.34 (*dd*, *J* = 10.2, 9.2, H–C(5)); 3.23 (*ddd*, *J* = 9.1, 6.2, 3.1, H–C(6)); 2.74–2.60 (*m*, H–C(3)); 2.33 (*q*, *J* = 10.2, H–C(4)); 2.16 (*dt*, *J* = 11.0, 5.6, CH$_2$–C(3)); 2.05 (*q*, *J* = 6.8, 2 H–C(3′)); 1.62 (*d*, *J* = 6.3, CH=CH*Me*); 1.39–1.32 (*m*, 2 H–C(4′)); 1.29–1.16 (*m*, 16 H); 0.85 (*t*, *J* = 6.7, Me). ^{13}C-NMR ($CDCl_3$, 150 MHz): 172.85 (*s*, C(2)); 138.49 (*d*, C(1′)); 128.73 (*d*, C(2′)); 128.91 (*d*, C*H*=CHMe); 126.49 (*d*, CH=*C*HMe); 68.53 (*d*, C(5)); 64.12 (*t*, *C*H$_2$–C(6)); 58.75 (*d*, C(6)); 47.62 (*d*, C(4)); 43.79 (*d*, C(3)); 32.66, 31.94 (2*t*); 29.68–29.20 (several *t*); 22.72 (*t*); 18.10 (*q*, CH=CH*Me*); 14.15 (*q*, Me). HR-MALDI-MS: 380.3156 (100, $[M+H]^+$, $C_{23}H_{42}NO_3^+$; calc. 380.3165).

Data of **46b**. ^{1}H-NMR ($CDCl_3$, 500 MHz; **46a**/**46b** 3:1): 6.65 (*s*, NH); 5.83 (*dt*, *J* = 14.9, 6.8, H–C(2′)); 5.76 (*dq*, *J* = 15.1, 6.9, CH=C*H*Me); 5.59–5.52 (*m*, C*H*=CHMe); 1.56 (*d*, *J* = 6.6, CH=CH*Me*). ^{13}C-NMR ($CDCl_3$, 125 MHz; **46a**/**46b** 3:1): 172.96 (*s*, C(2)); 128.13 (*d*, C(2′)); 126.63 (*d*, *C*H=CHMe); 125.95 (*d*, CH=*C*HMe); 68.48 (*d*, C(5)); 64.01 (*t*, *C*H$_2$–C(6)); 58.73 (*d*, C(6)); 48.13 (*d*, C(4)); 44.04 (*d*, C(3)); 18.08 (*q*, CH=CH*Me*); 13.26 (*q*, Me).

(3S,4S,5R,6S)-3-Butyl-5-hydroxy-6-(hydroxymethyl)-4-(tridecyl)piperidin-2-one (**47**). An ice-cold soln. of **45a**/**45b** 3:1 (23 mg, 0.04 mmol) in MeOH (5 ml) was treated with AcOH (0.5 ml) and 10% Pd/C (50 mg), and stirred under 8 bar of H_2 for 24 h. The mixture was filtered through *Celite* (washing with AcOEt). The combined filtrate and washings were evaporated. FC (CH_2Cl_2/MeOH 1:0→9:1) gave **47** (12 mg, 75%). Colourless gum. R_f (CH_2Cl_2/MeOH 9:1) 0.37. $[\alpha]_D^{25} = -26.2$ ($c = 0.41$, $CHCl_3$). IR (ATR): 3294*w* (br.), 3261*w*, 3156*w* (sh), 2953*w*, 2919*s*, 2852*m*, 1636*s*, 1484*w*, 1455*w*, 1439*m*, 1378*w*, 1324*w*, 1304*w*, 1220*m*, 1146*w*, 1068*m*, 1037*w*, 968*w*, 913*w*, 772*s*, 721*w*, 693*w*. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.30 (*s*, NH); 4.28 (*t*, $J = 5.0$, CH_2OH); 3.85–3.74 (*m*, CH_2–C(6)); 3.49 (*td*, $J \approx 9.7$, 5.3, H–C(5)); 3.25 (*d*, $J = 4.0$, HO–C(5)); 3.21 (*dt*, $J = 8.8$, 4.2, H–C(6)); 2.19 (*dt*, $J = 9.0$, 4.7, H–C(3)); 1.89–1.80 (*m*, H–C(4)); 1.77–1.70 (*m*, H_a–C(1′)); 1.63–1.47 (*m*, H_b–C(1′), CH_2–C(3)); 1.36–1.23 (*m*, 26 H); 0.89 (*t*, $J \approx 7.0$, 2 Me). ^{13}C-NMR ($CDCl_3$, 100 MHz): 176.26 (*s*, C(2)); 69.24 (*d*, C(5)); 61.75 (*t*, CH_2–C(6)); 58.88 (*d*, C(6)); 44.34 (*d*, C(3)); 42.05 (*d*, C(4)); 31.94, 30.55 (2*t*); 30.36, 30.22 (2*t*); 29.73–29.37 (several *t*); 27.94, 25.26 (2*t*); 22.93, 22.69 (2*t*); 14.10, 13.98 (2*q*, 2 Me). HR-MALDI-MS: 384.3470 (100, $[M + H]^+$, $C_{23}H_{46}NO_3^+$; calc. 384.3478).

*(4S,5R,6S)-5-(Benzyloxy)-6-[(benzyloxy)methyl]-1-[(*tert*-butoxy)carbonyl]-4-[(*E*)-tridec-1-enyl]-piperidin-2-one* (**48**). Analogously to the preparation of **40**, **32** (260 mg, 0.51 mmol) gave **48** (256 mg, 83%). Colourless gum. R_f (Et_2O/hexane 1:4) 0.17. $[\alpha]_D^{25} = +38.5$ ($c = 1.0$, $CHCl_3$). IR (ATR): 3034*w*, 2954*w*, 2923*s*, 2853*m*, 1771*m*, 1714*s*, 1496*w*, 1454*m*, 1389*w*, 1367*m*, 1295*s*, 1244*s*, 1206*m*, 1152*s*, 1094*s*, 1067*s*, 1027*m*, 969*m*, 937*w*, 911*w*, 853*w*, 804*w*, 780*w*, 733*s*, 696*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.37–7.26 (*m*, 10 arom. H); 5.52–5.39 (*m*, H–C(1′), H–C(2′)); 4.62, 4.46 (2*d*, $J = 12.0$, PhCH_2); 4.57–4.51 (*m*, H–C(6), PhCH_2); 3.81 (*t*, $J = 2.4$, H–C(5)); 3.58 (*dd*, $J = 9.8$, 4.0, CH_a–C(6)); 3.47 (*dd*, $J = 9.7$, 7.8, CH_b–C(6)); 2.81–2.74 (*m*, H–C(4)); 2.68 (*dd*, $J = 16.2$, 11.6, H_a–C(3)); 2.40 (*dd*, $J = 16.2$, 5.2, H_b–C(3)); 2.04–1.96 (*m*, 2 H–C(3′)); 1.49 (*s*, *t*-Bu); 1.36–1.27 (*m*, 18 H); 0.89 (*t*, $J = 6.7$, Me). ^{13}C-NMR ($CDCl_3$, 75 MHz): 170.87 (*s*, C(2)); 152.73 (*s*, C=O); 137.98, 137.58 (2*s*); 132.37 (*d*, C(1′)); 128.90 (*d*, C(2′)); 128.36–127.55 (several *d*); 82.92 (*s*, Me_3C); 75.45 (*d*, C(5)); 73.17, 71.36 (2*t*, 2 PhCH_2); 69.49 (*t*, CH_2–C(6)); 56.97 (*d*, C(6)); 36.88 (*d*, C(4)); 36.14 (*t*, C(3)); 32.45, 31.82 (2*t*); 29.61–29.09 (several *t*); 27.86 (*q*, Me_3C); 22.59 (*t*); 14.03 (*q*, Me). HR-MALDI-MS: 628.3980 (46, $[M + Na]^+$, $C_{38}H_{55}NNaO_5^+$; calc. 628.3978), 506.3631 (100, $[M - Boc + 2\,H]^+$, $C_{33}H_{48}NO_3^+$; calc. 506.3634). Anal. calc. for $C_{38}H_{55}NO_5$ (605.86): C 75.33, H 9.15, N 2.31; found: C 75.37, H 9.17, N 2.33.

*(3R/S,4R,5R,6S)-5-(Benzyloxy)-6-[(benzyloxy)methyl]-3-[(*E*)-but-2-enyl]-1-[(*tert*-(butoxy)carbonyl]-4-[(*E*)-tridec-1-enyl]piperidin-2-one* (**49a**/**49b**). Analogously to the preparation of **44a**/**44b**, **48** (75 mg, 0.12 mmol) gave **49a**/**49b** 3:1 (65 mg, 60%). Colourless gum. R_f (Et_2O/hexane 1:4) 0.22. $[\alpha]_D^{25} = +22.9$ ($c = 0.85$ $CHCl_3$). IR (ATR): 3062*w*, 3030*w*, 2953*w*, 2923*s*, 2853*m*, 1770*w*, 1715*s*, 1496*w*, 1454*m*, 1391*w*, 1367*m*, 1292*s*, 1251*m*, 1205*m*, 1155*s*, 1112*s*, 1069*s*, 1028*w*, 970*m*, 945*w*, 854*w*, 818*w*, 733*s*, 697*s*. ^{1}H-NMR ($CDCl_3$, 400 MHz; **49a**/**49b** 3:1): signals of **49a**: 7.29–7.18 (*m*, 10 arom. H); 5.39–5.28 (*m*, H–C(2′), *CH*=C*H*Me); 5.23–5.12 (*m*, H–C(1′)); 4.55 (*d*, $J = 11.9$, PhC*H*); 4.49 (*dt*, $J = 8.3$, 3.2, H–C(6)); 4.45 (*d*, $J = 12.2$, PhC*H*); 4.42 (*d*, $J = 12.0$, PhC*H*); 4.37 (*d*, $J = 12.2$, PhC*H*); 3.72 (br. *t*, $J \approx 2.4$, H–C(5)); 3.47 (*dd*, $J = 9.7$, 4.6, CH_a–C(6)); 3.32 (*dd*, $J = 9.7$, 8.4, CH_b–C(6)); 2.65–2.58 (*m*, H–C(3)); 2.55 (*m*, H–C(4), CH_aCH=C*H*Me); 2.05–1.99 (*m*, CH_bCH=C*H*Me); 1.97–1.91 (*m*, 2 H–C(3′)); 1.48 (*d*, $J = 6.3$, CH=CH*Me*); 1.42 (*s*, *t*-Bu); 1.30–1.19 (*m*, 18 H); 0.81 (*t*, $J = 6.9$, Me); signals of **49b**: 5.50 (*dq*, $J = 14.5$, 7.1, CH=C*H*Me); 5.04 (*ddt*, $J = 15.2$, 9.0, 1.3, H–C(1′)); 4.56 (*d*, $J = 11.9$, PhC*H*); 3.48 (*dd*, $J = 9.8$, 4.6, CH_a–C(6)); 3.34 (*dd*, $J = 10.3$, 8.4, CH_b–C(6)); 2.23–2.14 (*m*, CH_aCH=C*H*Me); 2.05–1.99 (*m*, CH_bCH=C*H*Me); 1.45 (*d*, $J = 6.3$, CH=CH*Me*); 1.41 (*s*, *t*-Bu). ^{13}C-NMR ($CDCl_3$, 100 MHz; **49a**/**49b** 3:1): signals of **49a**: 173.09 (br. *s*, C(2)); 153.34 (*s*, C=O); 138.24, 137.82 (2*s*); 133.62 (*d*, C(1′)); 129.40 (*d*, C(2′)); 127.80, 127.19 (2*d*, *C*H=*C*HMe); 128.46–127.59 (several *d*); 82.81 (*s*, Me_3C); 76.22 (*d*, C(5)); 73.22 (*t*, PhCH_2); 71.50 (br. *t*, PhCH_2); 69.66 (br. *t*, CH_2–C(6)); 56.23 (br. *d*, C(6)); 44.34 (*d*, C(4)); 40.62 (*d*, C(3)); 32.55, 31.94 (2*t*); 29.71–29.21 (several *t*); 28.00 (*q*, Me_3C); 22.70 (*t*); 17.93 (*q*, CH=CH*Me*); 14.11 (*q*, Me); signals of **49b**: 173.11 (*s*, C(2)); 153.38 (*s*, C=O); 138.22, 137.76 (2*s*); 133.58 (*d*, C(1′)); 129.60 (*d*, C(2′)); 126.54, 126.14 (2*d*, *C*H=*C*HMe); 128.44–127.75 (several *d*); 82.84 (Me_3C); 76.31 (*d*, C(5)); 73.31 (*t*, PhCH_2); 44.40 (*d*, C(4)); 41.07 (*d*, C(3)); 32.58, 31.15 (2*t*); 28.05 (*q*, CH=CH*Me*); 22.66 (*t*); 13.16 (*q*, Me). HR-MALDI-MS: 682.4440 (34, $[M + Na]^+$, $C_{42}H_{61}NNaO_5^+$; calc. 682.4447), 560.4098 (100, $[M - Boc + 2\,H]^+$, $C_{37}H_{54}NO_3^+$; calc. 560.4104).

*(3*R*/*S*,4*R*,5*R*,6*S*)-5-(Benzyloxy)-6-[(benzyloxy)methyl]-3-[(*E*)-but-2-enyl]-4-[(*E*)-tridec-1-enyl]piperidin-2-one* (**50a**/**50b** 3:1). Analogously to the preparation of **45a**/**45b**, **49a**/**49b** (55 mg, 0.083 mmol) gave **50a**/**50b** 3:1 (37 mg, 80%). Colourless gum. R_f (AcOEt/hexane 7:13) 0.20. IR (ATR): 3290*w*, 3208*w*, 3087*w*, 3066*w*, 3030*w*, 2953*m*, 2922*s*, 2853*s*, 1660*s*, 1496*w*, 1454*m*, 1407*w*, 1360*w*, 1336*w*, 1308*w*, 1253*w*, 1206*m*, 1162*s*, 1098*s*, 1069*s*, 1027*w*, 969*s*, 911*w*, 816*w*, 786*w*, 733*s*, 696*s*. ^{1}H-NMR ($CDCl_3$, 600 MHz; **50a**/**50b** 3:1): signals of **50a**: 7.35–7.25 (*m*, 10 arom. H); 6.82 (*s*, NH); 5.48–5.47 (*m*, H–C(2′), CH=C*H*Me); 5.41 (br. *ddt*, *J* = 15.2, 6.4, 1.1, H–C(1′)); 5.27 (*dtq*, *J* = 15.0, 7.4, 1.5, C*H*=CHMe); 4.52, 4.47 (2*d*, *J* = 11.9, PhCH_2); 4.50, 4.48 (2*d*, *J* = 12.0, PhCH_2); 3.71–3.66 (*m*, H–C(6)); 3.60 (*dd*, *J* = 5.3, 3.1, H–C(5)); 3.52 (*dd*, *J* = 9.3, 4.7, CH_a–C(6)); 3.32 (*dd*, *J* = 9.3, 7.4, CH_b–C(6)); 2.63–2.26 (several *m*, H–C(3), H–C(4), CH_2CH=CHMe); 2.03–1.97 (*m*, 2 H–C(3′)); 1.61 (br. *dd*, *J* = 6.4, 1.4, CH=CH*Me*); 1.37–1.30 (*m*, 2 H–C(4′)); 1.29–1.21 (*m*, 16 H); 0.86 (*t*, *J* = 7.0, Me); signals of **50b**: 6.88 (*s*, NH); 5.53–5.49 (*m*, H–C(2′), CH=C*H*Me); 5.24–5.20 (*m*, C*H*=CHMe); 3.61 (*dd*, *J* = 4.8, 3.1, H–C(5)); 3.51 (*dd*, *J* = 9.3, 4.9, CH_a–C(6)); 3.36 (*dd*, *J* = 9.3, 7.3, CH_b–C(6)); 1.56 (*dd*, *J* = 6.8, 1.7, CH=CH*Me*). ^{13}C-NMR ($CDCl_3$, 150 MHz; **50a**/**50b** 3:1): signals of **50a**: 174.78 (*s*, C(2)); 137.74 (br. *s*); 137.50 (*s*); 133.94 (*d*, C(1′)); 128.49 (*d*, C(2′)); 128.50–127.70 (several *d*); 127.66, 127.31 (2*d*, *C*H=*C*HMe); 73.75 (*d*, C(5)); 73.45, 71.39 (2*t*, 2 Ph*C*H_2); 71.28 (*t*, *C*H_2–C(6)); 53.82 (*d*, C(6)); 42.35 (*d*, C(4)); 38.94 (*d*, C(3)); 32.71, 31.93 (2*t*); 29.69–29.20 (several *t*); 22.69 (*t*); 17.92 (*q*, CH=CH*Me*); 14.11 (*q*, Me); signals of **50b**: 174.79 (*s*, C(2)); 137.49 (*s*); 133.91 (*d*, C(1′)); 127.84 (*d*, C(2′)); 126.55, 126.54 (2*d*, *C*H=*C*HMe); 74.26 (*d*, C(5)); 73.43 (*t*, Ph*C*H_2); 71.37, 71.35 (2*t*, Ph*C*H_2, *C*H_2–C(6)); 53.89 (*d*, C(6)); 42.31 (*d*, C(4)); 39.55 (*d*, C(3)); 32.68 (*t*); 26.85 (*t*); 13.18 (*q*, Me). HR-MALDI-MS: 560.4100 (100, $[M+H]^+$, $C_{39}H_{60}NO_3^+$; calc. 560.4104).

*(3*R*/*S*,4*R*,5*R*,6*S*)-3-[(*E*)-But-2-enyl]-5-hydroxy-6-(hydroxymethyl)-4-[(*E*)-tridec-1-enyl]piperidin-2-one* (**51a**/**51b** 3:1). Analogously to the preparation of **46a**/**46b**, **50a**/**50b** (18 mg, 0.032 mmol) gave **51a**/**51b** 3:1 (9.3 mg, 76%). Colourless gum. R_f (CH_2Cl_2/MeOH 9:1) 0.41. $[\alpha]_D^{25} = -1.5$ (*c* = 0.14, $CHCl_3$). IR (ATR): 3311*w* (br.), 3131*w*, 2957*w*, 2923*s*, 2853*m*, 1634*s*, 1466*w*, 1433*w*, 1374*w*, 1342*w*, 1261*w*, 1219*w*, 1150*w*, 1081*w*, 1024*w*, 969*w*, 772*s*, 721*w*. ^{1}H-NMR (CD_3OD, 600 MHz; **51a**/**51b** 3:1): signals of **51a**: 5.58–5.53 (*m*, H–C(1′), C*H*=C*H*Me); 5.56 (*dt*, *J* = 14.5, 7.3, H–C(2′)); 5.34 (*dtq*, *J* = 15.0, 7.0, 1.5, C*H*=C*H*Me); 3.95 (*t*, *J* = 3.2, H–C(5)); 3.54 (*d*, *J* = 6.3, CH_2–C(6)); 3.36 (*td*, *J* = 6.3, 3.8, H–C(6)); 2.59 (*dtd*, *J* = 13.8, 6.0, 1.2, CH_aCH=CHMe); 2.56 (*td*, *J* = 8.4, 2.6, H–C(4)); 2.42 (*ddd*, *J* = 8.9, 6.0, 4.2, H–C(3)); 2.24 (*ddd*, *J* = 13.5, 8.6, 4.6, CH_bCH=CHMe); 2.11–2.07 (*m*, 2 H–C(3′)); 1.68 (br. *dd*, *J* = 6.4, 0.8, CH=CH*Me*); 1.44–1.40 (*m*, 2 H–C(4′)); 1.36–1.31 (*m*, 16 H); 0.92 (*t*, *J* = 7.0, Me); signals of **51b**: 5.32–5.28 (*m*, H–C(1′)); 3.96 (br. *dd*, *J* = 3.6, 2.1, H–C(5)); 3.55 (*d*, *J* = 6.0, CH_2–C(6)); 3.38 (*td*, *J* = 6.5, 3.8, H–C(6)); 2.52–2.48 (*m*, 2 H); 2.42–2.38 (*m*, 1 H); 1.64 (*d*, *J* = 6.8, CH=CH*Me*). ^{13}C-NMR ($CDCl_3$, 150 MHz; **51a**/**51b** 3:1): signals of **51a**: 174.53 (br. *s*, C(2)); 135.93 (*d*, C(1′)); 128.51 (*d*, C(2′)); 127.37 (*d*, *C*H=CHMe); 126.93 (*d*, CH=*C*HMe); 65.99 (*d*, C(5)); 64.20 (*t*, *C*H_2–C(6)); 58.34 (*d*, C(6)); 43.10, 42.24 (2*d*, C(3), C(4)); 32.73, 31.92 (2*t*); 29.68–29.26 (several *t*); 22.69 (*t*); 17.97 (*q*, CH=CH*Me*); 14.12 (*q*, Me); signals of **51b**: 135.80 (*d*, C(1′)); 126.78 (*d*, *C*H=CHMe); 126.67 (*d*, CH=*C*HMe); 66.41 (*d*, C(5)); 64.27 (*t*, *C*H_2–C(6)); 58.52 (*d*, C(6)); 42.52 (*d*, C(3) or C(4)); 33.32 (*t*); 13.13 (*q*, Me). HR-MALDI-MS: 380.3158 (100, $[M+H]^+$, $C_{23}H_{42}NO_3^+$; calc. 380.3165).

*(3*R*,4*R*,5*R*,6*S*)-3-Butyl-5-hydroxy-6-(hydroxymethyl)-4-(tridecyl)piperidin-2-one* (**52**). Analogously to the preparation of **47**, **50a**/**50b** 3:1 (9 mg, 0.016 mmol) gave **52** (4.5 mg, 74%). Colourless gum. R_f (CH_2Cl_2/MeOH 9:1) 0.36. $[\alpha]_D^{25} = -24.3$ (*c* = 0.23, $CHCl_3$). IR (ATR): 3307*w* (br.), 2957*w*, 2922*s*, 2853*s*, 1638*s*, 1465*m*, 1417*w*, 1378*w*, 1342*w*, 1314*w*, 1261*w*, 1223*w*, 1156*w*, 1075*m*, 1037*w*, 968*w*, 769*s*, 721*w*. ^{1}H-NMR (CD_3OD, 300 MHz): 4.01 (*dd*, *J* = 6.0, 3.2, irrad. at 1.80 → *d*, *J* = 5.9, H–C(5)); 3.62 (*dd*, *J* = 11.2, 5.2, CH_a–C(6)); 3.53 (*dd*, *J* = 11.2, 5.6, CH_b–C(6)); 3.35–3.32 (*m*, H–C(6)); 2.27 (*q*, *J* = 5.8, irrad. at 1.80 → *t*, *J* = 5.1, H–C(3)); 1.80 (*qd*, *J* = 6.4, 3.2, irrad. at 4.01 → *q*, *J* = 6.5, H–C(4)); 1.68 (*td*, *J* = 13.7, 6.5, 2 H–C(1′)); 1.39–1.21 (*m*, 28 H); 0.92 (*t*, *J* ≈ 6.9, Me); 0.89 (*t*, *J* ≈ 7.2, Me). ^{13}C-NMR ($CDCl_3$, 150 MHz): 175.57 (*s*, C(2)); 65.30 (*d*, C(5)); 64.26 (*t*, *C*H_2–C(6)); 57.09 (*d*, C(6)); 43.97 (*d*, C(3)); 39.63 (*d*, C(4)); 31.94, 30.85 (2*t*); 29.83–29.37 (several *t*); 27.33, 27.18 (2*t*); 22.70, 22.68 (2*t*); 14.12, 13.98 (2*q*, 2 Me). HR-MALDI-MS: 384.3465 (100, $[M+H]^+$, $C_{23}H_{46}NO_3^+$; calc. 384.3478).

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