Total synthesis of pachastrissamine together with its 4-*epi*-congener via [3,3]-sigmatropic rearrangements and antiproliferative/cytotoxic evaluation

Miroslava Martinková, Eva Mezeiová, Milica Fabiš íková, Jozef Gonda, Martina Pilátová, Ján Mojžiš

PII: S0008-6215(14)00420-0
DOI: http://dx.doi.org/10.1016/j.carres.2014.11.004
Reference: CAR 6886

To appear in: *Carbohydrate Research*

Received Date: 22 September 2014
Revised Date: 10 November 2014
Accepted Date: 17 November 2014

Please cite this article as: Martinková, M., Mezeiová, E., Fabiš íková, M., Gonda, J., Pilátová, M., Mojžiš, J., Total synthesis of pachastrissamine together with its 4-*epi*-congener via [3,3]-sigmatropic rearrangements and antiproliferative/cytotoxic evaluation, *Carbohydrate Research* (2014), doi: http://dx.doi.org/10.1016/j.carres.2014.11.004

Total synthesis of pachastrissamine together with its 4-*epi*-congener via [3,3]-sigmatropic rearrangements and antiproliferative/cytotoxic evaluation

Miroslava Martinková [a,*], Eva Mezeiová [a], Milica Fabišíková [a], Jozef Gonda [a], Martina Pilátová [b], Ján Mojžiš [b]

[a]*Department of Organic Chemistry, Institute of Chemical Sciences, Faculty of Science, P.J. Šafárik University, Moyzesova 11, 040 01 Košice, Slovak Republic*

[b]*Department of Pharmacology, Faculty of Medicine, P.J. Šafárik University, SNP 1, 040 66 Košice, Slovak Republic*

Dedicated to Associated Professor Ladislav Kniežo on the occasion of his 70th birthday

ARTICLE INFO

Article history:

Received

Accepted

Available online

Keywords:

Anhydrophytosphingosines, Jaspine B, Pachastrissamine, [3,3]-Heterosigmatropic rearrangements, Stereoselective synthesis, Anticancer activity

ABSTRACT

Synthesis of the HCl salts of two anhydrophytosphingosines, jaspine B (**1**) and its 4-*epi*-congener **5** from easily available dimethyl L-tartrate and/or L-arabinose, is described. The key transformations are the efficient incorporation of a chiral amino group via [3,3]-sigmatropic rearrangements, a Wittig olefination for the instalment of the carbon backbone and the acid-promoted building-up of a tetrahydrofuran framework. Evaluation for in vitro antiproliferative/cytotoxic activity with a panel of human tumor cell lines using a MTT assay revealed for some compounds of our strategy noteworthy activity. Compound **1.HCl** (IC_{50}: 0.41-2.35 μM), its antipode *ent*-**1.HCl** (IC_{50}: 4.07-5.69 μM) and also stereoisomer **4.HCl** (IC_{50}:

∗ Corresponding author. Tel.: +421-55-6222329: fax: +421-55-6222124.

E-mail address: miroslava.martinkova@upjs.sk (M. Martinková).

4.28-6.10 μM) exhibited significant potency compared with clinically available anticancer drugs such as cisplatin (IC_{50}: 11.4-14.7 μM) and etoposide (IC_{50}: 1.2-21.2 μM) on MDA-MB-231, MCF-7 and Jurkat cells.

1. Introduction

Tetrahydrofuran ring systems are highly prevalent substructures found in many natural bioactive molecules.[1] Among these, a class of unusual sphingolipid tetrahydrofuran derivatives substituted with an alkyl side chain functionality and possessing a vicinal amino alcohol motif termed the anhydrophytosphingosines, have drawn much attention from the synthetic and medicinal chemists owing to significant biological properties (vide infra). (+)-Jaspine B (**1**) (also known as pachastrissamine, Fig. 1) is one of the anhydrophytosphingosine analogues that has been isolated independently from two marine sponges (*Pachastrissa* sp.[2] and *Jaspis* sp.[3]) together with its oxazolidine congener, jaspine A (**2**, Fig. 1).[3]

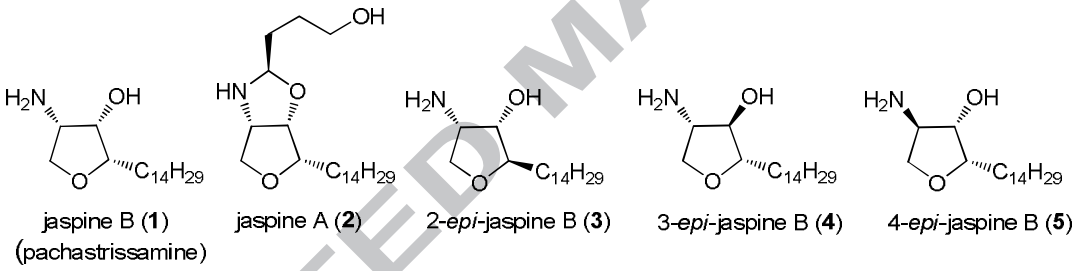


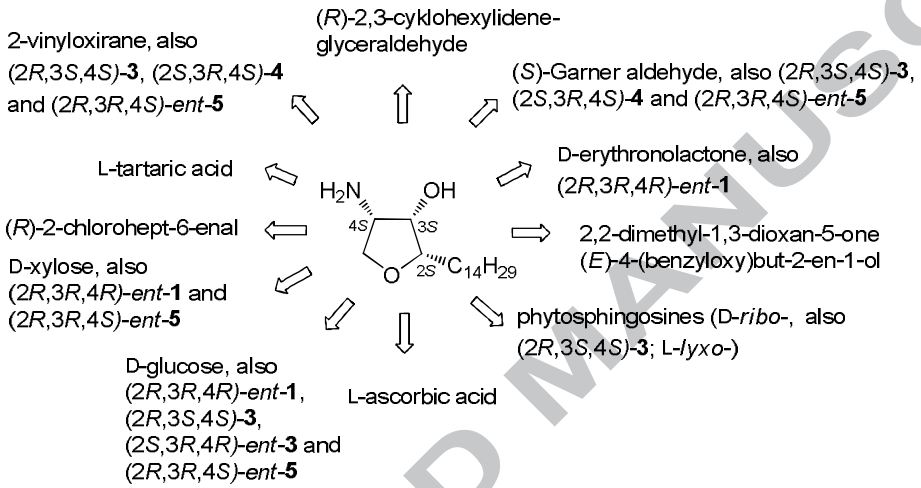
Figure 1. Structures of anhydrophytosphingosines.

The structure of **1** was determined by extensive spectroscopic studies[2,3] including NOE experiments[2] to be unprecedented sphingolipid related cyclic molecule, which is characterized by the presence of a (2*S*,3*S*,4*S*)-configured tetrahydrofuran skeleton with the amino, hydroxyl and C_{14} alkyl chain functionalities. All these structural features have been revealed to be crucial for its biological activity (vide infra). Jaspine B has been reported to exhibit a significant in vitro cytotoxicity against several different cancer cell lines including A-549,[2,3,4a-b] P-388,[2] HT-29,[2] MeL-28,[2,4c] MCF-7,[4b,4d-e] KB,[4b] HTC-116,[4f] U2OS,[4f] MDA-231,[4g] HeLa,[4g] CNE,[4g] MGC-803,[4e] EC-9706[4e] with IC_{50} in the micromolar to sub-micromolar ranges. It should be noted, that there are two reports incorporating the cytotoxicity of pachastrissamine **1**,[4b,4f] its TFA salt[4b] and also antipode (*ent*-**1**)[4f] towards non-malignant cells,

concretely NiH 3T3 (mouse fibroblasts)[4b] and GM-637 (human fibroblasts);[4f] to allow comparison, IC_{50} = 0.4 μM[4f] for **1** on GM-637 and IC_{50} = 7.80 μM[4b] for **1** on NiH 3T3. Andrieu-Abadie's studies[4c] have shown that **1** induces apoptosis on melanoma cells (murine B16 and human MeL-28). This effect is due to its potent inhibitory activity against sphingomyelin synthase (SMS), an essential enzyme involved in the biosynthesis of sphingomyelins.[5] With the aim to elucidate the structure-activity relationships in **1** and its congeners, the role of the stereochemical arrangement of substituents on the tetrahydrofuran backbone on the biological profile has been investigated.[4a,4d,4f,6] Delgado and co-workers[4a] and also Génisson et al.[4f] confirmed that the absolute configuration of the tetrahydrofuran core is the decisive factor for the cytotoxic properties. *ent*-Jaspine B (*ent*-**1**), for instance, was found to display a lower activity against some aforementioned cell lines [HTC-116,[4f] U2OS[4f] and MCF-7[4d] (**1** in the form of TFA salt)]. Furthermore, compounds **3** (A-549[4a] and MCF-7[4d]), **4** (A-549[4a]) and *ent*-**5** (A-549[4a]) were less potent than pachastrissamine, but still retained the activity. To promote these aforementioned findings concerning the SAR, other studies focused on the side-chain modified analogues of **1**[4e,7] and **5**,[6b] as well as the core ring-modified derivatives[8] of **1** have been developed. According to a recently Liu's study, for example, some 1,2,3-triazole-jaspine B hybrids were found to indicate excellent cytotoxicity.[4e] Further biological screening realized by Fujii et al.[6a] revealed that jaspine B and all its isomers inhibit both forms of sphingosine kinase (SphK1 and SphK2) with moderate to high activities, at which compounds *ent*-**4** and **5** (Fig. 1) exhibited the most potent inhibitory profile. The same authors also have demonstrated that SphK inhibitory activity depends on the length of the hydrocarbon side chain and the naturally C_{14} carbon functionality was found to be the most optimal.[6b]

The remarkable biological activity, simple, but unique structural features and limited availability of the natural anhydrophytosphingosines have resulted in the development of numerous total syntheses of **1**, as well as its stereoisomers. In 2008, Davies et al.[9] excellently reviewed the isolation, characterization, stereochemical assignment, and syntheses of jaspine B together with the construction of 2-*epi*-jaspine B (**3**). In recent six years a number of synthetic chemists have undertaken studies on the preparation of pachastrissamine and its analogues employing different approaches and various starting materials (Scheme 1). However the most straightforward routes still appear to be those utilizing the chiral pool commencing substrates, such as (*S*)-Garner's aldehyde,[10] (*R*)-Garner's aldehyde,[11] D-serine methyl ester,[12] D-glucose,[13] D-xylose,[14] D-ribose,[15] 3-amino-3-deoxy-D-ribofuranose,[16] D-mannose,[17] L-ascorbic acid,[18] D-isoascorbic acid,[19] D-erythronolactone,[20] D-glyceraldehyde,[21]

L-tartaric acid,[22] L-threitol,[23] phytosphingosines (D-*ribo*-,[24] L-*lyxo*-,[4a] L-*arabino*-,[4a] D-*xylo*-[4a]), (*R*)-2-chlorohept-6-enal,[25] (3*R*,4*R*)-hexa-1,5-diene-3,4-diol[26] since majority of them include parts of the chiral fragments that are present in the final products mentioned above. Further, a few enantioselective syntheses starting from the simple molecules such as 2,2-dimethyl-1,3-dioxan-5-one,[27] (*E*)-4-(benzyloxy)but-2-en-1-ol[28] and 2-vinyloxirane[29] have been realized. These procedures involved an organocatalytic aldol reaction,[27] Sharpless asymmetric epoxidation[28] and an enantioselective palladium-catalyzed allylic amination[29] as the key transformations (Scheme 1).



Scheme 1. Published total syntheses of jaspine B together with its some isomers after Davies's review.[9]

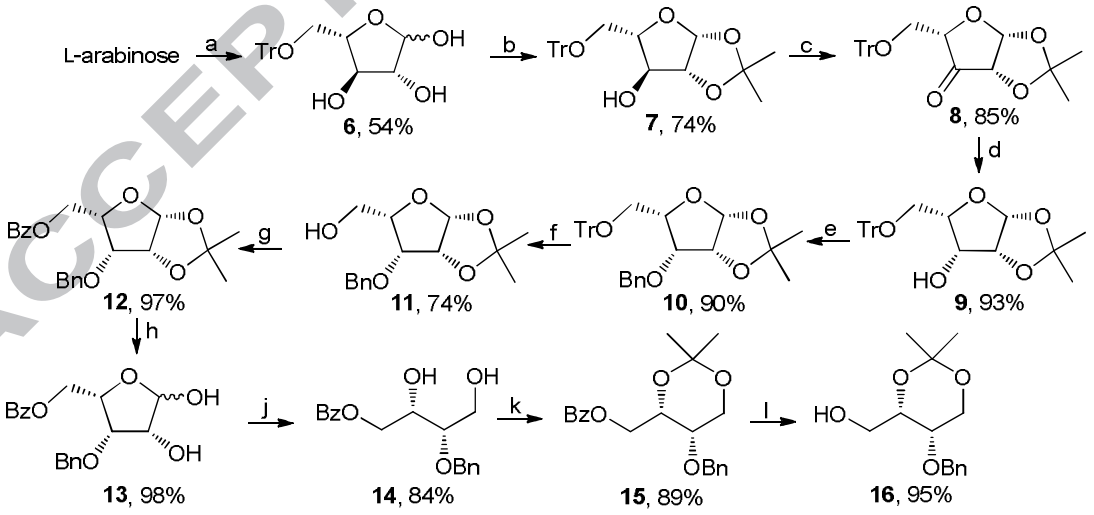
Recently, we have reported the total synthesis of four pachastrissamine stereoisomers (*ent*-**1**, *ent*-**5**[14b] and *ent*-**3** and **4**[17] as HCl salts) based on the concept to obtain biologically active and complex natural products using [3,3]-heterosigmatropic rearrangements on allylic scaffolds (thiocyanates and trichloroacetimidates) derived from the monosaccharide templates, as the key transformation for the effective incorporation of the chiral amino group. Until now, there was only one report utilizing the aforementioned rearrangements for the construction of jaspine B published by Ichikawa et al.[22a] We present herein the preparation of two further members of anhydrophytosphingosine family, jaspine B (**1**) and its unnatural 4-*epi*-analogue **5** (Fig. 1), using our successful approach[14b] starting from the synthon **16**[30] (for the construction of *ent*-**16**, see lit.[31]) which was elaborated from two different starting materials, L-arabinose and dimethyl L-tartrate.

2. Results and discussion

2.1. Chemistry

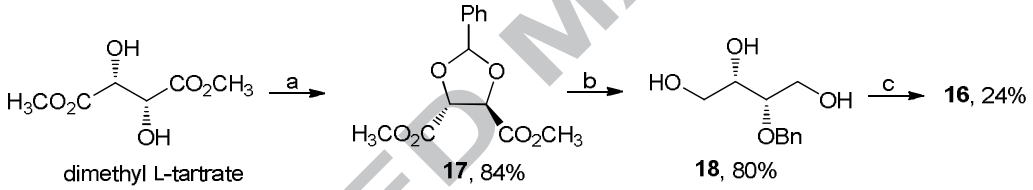
2.1.1. Preparation of the chiral building block, acetonide 16[30]

Because our developed strategy based on the application of the [3,3]-sigmatropic rearrangements in natural product synthesis has employed the simple carbohydrates as the chiral pool starting point, we began the synthesis of the required scaffold **16**[30] (Scheme 2) from inexpensive and readily available L-arabinose. Its regioselective tritylation (TrCl, pyridine, DMAP) afforded 5-*O*-trityl-L-arabinofuranose **6**[32] (54%) which was converted into the isopropylidene derivative **7** in 74% yield by treatment with 2,2-dimethoxypropane (2,2-DMP) and catalytic amounts of CSA in dry acetone. The configuration at the C-3 position in **7** was inverted through an oxidation–stereoselective reduction sequence. Thus, IBX[33] mediated transformation of **6** resulted in the formation of the corresponding ulose **8** (85%) whose reduction with $NaBH_4$ in EtOH provided the requisite β-L-lyxofuranose **9** as a single diastereoisomer in 93% yield (Scheme 2). The remaining hydroxyl group in **9** was protected as the benzyl ether **10** (90%) using the conventional conditions (BnBr, NaH, DMF). Removal of the *O*-trityl group in **10** (CSA, CH_2Cl_2/MeOH) followed by benzoylation of **11** (74%) produced derivative **12** in 97% yield. Cleavage of the 1,2-*O*-isopropylidene moiety in **12** was achieved with 80% TFA to give lactol **13** (98%) whose sodium metaperiodate fragmentation ($NaIO_4$, MeOH/H_2O) followed by $NaBH_4$ treatment provided diol **14** in 84% yield (Scheme 2).



Scheme 2. *Reagents and conditions:* (a) TrCl, DMAP, pyridine, 40 °C→rt; (b) 2,2-DMP, acetone, CSA, rt; (c) IBX, MeCN, reflux; (d) $NaBH_4$, EtOH, 0 °C→rt; (e) BnBr, DMF, NaH, TBAI, 0 °C→rt; (f) CSA, CH_2Cl_2/MeOH (2:1), rt; (g) BzCl, DMAP, pyridine, 0 °C→rt; (h) 80% TFA, 0 °C; (j) (i) $NaIO_4$, MeOH/H_2O (1:1), rt; (ii) $NaBH_4$, MeOH/CH_2Cl_2, 0° C→rt; (k) 2,2-DPM, CH_2Cl_2, *p*-TsOH, rt; (l) K_2CO_3, MeOH, 0 °C→rt.

Conversion of the generated 1,3-diol moiety in **14** to acetonide (2,2-dimethoxypropane, *p*-TsOH, CH_2Cl_2) led to the production of **15** (89%, Scheme 2) and the subsequent base-induced hydrolysis of the ester functionality in **15** provided the desired derivative **16**[30] in 95% yield {$[\alpha]_D^{25}$ = +64.7 (*c* 0.30, $CHCl_3$); lit.[30] $[\alpha]_D$ = +64.0 (*c* 0.30, temperature and solvent not reported)}. Because we required great amounts of the pure scaffold **16**, the aforementioned strategy did not appear to be practical; 12 reaction steps, recorded low, 14% overall yield. Therefore, we looked for a more economic approach leading to **16** and adopted the known three-step protocols,[30] commencing from the commercially accessible dimethyl L-tartrate (Scheme 3). This sequence involved the production of the benzylidene derivative **17**[30,34] (84%), its reductive cleavage with $LiAlH_4/AlCl_3$ system and the selective protection of the corresponding triol **18**[30,34] (80%) which afforded **16** (24%) in 16% overall yield.

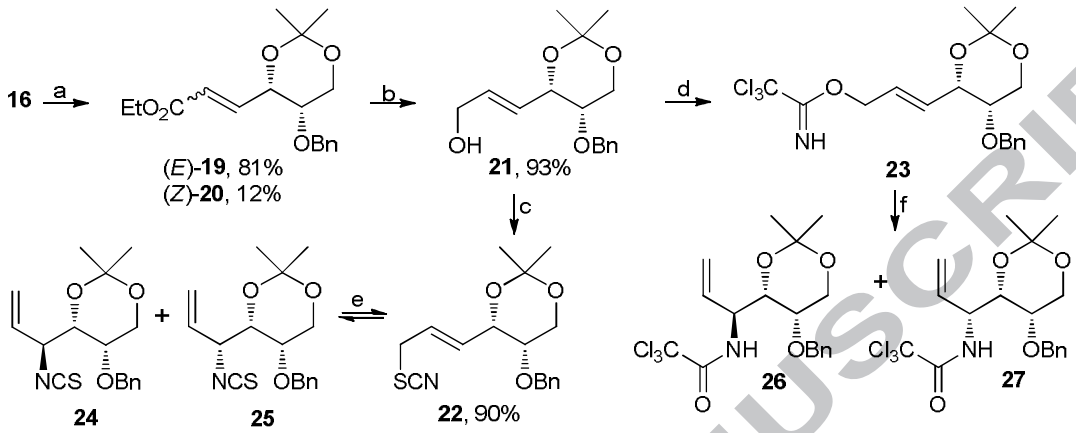


Scheme 3. *Reagents and conditions:* (a) *p*-TsOH, PhCHO, benzene, reflux; (b) $LiAlH_4$, $AlCl_3$, Et_2O/CH_2Cl_2, 0 °C→reflux; (c) 2-methoxypropene, PPTS, DMF, –15 °C→rt.

2.1.2. [3,3]-Heterosigmatropic rearrangements

Having successfully completed the synthesis of **16**, we turned our attention towards the construction of suitable allylic substrates for the [3,3]-sigmatropic rearrangements. As shown in Scheme 4, IBX oxidation of the hydroxyl group in **16** followed by a Horner-Wadsworth-Emmons (HWE) olefination with triethyl phosphonoacetate (NaH, THF) provided an easily separable mixture of α,β-unsaturated esters (*E*)-**19** and (*Z*)-**20** (*E*:*Z* = 88:12 ratio, as determined by ^{1}H NMR spectroscopy) in 81% and 12% isolated yields, respectively. Geometry of the double bonds in these isomers was identified through the vinyl proton coupling constant values; $J_{3,2}$ = 15.7 Hz for (*E*)-**19** and $J_{3,2}$ = 11.8 Hz for (*Z*)-**20**. For further transformations we used (*E*)-**19** as the major product. Its reduction was achieved with DIBAl-H in CH_2Cl_2 to furnish the corresponding alcohol **21** (93%, Scheme 4). On one hand,

mesylation of **21** (MsCl, Et_3N) followed by KSCN treatment afforded thiocyanate **22** in 90% yield after two steps. On the other hand, alcohol **21** was transformed into trichloroacetimidate **23** using trichloroacetonitrile (CCl_3CN) and NaH in THF.



Scheme 4. *Reagents and conditions:* (a) (i) IBX, MeCN, reflux; (ii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C→rt; (b) DIBAl-H, CH_2Cl_2, –50 °C→rt; (c) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C→rt; (ii) KSCN, MeCN, 0 °C→rt; (d) NaH, Cl_3CCN, NaH, THF, 0 °C→rt; (e) Table 1; (f) Table 2.

As we had already prepared suitable substrates **22** and **23** from the common alcohol **21**, our next task was to realize individual rearrangements. The thermal reaction of thiocyanate **22** was carried out in heptane at 70 °C and 90 °C and afforded the corresponding isothiocyanates **24** and **25** as a readily separable mixture of diastereoisomers in very good yields (85–91%) and with satisfactory selectivity (Table 1, entries 1-3).

Table 1
[3,3]-Sigmatropic rearrangement of thiocyanate **22**

Entry	Thiocyanate	Conditions[a]	Time (h)	Ratio[b] **24**:**25**	Yield[c] (%)
1	**22**	Δ, 70 °C	8	90:10	85
2	**22**	MW, 70 °C	1.5	86:14	91
3	**22**	Δ, 90 °C	2	85:15	91
4	**22**	MW, 90 °C	0.5	76:24	88

[a] In *n*-heptane.
[b] Ratio in the crude reaction mixtures. Determined by ^{1}H NMR spectroscopy.
[c] Isolated combined yields.

On the other hand, the application of microwave energy at the same temperatures required shorter reaction times (1.5 h and 0.5 h, entries 2 and 4, respectively, Table 1) and produced the rearranged products **24** and **25** with yields and stereoselectivities similar to the thermal

driven reaction. Allylic imidate **23** rearranged using both the conventional thermal and microwave irradiation conditions in *o*-xylene in the presence of K_2CO_3[35] (Table 2). As expected, two Owerman's trichloroacetamides **26** and **27** were isolated from these reactions in very good yields (75–90%), but unfortunately none diastereoselectivity was observed (Table 2, entries 1-4). As well as in the case of aza-Claisen reaction of **22**, the use of microwave heating was shown to be the most effective.

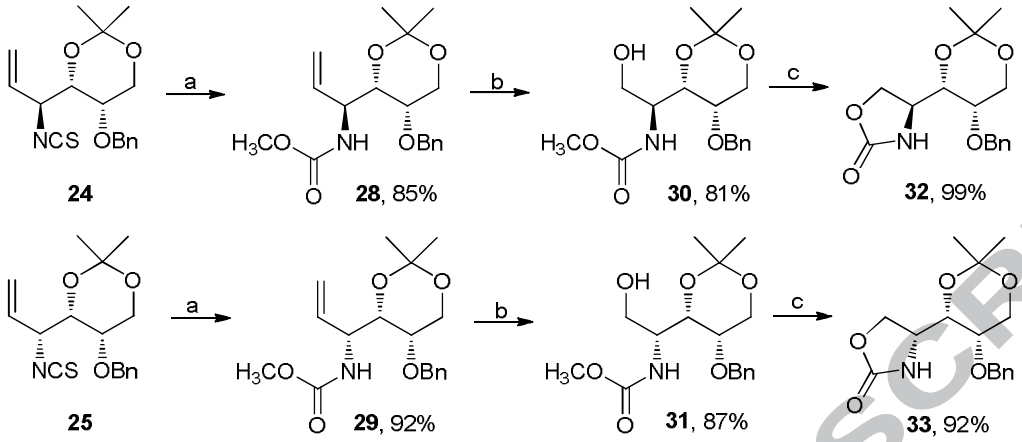
Table 2
Overman rearrangement of imidate **23**

Entry	Imidate	Conditions[a]	Time (h)	Ratio[b] **26**:**27**	Yield[c] (%)
1	**23**	MW, 130 °C	3	54:46	87
2	**23**	MW, 150 °C	1.5	54:46	90
3	**23**	MW, 170 °C	0.5	54:46	86
4	**23**	Δ, 140 °C	52	54:46	75

[a] In *o*-xylene, in the presence of K_2CO_3.
[b] Ratio in the crude reaction mixtures. Determined by ^{1}H NMR spectroscopy.
[c] Isolated combined yields.

2.1.3. Synthesis of common oxazolidinones: confirmation of the stereochemistry

At this stage, the newly constructed stereochemistry in the key scaffolds **24**-**27** could be preliminarily assigned by analogy to previously obtained antipodes *ent*-**24**–*ent*-**27**.[14b] As expected, the prepared rearranged products **24**-**27** had spectroscopic data in excellent agreement with those reported.[14b] The specific rotations were opposite in sign but matched almost equal magnitudes (see experimental part) to those reported for the corresponding enantiomers.[14b] The configuration of the built chiral amino group in aza-Claisen product series was later exactly determined by X-ray crystallographic analysis of the more advanced derivative **28** and in the corresponding Overman product series by chemical correlations (vide infra). Thus, for this purpose the major diastereoisomer **24** was through a two-step procedure converted into crystalline derivative **28** in overall 83% yield (Scheme 5), the structure of which has been unequivocally confirmed by a single crystal X-ray diffraction analysis (Fig. 2) revealing (*S*) arrangement of the installed stereocentre. In a parallel fashion, the minor isothiocyanate **25** was converted into carbamate **29** (89% yield over two steps, Scheme 5). To achieve a synthesis of the common oxazolidinones **32** and **33**, ozonolysis of both products **28** and **29** followed by a reductive work up ($NaBH_4$) resulted in the formation of alcohols **30** (81%) and **31** (87%) those NaH-mediated cyclization furnished the required cyclic derivatives **32** and **33** in 99% and 92% yields, respectively (Scheme 5).



Scheme 5. *Reagents and conditions:* (a) (i) MeONa, MeOH, 0 °C→rt, 97% from both **24** and **25**; (ii) MNO, MeCN, rt; (b) (i) O_3, MeOH or MeOH/CH_2Cl_2, –78 °C; (ii) $NaBH_4$, MeOH or MeOH/CH_2Cl_2, –78 °C→rt; (c) NaH, THF, 0 °C→rt.

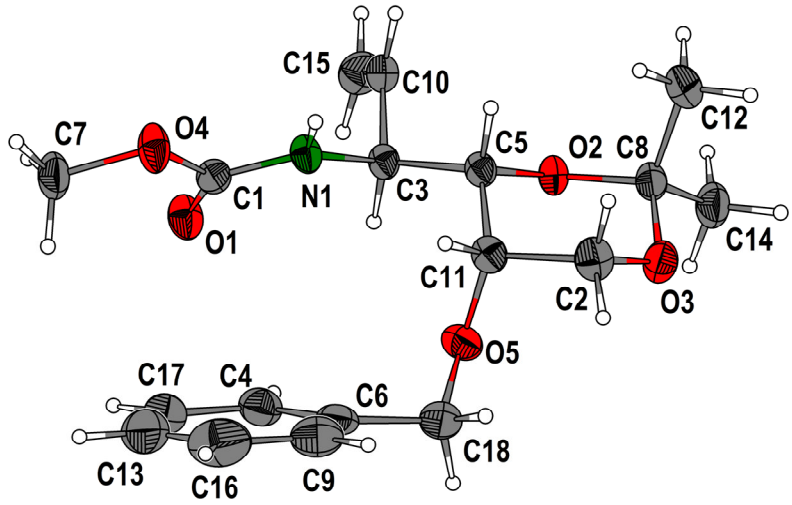
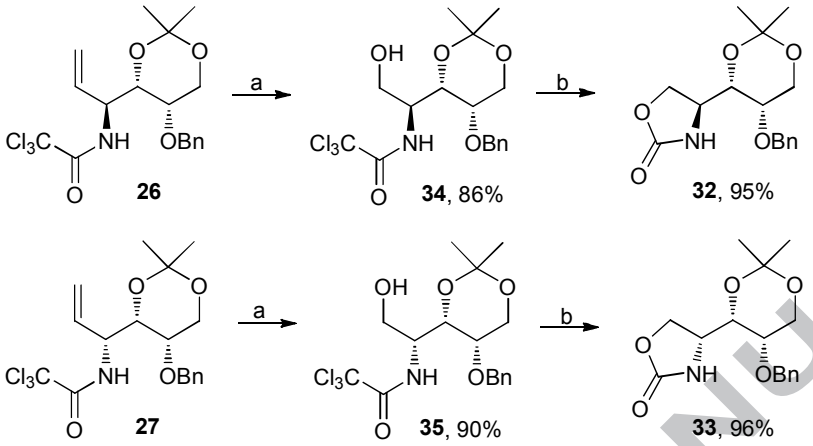


Figure 2. ORTEP structure of **28** showing the crystallographic numbering.

Having secured a reliable route to **32** and **33** from the products of aza-Claisen rearrangement **24** and **25**, respectively, out next task was to build the same structures from the Overman's trichloroacetamides **26** and **27**. It was achieved via a two-step approach involving the ozonolysis followed by $NaBH_4$ treatment to afford alcohols **34** (86%) and **35** (90%, Scheme 6). Their elaboration with catalytic amounts of DBU induced the production of carbamates **32**

and **33** in 95% and 96% yields, respectively. The prepared material had physical and spectroscopic properties in excellent accord with those found for structures **32** and **33** previously obtained from isothiocyanates **24** and **25** confirming (*S*)-configured stereocentre with nitrogen in the prevalent diastereoisomer **25**.



Scheme 6. *Reagents and conditions:* (a) O_3, MeOH/CH_2Cl_2, –78 °C; (ii) $NaBH_4$, MeOH/CH_2Cl_2 –78 °C→rt; (b) DBU, CH_2Cl_2, 0 °C→rt.

Table 3

Crystal data and structure refinement parameters for compound **28**

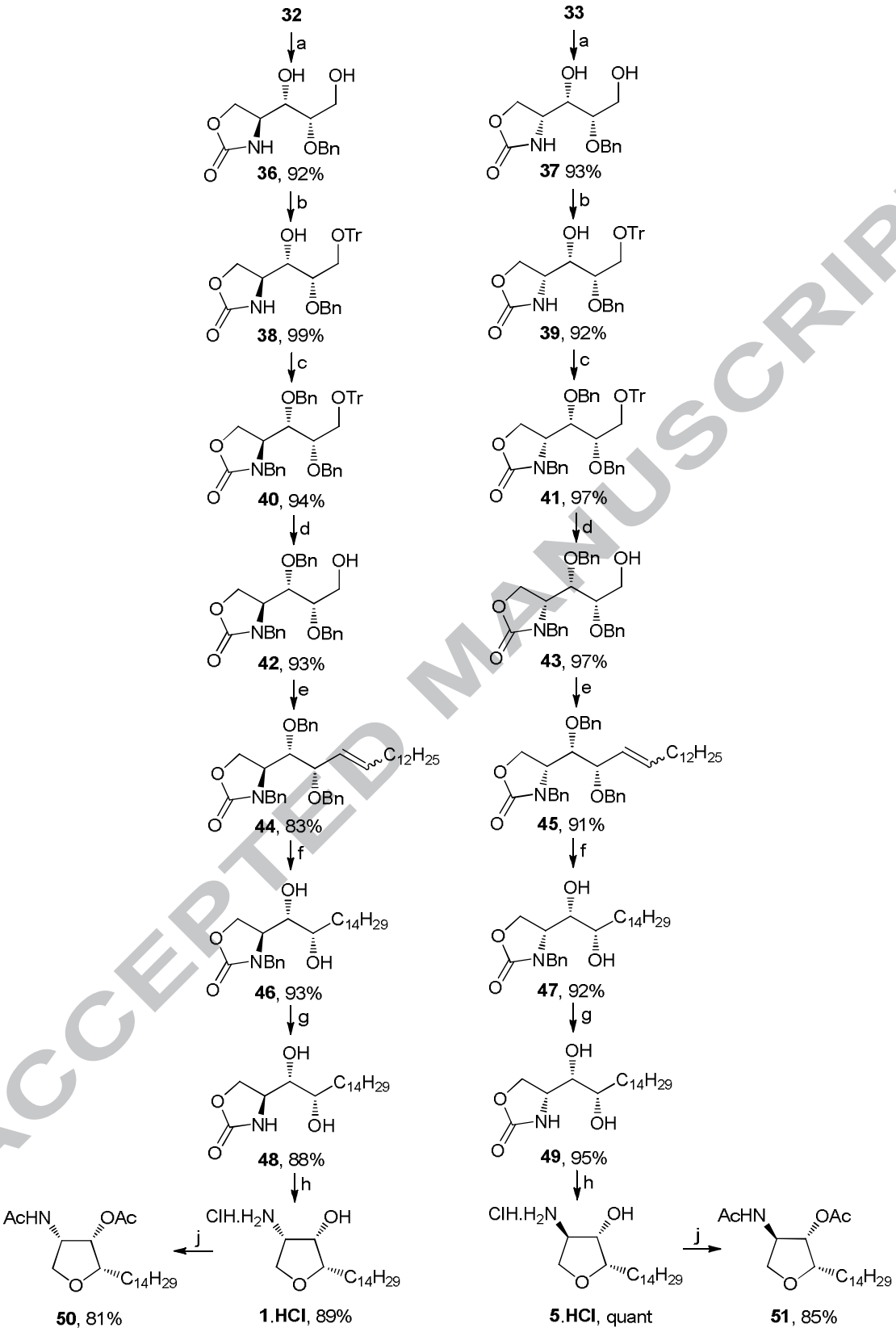
28	
Empirical formula	$C_{18}H_{25}NO_5$
Formula weight	335.39
Temperature, T (K)	173(2)
Wavelength, λ (Å)	0.71073
Crystal system	Orthorhombic
Space group	P $2_12_12_1$
Unit cell dimensions	
a (Å)	8.7887(3)
b (Å)	9.0093(3)
c (Å)	22.5649(9)
V (Å^3)	1786.69(11)
Formula per unit cell, Z	4
D_{calcd} (g/cm^3)	1.247
Absorption coefficient, μ (mm^{-1})	0.091
F(0 0 0)	720
Crystal size (mm)	0.49 × 0.29 × 0.18
θ Range for data collection (°)	2.938-26.493
Index ranges	$-10 \le h \le 11$ $-11 \le k \le 11$

	$-28 \leq l \leq 27$
Independent reflections (*R*int)	3629(0.0280)
Absorption correction	Analytical
Max. and min. transmission	0.987 and 0.970
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3639/0/220
Goodness-of-fit on F^2	1.055
Final *R* indices [$I>2\sigma(I)$]	$R_1 = 0.0330$, $wR_2 = 0.0687$
R indices (all data)	$R_1 = 0.0418$, $wR_2 = 0.0724$
Largest diff. peak and hole (e/Å^{-3})	0.136 and –0.178

2.1.4. Coupling reaction and completion of the total synthesis

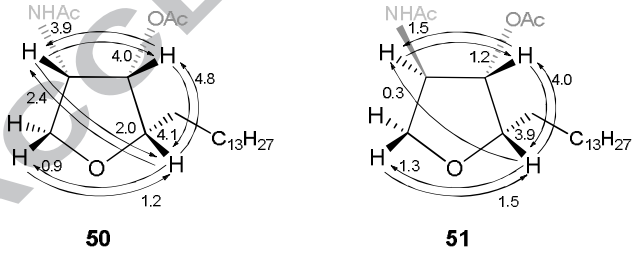
The modification of both oxazolidinone foldamers **32** and **33** to alcohols **42** and **43**, as the requisite handle for the attachment of the alkyl side chain, was a further task. As seen in Scheme 7, the acid hydrolysis of the acetonide moiety in **32** and **33** in the presence of *p*-TsOH in MeOH afforded the corresponding diols **36** (92%) and **37** (93%).Their treatment with trityl chloride in dry pyridine resulted in the regioselective blocking of the primary hydroxyl group to furnish derivatives **38** and **39** in 99% and 92% yields, respectively. The free remaining functionalities in **38** and **39** were capped with a benzyl group to provide compounds **40** (94%) and **41** (97%) before the subsequent transformations. Exposure of **40** and **41** to *p*-TsOH in CH_2Cl_2/MeOH resulted in the deprotection of the triphenylmethyl moiety delivering the desired products **42** (93%) and **43** (97%, Scheme 7). IBX oxidation of the unprotected alcohol function in **42** and **43** generated the corresponding aldehydes which immediately reacted with destabilized Wittig reagent, derived from tridecyltriphenylphosphonium bromide[36] and LHMDS as a base, affording barely separable mixtures of olefins **44** and **45** (*Z*:*E* ≈ 88:12 for **44**, *Z*:*E* ≈ 86:14 for **45**, determined by ^{1}H NMR spectroscopic analysis) with 83% and 91% isolated yields, respectively (Scheme 7). Repeated chromatography of the small amounts of the obtained mixtures of alkenes **44** and **45** furnished only (*Z*)-**45** in pure form as analytical sample. Having successfully constructed the carbon backbone with three neighbouring stereogenic centres, all that remained was to build up a tetrahydrofuran skeleton. Thus, both **44** and **45** were hydrogenated under atmospheric pressure using 10% Pd/C as catalyst to give **46** (93%) and **47** (92%) with saturated alkyl chains and recovered secondary hydroxyl groups. Subsequently, derivatives **46** and **47** were *N*-debenzylated by the catalytic hydrogenation at 60 °C providing the corresponding protected L-*lyxo*- and L-*xylo*-phytosphingosines **48** (88%) and

49 (95%), respectively. Their exposure to 6 M HCl at reflux resulted in cleavage of the cyclic carbamate fragment and concomitant cyclization afforded the HCl salts of **1** (89%) and **5** (93%, Scheme 7). The $[\alpha]_D$ value for **1.HCl** {$[\alpha]_D^{23}$ = +2.8 (*c* 0.36, MeOH); lit.[37] $[\alpha]_D^{23}$ = +2.6 (*c* 0.38, MeOH); lit.[14b] $[\alpha]_D^{27}$ = –2.9 (*c* 0.28, MeOH) for *ent*-**1.HCl**} and spectroscopic data



Scheme 7. *Reagents and conditions:* (a) *p*-TsOH, MeOH, rt; (b) TrCl, DMAP, pyridine, 60 °C; (c) BnBr, NaH, DMF, TBAI, 0 °C→rt; (d) *p*-TsOH, CH_2Cl_2/MeOH, rt; (e) (i) IBX, MeCN, reflux; (ii) LHMDS, $C_{13}H_{27}PPh_3Br$, THF, rt; (f) H_2, 10% Pd/C, EtOH, rt; (g) H_2, 10% Pd/C, EtOH, 35% HCl, 60 °C; (h) 6 M HCl, reflux; (j) Ac_2O, pyridine, DMAP, rt.

showed very good concordance with those previously reported. Compound **5.HCl** {$[\alpha]_D^{24}$ = –7.3 (*c* 0.46, MeOH); lit.[14b] $[\alpha]_D^{27}$ = +7.5 (*c* 0.52, MeOH)} also matched the published magnitude for *ent*-**5.HCl** but was opposite in sign.[14b] As an additional confirmation of structure, we transformed **1.HCl** to the known *N*,*O*-diacetate **50** (Ac_2O, pyridine, DMAP, 81%). Again, its specific rotation {$[\alpha]_D^{22}$ = –29.2 (*c* 0.24, $CHCl_3$); lit.[18] $[\alpha]_D^{26}$ = –24.0 (*c* 0.60, $CHCl_3$); lit.[22a] $[\alpha]_D^{23}$ = –23.5 (*c* 0.40, $CHCl_3$); lit.[37] $[\alpha]_D^{23}$ = –26.4 (*c* 0.50, $CHCl_3$); lit.[38] $[\alpha]_D^{22}$ = –22.6 (*c* 1.00, $CDCl_3$)} as well as spectroscopic data were in good agreement with those, previously reported. In the same manner, compound **5.HCl** was elaborated into fully acetylated derivative **51** in 85% yield. The magnitude we obtained for specific rotation of **51** {$[\alpha]_D^{23}$ = –8.2 (*c* 0.15, $CHCl_3$)} was comparable with the values present in literature for *ent*-**51** {lit.[14b] $[\alpha]_D^{23}$ = +9.9 (*c* 0.26, $CHCl_3$); lit.[4d] $[\alpha]_D^{28}$ = +7.4 (*c* 0.002, $CHCl_3$)} but had opposite sense. In order to further verify the configuration of the prepared structures of anhydrophytosphingosines **1.HCl** and **5.HCl** through their acetylated products **50** and **51**, respectively, NOE differential experiments were conducted. As shown in Fig. 3, in the case of **50**: there is a series of larger enhancements between H-2 and H-3, between H-3 and H-4 and between and H-2 and H-4 protons indicating that substituents on the tetrahydrofuran unit are in the *cis*-relationship to each other. On the other hand, NOE experiments of **51** showed *cis*-relationship between protons H-2 and H-3, and *trans* between H-3 and H-4 and also between H-2 and H-4 protons on the tetrahydrofuran core (Fig. 3).



50 **51**

Figure 3. Some selected NOE enhancements for **50** and **51**.

2.2. Antiproliferative/cytotoxic activity

A series of the prepared compounds (Table 4) was evaluated for the antiproliferative/cytotoxic activities against six human cancer cell lines MDA-MB-231 (mammary gland adenocarcinoma), MCF-7 (mammary gland adenocarcinoma), HTC-116 (colon carcinoma), Caco-2 (colon carcinoma), Jurkat (acute T-lymphoblastic leukemia), and HeLa (cervical adenocarcinoma); and a non-malignant cell line NiH 3T3 (mouse fibroblasts) using the MTT assay. The obtained results are summarized in Table 4 as IC_{50} values. Commercially available anticancer substances etoposide, cisplatin and doxorubicin were included as positive control in the case of cell lines Jurkat, HeLa, MCF-7 and MDA-MB-231[39] (Table 4), on HTC-116 and Caco-2 cell lines they were not tested. In an effort to find new candidates with the enhanced anticancer activity and with the aim to compare, the aforementioned table also includes IC_{50} values for several derivatives (compounds: *ent*-**24**,[14b] *ent*-**25**,[14b] *ent*-**32**,[14b] *ent*-**33**,[14b] *ent*-**46**,[14b] *ent*-**47**,[14b] *ent*-**48**,[14b] *ent*-**49**,[14b] *ent*-**1.HCl**,[14b] *ent*-**50**,[14b] *ent*-**51**,[14b] *ent*-**3.HCl**[17] and **4.HCl**[17]) syntheses of which were reported previously.

Table 4

Antiproliferative activities on six human cancer cell lines (MDA-MB-231, MCF-7, HCT-116, Caco-2, Jurkat and HeLa) and non-malignant mouse fibroblasts NiH 3T3

Compd no.	Cell line, IC_{50}[a] ± SD (μmol × L^{-1})						
	MDA-MB-231	MCF-7	HCT-116	Caco-2	Jurkat	HeLa	NiH 3T3
ent-**24**[b]	40.26±5.59	25.40±4.70	31.63±0.99	39.66± 3.88	14.00±4.47	ND	61.04±8.74
ent-**25**[b]	38.49±7.94	23.26±4.55	23.77±3.74	29.59±4.88	6.25±1.37	34.88±3.30	40.85±8.57
ent-**32**[b]	>100	>100	>100	>100	>100	>100	>100
ent-**33**[b]	>100	>100	>100	>100	>100	>100	>100
ent-**46**[b]	8.61±1.24	11.80±4.96	15.81±1.92	16.80±10.34	7.06±0.19	9.07±0.55	7.76±0.88
ent-**47**[b]	>100	>100	>100	>100	>100	>100	>100
ent-**48**[b]	37.35±5.59	32.85±0.44	37.34±6.88	40.07±4.55	28.93±2.66	46.20±12.23	35.06±6.87
ent-**49**[b]	38.34±4.61	31.63±2.20	30.77±0.96	27.68±1.26	26.14±2.37	ND	33.88±3.71
ent-**1.HCl**[b]	5.69±1.74	4.07±2.54	5.83±0.41	5.77±3.19	5.66±2.14	16.08±6.68	8.05±1.16
ent-**50**[b]	>100	>100	>100	>100	>100	>100	>100
ent-**51**[b]	28.64±0.29	28.04±0.62	27.77±0.54	30.20±0.14	28.03±1.07	>100	34.79±10.08
24	68.04±9.69	46.07±2.15	46.09±2.86	64.62±4.44	24.77±6.91	34.90±4.05	75.27±3.73
25	45.96±5.59	23.99±6.58	25.11±3.66	29.65±3.66	7.54±2.11	32.41±7.87	42.21±15.15
32	>100	>100	>100	>100	>100	>100	>100
46	17.83±8.34	ND	17.93±2.73	11.40±3.51	7.46±0.30	25.00±9.08	14.85±5.33
47	>100	>100	>100	>100	>100	>100	>100
48	41.13±8.77	33.15±1.57	40.09±1.71	43.26±10.17	29.12±1.98	>100	33.57±8.77

49	44.45±4.19	38.07±1.58	31.14±1.40	34.36±3.46	31.12±4.26	32.32±4.44	37.44±2.37
1.**HCl**	2.35±1.20	0.41±0.09 (11.22)[e]	2.59±1.02	0.35±0.11 (13.14)[e]	0.50±0.27 (9.20)[e]	0.61±0.27 (7.54)[e]	4.60±0.90
50	>100	>100	>100	>100	>100	>100	>100
51	34.06±3.92	29.33±0.78	27.52±2.08	32.65±0.81	26.86±1.20	37.18±4.39	37.06±5.71
4.**HCl**[c]	6.10±1.52	4.30±2.08	6.41±1.70	3.73±2.21	4.28±1.39	19.24±9.32	8.02±0.14
ent-**3**.**HCl**[c]	21.94±1.90	12.50±5.06	8.44±1.09	5.96±0.51	6.45±1.06	23.28±1.31	17.30±6.60
cisplatin[d]	14.7±2.7	11.4±2.4	NT	NT	12 ±1.8	7.7±2.3	NT
etoposide[d]	21.2±4.2	10.9±2.1	NT	NT	1.2±1.5	3.9±2.3	NT
doxorubicin[d]	0.2±0.8	0.5±0.024	NT	NT	0.078±0.02	0.2±0.06	NT

NT-not tested.
ND-not detected.
[a] The potency of compounds was determined using the MTT assay after 72 h incubation of cells and given as IC_{50} (concentration of a tested compound that decreased amount of viable cells to 50% relative to untreated control cells, see Experimental part, section 4.2.2.
[b] Prepared according the reported procedures.[14b]
[c] Prepared according the reported procedures.[17]
[d] Values for the clinically available anticancer drugs are reported in ref. 39 and were utilized from the same source.
[e] Selectivity index (SI = IC_{50} against NiH 3T3 cells/IC_{50} against cancer cells).

To the best of our knowledge, this is the first report implementing the antiproliferative/cytotoxic activity of jaspine B in the form of HCl salt (**1.HCl**) and also its stereoisomeric analogues (*ent*-**1.HCl**, **4.HCl**, and *ent*-**3.HCl**) towards human cancer cell line Caco-2. Compound **1.HCl** exhibited remarkable in vitro potency against all tested cancer cell lines (IC_{50} values between 0.35 and 2.59 μM), especially on Caco-2 (colon carcinoma) in micro- and sub-micromolar ranges and proved to be significantly more potent than its enantiomer *ent*-**1.HCl** (IC_{50} values between 4.07 and 16.08 μM). Similarly, substances **4.HCl** and *ent*-**3.HCl** (stereoisomers of **1**) have exhibited comparable or higher (in the case of **4.HCl**) in vitro activity than *ent*-**1.HCl** (Table 4). Moreover, compounds **4.HCl** and *ent*-**1.HCl** displayed greater the antiproliferative/cytotoxic activity against MCF-7 and MDA-MB-231 breast cancer cell lines than commercially available anticancer agents cisplatin and etoposide. Notably, IC_{50} value (0.41 μM) for the natural compound **1.HCl** on MCF-7 cells was comparable to that published for doxorubicin (IC_{50} = 0.5 μM).[39] These aforementioned results reveal that the stereochemical arrangement of the tetrahydrofuran skeleton is one of determining factors for the antiproliferative/cytotoxic activity and the study of the unnatural derivatives (compounds *ent*-**1.HCl**, **4.HCl** and *ent*-**3.HCl**) may be useful for further structural optimization with a view to establish new candidates with enhanced anticancer activity. In Table 4 are also incorporated IC_{50} values for the precursors, from which jaspine B and its antipode *ent*-**1.HCl** were constructed. Of them, only compound *ent*-**46**,[14b] which represents

the protected form of D-*lyxo*-phytospinhgosine exhibited good activity, mainly against MCF-7, MDA-MB-231 and Jurkat cancer cell lines with IC_{50} values comparable to those reported for cisplatin,[39] while its enantiomer, compound **46** was found to be less active (Table 4). Worthy of note, compounds **25** and *ent*-**25**[14b] were at least 1.5× more potent than cisplatin on Jurkat cells.

The antiproliferative/cytotoxic activity of substances included in Table 4 was also screened on non-malignant mouse fibroblasts NiH 3T3. Among them, compounds **1.HCl**, **4.HCl**, *ent*-**1.HCl** and *ent*-**3.HCl** demonstrated in some cases a quite promising selectivity of the aforementioned effects against cancer cells relative to the non-malignant NiH 3T3 cells. As seen in Table 4, the high selectivity index (SI), calculated as IC_{50} for NiH 3T3 divided by IC_{50} for the corresponding cancer cells, was found on MCF-7 (SI = 11.22), Caco-2 (SI = 13.14), Jurkat (SI = 9.20) and HeLa (SI = 7.54) cell lines for compound **1.HCl**.

3. Conclusions

In summary, we have developed a straightforward route to two anhydrophytosphingosines, jaspine B (**1**) and its 4-*epi*-analogue **5**, from easily available dimethyl L-tartrate and/or L-arabinose. The described synthesis relies on two key reactions which are [3,3]-sigmatropic rearrangements affording the required chiral amino group and the acid-promoted intramolecular cyclization providing the tetrahydrofuran ring. Moreover, the elaborated strategy allowed for the creation of two phytosphingosine molecules **48** and **49** with L-*lyxo* and L-*xylo* configurations, respectively. Further, used Wittig olefination permits variations in the length of the side chain to synthesize diverse analogues. A series of the prepared derivatives was assessed for the antiproliferative/cytotoxic activity against six cancer cell lines (Jurkat, HeLa, MDA-MB-231, MCF-7, HTC-116 and Caco-2) using the MTT assay. Among them, compounds *ent*-**46**, *ent*-**1.HCl**, **1.HCl**, **4.HCl** and *ent*-**3.HCl** were the most promising molecules and were selected as candidates for further screening and evaluation. In terms of the selectivity index (SI), structures, which were found to be the most potent, will be also examined on human non-malignant endothelial cells HUVEC (human umbilical vein endothelial cells) and progress will be reported in due course.

4. Experimental

4.1. Chemistry

All commercial reagents were used in the highest available purity from Aldrich, Fluka, Merck or Acros Organics without further purification. Solvents were dried and purified before use according to standard procedures. For flash column chromatography on silica gel, Kieselgel 60 (0.040-0.063 mm, 230-400 mesh, Merck) was used. Solvents for flash chromatography (hexane, ethyl acetate, methanol, dichloromethane) were distilled before use. Thin layer chromatography was run on Merck silica gel 60 F_{254} analytical plates; detection was carried out with either ultraviolet light (254 nm), or spraying with a solution of phosphomolybdic acid, a basic potassium permanganate solution, or a solution of concentrated H_2SO_4, with subsequent heating. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3OD and C_6D_6 on a Varian Mercury Plus 400 FT NMR (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) or on a Varian Premium COMPACT 600 (599.87 MHz for ^{1}H and 150.84 MHz for ^{13}C) spectrometer using TMS as internal reference. For ^{1}H, δ are given in parts per million (ppm) relative to TMS (δ = 0.0), CD_3OD (δ = 4.84), C_6D_6 (δ = 7.15) and CD_3COCD_3 (δ = 2.05) and for ^{13}C relative to $CDCl_3$ (δ = 77.00), CD_3OD (δ = 49.05), C_6D_6 (δ = 128.02) and CD_3COCD_3 (δ = 30.83). The multiplicity of the ^{13}C NMR signals concerning the ^{13}C-^{1}H coupling was determined by the DEPT method. Chemical shifts (in ppm) and coupling constants (in Hz) were obtained by first-order analysis; assignments were derived from COSY and H/C correlation spectra. Infrared (IR) spectra were measured with a Nicolet 6700 FT-IR spectrometer and expressed in ν values (cm^{-1}). Optical rotations were measured on a P-2000 Jasco polarimeter and reported as follows: $[\alpha]_D$ (c in grams per 100 mL, solvent). Melting points were recorded on a Kofler hot block, and are uncorrected. Microwave reactions were carried out on the focused microwave system (CEM Discover). The temperature content of the vessel was monitored using a calibrated infrared sensor mounted under the vessel. At the end of all reactions the contents of vessel were cooled rapidly using a stream of compressed air. Small quantities of reagents (μL) were measured with appropriate syringes (Hamilton). All reactions were performed under an atmosphere of nitrogen, unless otherwise noted.

4.1.1. 1,2-*O*-Isopropylidene-5-*O*-trityl-β-L-arabinofuranose (7)

To a suspension of L-arabinose (2.50 g, 16.65 mmol) in dry pyridine (20 mL) were successively added trityl chloride (4.64 g, 16.65 mmol) and DMAP (1.02 g, 8.33 mmol). The resulting mixture was stirred 72 h at room temperature, then concentrated and co-evaporated three times with toluene. The residue obtained was partitioned between CH_2Cl_2 (40 mL) and a

saturated $NaHCO_3$ solution (25 mL), the aqueous phase was extracted with further portions of CH_2Cl_2 (2 × 40 mL). The combined organic layers were dried over Na_2SO_4, the solvent was taken down, and the residue was subjected to flash chromatography through a short column of silica gel (*n*-hexane/ethyl acetate, 1:3) to afford 3.53 g (54%) of lactol **6**[32] as a colourless foam. The material had spectroscopic data in accord with those reported previously.[32]

To a solution of **6** (3.51 g, 8.94 mmol) in dry acetone (23 mL) were successively added 2,2-dimethoxypropane (23 mL) and a catalytic amount of CSA (16.6 mg, 0.07 mmol). After stirring for 3 h at room temperature, MeOH (0.35 mL) was added, and the mixture was partitioned between $CHCl_3$ (105 mL) and a saturated $NaHCO_3$ solution (32 mL). The organic layer was dried over Na_2SO_4, the solvent was evaporated in vacuo, and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 3:1) to furnish 2.86 g (74%) of compound **7** as a white foam; {$[\alpha]_D^{25}$ +5.5 (*c* 0.40, $CHCl_3$); lit[40] $[\alpha]_D^{21}$ −1.0 (*c* 1.0, $CHCl_3$) for *ent*-**7**}. IR (neat) υ_{max} 3415, 3057, 2936, 1596, 1448, 1374, 1210, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 2.13 (br s, 1H, OH), 3.25 (dd, 1H, $J_{5,5}$ = 9.3 Hz, $J_{5,4}$ = 7.7 Hz, H-5), 3.40 (dd, 1H, $J_{5,5}$ = 9.3 Hz, $J_{5,4}$ = 5.8 Hz, H-5), 4.15 (ddd, 1H, $J_{5,4}$ = 7.7 Hz, $J_{5,4}$ = 5.8 Hz, $J_{4,3}$ = 2.3 Hz, H-4), 4.32 (m, 1H, H-3), 4.49 (d, 1H, $J_{2,1}$ = 4.0 Hz, H-2), 5.87 (d, 1H, $J_{2,1}$ = 4.0 Hz, H-1), 7.20–7.45 (m, 15H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.0 (CH_3), 26.6 (CH_3), 63.8 (C-5), 76.6 (C-3), 86.6 (C-4), 2 × 86.8 (C-2, C_q), 105.6 (C-1), 112.4 (C_q), 127.0 (3 × CH_{Ph}), 127.8 (6 × CH_{Ph}), 128.6, (6 × CH_{Ph}), 143.7 (3 × C_i). Anal. Calcd for $C_{27}H_{28}O_5$: C, 74.98; H, 6.53. Found: C, 75.05; H, 6.48.

4.1.2. 1,2-*O*-Isopropylidene-5-*O*-trityl-β-L-*erythro*-pentofuranos-3-ulose (8)

o-Iodoxybenzoic acid (3.64 g, 13.01 mmol) was added to a solution of **7** (2.80 g, 6.50 mmol) in acetonitrile (60 mL), and the resulting suspension was stirred at reflux for 30 min. The mixture was allowed to cool to room temperature, the insoluble material was filtered off, and the filtrate was concentrated. The residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate, 5:1) to give 2.37 g (85%) of ulose **8** as a colourless foam; $[\alpha]_D^{22}$ +11.4 (*c* 0.28, $CHCl_3$). IR (neat) υ_{max} 3422, 2937, 1771, 1597, 1447, 1375, 1216, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 3.37 (dd, 1H, $J_{5,5}$ = 10.3 Hz, $J_{5,4}$ = 4.0 Hz, H-5), 3.45 (dd, 1H, $J_{5,5}$ = 10.3 Hz, $J_{5,4}$ = 7.3 Hz, H-5), 4.32 (dd, 1H, $J_{5,4}$ = 7.3 Hz, $J_{5,4}$ = 3.8 Hz, H-4), 4.36 (dd, 1H, $J_{2,1}$ = 4.2 Hz, $J_{4,2}$ = 0.5 Hz, H-2), 6.03 (d, 1H, $J_{2,1}$ = 4.2 Hz, H-1), 7.20–7.48 (m, 15H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.7 (CH_3), 27.3 (CH_3), 64.4 (C-5), 76.6 (C-2), 80.9 (C-4), 87.0 (C_q), 102.7 (C-1), 115.0 (C_q), 127.0 (3 ×

CH_{Ph}), 127.8 (6 × CH_{Ph}), 128.7 (6 × CH_{Ph}), 143.4 (3 × C_i), 207.0 (C=O). Anal. Calcd for $C_{27}H_{26}O_5$: C, 75.33; H, 6.09. Found: C, 75.39; H, 6.04.

4.1.3. 1,2-*O*-Isopropylidene-5-*O*-trityl-β-L-lyxofuranose (9)

To a solution of **8** (2.26 g, 5.25 mmol) in EtOH (75 mL) that had been pre-cooled to 0 °C was added $NaBH_4$ (0.397 g, 10.50 mmol). The resulting mixture was stirred at 0 °C for 10 min and then for another 30 min at room temperature before evaporation of the solvent. The residue obtained was partitioned between a saturated NaCl (68 mL) solution and CH_2Cl_2 (95 mL), the aqueous layer was washed with another portion of CH_2Cl_2 (95 mL). The combined organic extracts were dried over Na_2SO_4, the solvent was removed under reduced pressure, and the crude product was subjected to flash chromatography through a short column of silica gel (*n*-hexane/ethyl acetate, 4:1) to afford 2.12 g (93%) of compound **9** as white crystals; mp 61–63 °C (recrystallized from *n*-hexane/ethyl acetate); $[\alpha]_D^{24}$ +11.1 (*c* 0.66, $CHCl_3$). IR (neat) υ_{max} 3497, 3057, 2935, 1448, 1373, 1209, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 2.73 (d, 1H, $J_{3,OH}$ = 7.2 Hz, OH), 3.44 (dd, 1H, $J_{5,5}$ = 9.8 Hz, $J_{5,4}$ = 5.5 Hz, H-5), 3.49 (dd, 1H, $J_{5,5}$ = 9.8 Hz, $J_{5,4}$ = 6.4 Hz, H-5), 4.22–4,31 (m, 2H, H-3, H-4), 4.56 (dd, 1H, $J_{3,2}$ = 5.6 Hz, $J_{2,1}$ = 4.1 Hz, H-2), 5.72 (d, 1H, $J_{2,1}$ = 4.1 Hz, H-1), 7.19–7.49 (m, 15H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.5 (CH_3), 26.6 (CH_3), 63.0 (C-5), 70.9 (C-3), 79.6 (C-2), 80.5 (C-4), 87.0 (C_q), 104.8 (C-1), 114.0 (C_q), 127.0 (3 × CH_{Ph}), 127.8 (6 × CH_{Ph}), 128.7 (6 × CH_{Ph}), 143.8 (3 × C_i). Anal. Calcd for $C_{27}H_{28}O_5$: C, 74.98; H, 6.53. Found: C, 74.93; H, 6.60.

4.1.4. 3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-trityl-β-L-lyxofuranose (10)

To a solution of **9** (2.06 g, 4.76 mmol) in dry DMF (11.50 mL) that had been pre-cooled to 0 °C were successively added NaH (0.171 g, 7.14 mmol, 60% dispersion in mineral oil), BnBr (0.68 mL, 5.72 mmol) and TBAI (45.20 mg, 0.01 mmol). The resulting mixture was stirred at 0 °C for 10 min, and then for a further 20 min at room temperature. The excess hydride was decomposed by the addition of MeOH (0.5 mL), the mixture was poured into ice-water (20 mL) and extracted with Et_2O (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated in vacuo, and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 11:1) to give 2.24 g (90%) of compound **10** as a white foam; $[\alpha]_D^{22}$ –13.5 (*c* 0.40, $CHCl_3$). IR (neat) υ_{max} 3058, 2933, 1596, 1448, 1373, 1208, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.18 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 3.45 (dd, 1H, $J_{5,5}$ = 10.4 Hz, $J_{5,4}$ = 3.5 Hz, H-5), 3.62 (dd, 1H, $J_{5,5}$ = 10.4 Hz, H5, $J_{5,4}$ = 7.5 Hz, H-5), 4.01 (dd, 1H, $J_{4,3}$

= 7.3 Hz, $J_{3,2}$ = 5.1 Hz, H-3), 4.38 (dt, 1H, $J_{5,4}$ = 7.4 Hz, $J_{4,3}$ = 7.4 Hz, $J_{5,4}$ = 3.5 Hz, H-4), 4.47 (d, 1H, $J_{H,H}$ = 12.1 Hz, OCH_2Ph), 4.53 (dd, 1H, $J_{3,2}$ = 5.0 Hz, $J_{2,1}$ = 4.0 Hz, H-2), 4.54 (d, 1H, $J_{H,H}$ = 12.1 Hz, OCH_2Ph), 5.71 (d, 1H, $J_{2,1}$ = 4.0 Hz, H-1), 7.13–7.52 (m, 20H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.9 (CH_3), 26.2 (CH_3), 63.8 (C-5), 72.4 (OCH_2Ph), 77.2 (C-3), 78.4 (C-2), 80.4 (C-4), 86.7 (C_q), 104.6 (C-1), 113.4 (C_q), 126.8 (3 × CH_{Ph}), 127.7 (8 × CH_{Ph}), 127.8 (CH_{Ph}), 128.3 (CH_{Ph}), 128.8 (7 × CH_{Ph}), 137.4 (C_i), 144.2 (3 × C_i). Anal. Calcd for $C_{34}H_{34}O_5$: C, 78.14; H, 6.56. Found: C, 78.10; H, 6.60.

4.1.5. 3-*O*-Benzyl-1,2-*O*-isopropylidene-β-L-lyxofuranose (11)

Camphorsulfonic acid (46 mg, 0.20 mmol) was added to a solution of **10** (2.07 g, 3.96 mmol) in a mixture of CH_2Cl_2/MeOH (2:1, 16 mL), and the resulting solution was stirred at room temperature for 2.5 h. The reaction was quenched by neutralization with Na_2CO_3, the solvents were evaporated, and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 2:1) to yield 0.82 g (74%) of compound **11** as white crystals mp 56.5–58 °C (recrystallized from *n*-hexane/ethyl acetate); $[\alpha]_D^{24}$ +53.8 (*c* 0.32, $CHCl_3$). IR (neat) υ_{max} 3510, 2993, 2956, 2941, 2889, 1454, 1373, 1208, 1145 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 2.32 (br s, 1H, OH), 3.91−3.96 (m, 2H, 2 × H-5), 4.18 (dd, 1H, $J_{4,3}$ = 7.5 Hz, $J_{3,2}$ = 5.1 Hz, H-3), 4.22–4.27 (m, 1H, H-4), 4.57 (d, 1H, $J_{H,H}$ = 11.9 Hz, OCH_2Ph), 4.62 (dd, 1H, $J_{3,2}$ = 5.0 Hz, $J_{2,1}$ = 4.1 Hz, H-2), 4.78 (d, 1H, $J_{H,H}$ = 11.9 Hz, OCH_2Ph), 5.75 (d, 1H, $J_{2,1}$ = 4.0 Hz, H-1), 7.26–7.39 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.9 (CH_3), 26.6 (CH_3), 62.3 (C-5), 72.6 (OCH_2Ph), 77.8 (C-3), 77.9 (C-2), 80.4 (C-4), 104.9 (C-1), 113.7 (C_q), 127.8 (2 × CH_{Ph}), 128.1 (CH_{Ph}), 128.6 (2 × CH_{Ph}), 137.1 (C_i). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.32; H, 7.15.

4.1.6. 5-*O*-Benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-lyxofuranose (12)

To a solution of **11** (0.74 g, 2.64 mmol) that had been pre-cooled to 0 °C were successively added BzCl (0.61 mL, 5.28 mmol) and DMAP (32.20 mg, 0.26 mmol), and the resulting mixture was stirred at 0 °C for 10 min and then for another 1 h at room temperature. The reaction mixture was concentrated and partitioned between ethyl acetate (14 mL) and water (7 mL). The aqueous layer was washed with a further portion of ethyl acetate (14 mL). The combined organic extracts were dried over Na_2SO_4, the solvent was taken down, and the residue was subjected to flash chromatography on silica gel (*n*-hexane/ethyl acetate, 7:1) to afford 0.98 g (97%) of compound **12** as a colourless oil; $[\alpha]_D^{24}$ –27.3 (*c* 0.32, $CHCl_3$). IR (neat) υ_{max} 2939, 1713, 1602, 1452, 1269, 1095, 1021 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ

1.35 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 4.17 (dd, 1H, $J_{4,3}$ = 7.4 Hz, $J_{3,2}$ = 5.0 Hz, H-3), 4.48 (dt, 1H, $J_{5,4}$ = 7.1 Hz, $J_{4,3}$ = 7.1 Hz, $J_{5,4}$ = 5.1 Hz, H-4), 4.65 (dd, 1H, $J_{3,2}$ = 4.9 Hz, $J_{2,1}$ = 3.9 Hz, H-2), 4.67 (d, 1H, $J_{H,H}$ = 11.7 Hz, OCH_2Ph), 4.73–4.78 (m, 3H, 2 × H-5, OCH_2Ph), 5.77 (d, 1H, $J_{2,1}$ = 3.9 Hz, H-1), 7.23–7.49 (m, 7H, Ph), 7.50–7.57 (m, 1H, Ph), 8.06–8.15 (m, 2H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.0 (CH_3), 26.6 (CH_3), 65.0 (C-5), 72.6 (OCH_2Ph), 77.3 (C-3), 78.1 (C-2), 78.4 (C-4), 104.8 (C-1), 113.8 (C_q), 127.9 (2 × CH_{Ph}), 128.0 (CH_{Ph}), 128.2 (2 × CH_{Ph}), 128.5 (2 × CH_{Ph}), 129.7 (2 × CH_{Ph}), 130.2 (C_i), 132.8 (CH_{Ph}), 137.2 (C_i), 166.4 (C=O). Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29. Found: C, 68.79; H, 6.25.

4.1.7. (2*S*,3*S*)-3-(Benzyloxy)-2,4-dihydroxybutyl benzoate (14)

Compound **12** (0.78 g, 2.03 mmol) was treated with a solution of 80% TFA (3.60 mL) at 0 °C, and the resulting mixture was stirred at 0 °C for 4 h. The mixture was allowed to warm to room temperature, then was partitioned between ethyl acetate (8 mL) and water (7 mL), and subsequently the solid $NaHCO_3$ (3.36 g) was added. The insoluble material was filtered off and the filtrate was washed with ethyl acetate (2 × 8 mL). The combined organic layers were dried over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography through a short column of silica gel (*n*-hexane/ethyl acetate, 1:1) to give 0.685 g (98%) of 5-*O*-benzoyl-3-*O*-benzyl-L-lyxofuranose **13** as a colourless oil that was used immediately in the next reaction without spectral characterization.

To a solution of **13** (0.685 g, 1.99 mmol) in a mixture of MeOH/H_2O (1:1, 4.60 mL) was added $NaIO_4$ (0.51 g, 2.37 mmol), and the reaction mixture was stirred at room temperature for 1 h. Then, the mixture was diluted with CH_2Cl_2 (13.50 mL), the insoluble parts were filtered off, and the filtrate was concentrated. The residue obtained was dissolved in CH_2Cl_2 (9 mL), washed with a saturated $NaHCO_3$ solution (5 mL), and the aqueous layer was extracted with another portion of CH_2Cl_2 (9 mL). The combined organic phases were dried over Na_2SO_4, the solvent was evaporated in vacuo, and the crude aldehyde (0.68 g, 1.99 mmol) was dissolved in a mixture of CH_2Cl_2/MeOH (1:4, 8.70 mL). To this solution that had been pre-cooled to 0 °C was added $NaBH_4$ (90 mg, 2.38 mmol), and the resulting mixture was stirred at 0 °C for 10 min and then for another 30 min at room temperature. The reaction was quenched by neutralization with Amberlite IR 120 (H^+ form), the solid parts were removed by filtration, and the filtrate was concentrated. The residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 1:3) to afford 0.53 g (84%) of compound **14** as white crystals; mp 85−86 °C (recrystallized from *n*-hexane/ethyl acetate); {$[\alpha]_D^{22}$ +25.6 (*c* 0.34, $CHCl_3$); lit.[14b] $[\alpha]_D^{25}$

−30.7 (*c* 0.28, $CHCl_3$) for *ent*-**14**}. IR (neat) υ_{max} 3312, 3064, 3035, 2958, 2921, 2858, 1714, 1450, 1275, 1091 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 3.54–3.58 (m, 1H, H-3), 3.72 (dd, 1H, $J_{4,4}$ = 11.2 Hz, $J_{4,3}$ = 5.3 Hz, H-4), 3.79 (dd, 1H, $J_{4,4}$ = 11.4 Hz, $J_{4,3}$ = 5.5 Hz, H-4), 4.04–4.08 (m, 1H, H-2), 4.29 (dd, 1H, $J_{1,1}$ = 10.8 Hz, $J_{2,1}$ = 5.7 Hz, H-1), 4.33 (dd, 1H, $J_{1,1}$ = 10.5 Hz, $J_{2,1}$ = 5.0 Hz, H-1), 4.57 (d, 1H, $J_{H,H}$ = 11.6 Hz, OCH_2Ph), 4.71 (d, 1H, $J_{H,H}$ = 11.6 Hz, OCH_2Ph), 7.15–7.33 (m, 5H, Ph), 7.39–7.42 (m, 2H, Ph), 7.52–7.56 (m, 1H, Ph), 7.93–7.95 (m, 2H, Ph); ^{13}C NMR (100 MHz, CD_3OD): δ 61.8 (C-4), 66.9 (C-1), 70.1 (C-2), 73.9 (OCH_2Ph), 80.6 (C-3), 128.8 (CH_{Ph}), 129.3 (2 × CH_{Ph}), 129.4 (2 × CH_{Ph}), 129.6 (2 × CH_{Ph}), 130.7 (2 × CH_{Ph}), 131.4 (C_i), 134.3 (CH_{Ph}), 139.8 (C_i), 167.9 (C=O). Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.38; H, 6.33.

4.1.8. [(4'*S*,5'*S*)-5'-(Benzyloxy)-2',2'-dimethyl-1',3'-dioxan-4'-yl]methyl benzoate (15)

To a solution of **14** (0.45 g, 1.42 mmol) in dry CH_2Cl_2 (8 mL) were successively added 2,2-dimethoxypropane (0.53 mL, 4.27 mmol) and *p*-TsOH (10.80 mg, 0.06 mmol), and the reaction mixture was stirred at room temperature for 2 h. After cautious washing with a saturated $NaHCO_3$ solution (2 × 7.70 mL), the combined organic layers were dried over Na_2SO_4, the solvent was taken down, and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 5:1) to give 0.45 g (89%) of compound **15** as white crystals mp 46.5–48 °C (recrystallized from *n*-hexane/ethyl acetate); {$[\alpha]_D^{23}$ +50.3 (*c* 0.32, $CHCl_3$); lit.[14b] $[\alpha]_D^{25}$ −52.7 (*c* 0.26, $CHCl_3$) for *ent*-**15**}. IR (neat) υ_{max} 2986, 2947, 1714, 1603, 1267, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.46 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.36–3.40 (m, 1H, H-5'), 3.92 (dd, 1H, $J_{6',6'}$ = 12.9 Hz, $J_{6',5'}$ = 2.1 Hz, H-6'), 4.07 (dd, 1H, $J_{6',6'}$ = 12.9 Hz, $J_{6',5'}$ = 2.0 Hz, H-6'), 4.27 (dt, 1H, $J_{4',1}$ = 6.2 Hz, $J_{4',1}$ = 6.2 Hz, $J_{5',4'}$ = 2.0 Hz, H-4'), 4.44 (dd, 1H, $J_{1,1}$ = 11.0 Hz, $J_{4',1}$ = 6.3 Hz, H-1), 4.48–4.52 (m, 2H, H-1, OCH_2Ph), 4.77 (d, 1H, $J_{H,H}$ = 12.3 Hz, OCH_2Ph), 7.19–7.36 (m, 5H, Ph), 7.39–7.43 (m, 2H, Ph), 7.53–7.57 (m, 1H, Ph), 7.93–7.97 (m, 2H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0 (CH_3), 28.8 (CH_3), 61.0 (C-6'), 64.0 (C-1), 69.1 (C-5'), 69.5 (C-4'), 70.8 (OCH_2Ph), 98.8 (C_q), 127.7 (CH_{Ph}), 128.0 (2 × CH_{Ph}), 128.2 (2 × CH_{Ph}), 128.3 (2 × CH_{Ph}), 129.6 (2 × CH_{Ph}), 129.9 (C_i), 132.9 (CH_{Ph}), 137.7 (C_i), 166.2 (C=O). Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.81; H, 6.75.

4.1.9. Dimethyl (4*R*,5*R*)-2-phenyl-1,3-dioxolane-4,5-dicarboxylate (17)[30,34]

To a solution of dimethyl L-tartrate (22 g, 0.15 mol) in dry benzene (220 mL) were successively added benzaldehyde (18.3 mL, 0.18 mol) and *p*-TsOH (0.73 g, 3.84 mmol), and

the resulting mixture was stirred at reflux for 38.5 h using a Dean-Stark device. Then, the reaction mixture was neutralized with Et_3N (0.73 mL), the solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate, 5:1) to give 32.77 g (84%) of compound **17** as white crystals mp 71–71.5 °C (recrystallized from *n*-hexane/ethyl acetate); {$[\alpha]_D^{27}$ –43.1 (*c* 0.54, MeOH); lit[30] $[\alpha]_D$ −42.0 (*c* 0.50, temperature and solvent not reported); lit.[34] $[\alpha]_D^{20}$ −47.2 (*c* 1.00, MeOH)}. IR (neat) υ_{max} 2958, 2909, 1751, 1429, 1236, 1214, 1102, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.87 (d, 1H, J = 4.0 Hz, CH), 4.98 (d, 1H, J = 4.0 Hz, CH), 6.14 (s, 1H, H-2), 7.39–7.41 (m, 3H, Ph), 7.57–7.59 (m, 2H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.9 (2 × OCH_3), 77.2 (CH), 77.4 (CH), 106.7 (C-2), 127.2 (2 × CH_{Ph}), 128.4 (2 × CH_{Ph}), 130.0 (CH_{Ph}), 135.2 (C_i), 169.4 (C=O), 170.0 (C=O). Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.60; H, 5.35.

4.1.10. (2*S*,3*S*)-3-(Benzyloxy)butane-1,2,4-triol (18)[30,34]

To a suspension of $LiAlH_4$ (17.60 g, 0.46 mol) in a mixture of Et_2O (195 mL) and CH_2Cl_2 (180 mL), pre-cooled to 0 °C, was added compound **17** (32.43 g, 0.12 mol), and the mixture was stirred at 0 °C for 40 min. A solution of $AlCl_3$ (52.90 g, 0.40 mol) in dry Et_2O (195 mL) was added, and the reaction mixture was stirred at reflux for 2.5 h. After cooling to room temperature and cautious addition of water (111 mL) and a 15% NaOH solution (240 mL), the solids parts were filtered through a small pad of Celite. The aqueous phase was washed with ethyl acetate (2 × 250 mL), the combined organic layers were dried over Na_2SO_4, the solvent was evaporated, and the residue was flash-chromatographed through a short column of silica gel to furnish 20.7 g (80%) of compound **18** as white crystals; mp 73–74.5 °C (recrystallized from ethyl acetate); {$[\alpha]_D^{25}$ +14.7 (*c* 0.58, MeOH); lit[34] $[\alpha]_D^{22}$ +15.7 (*c* 1.00, MeOH); lit[30] $[\alpha]_D$ not reported}. IR (neat) υ_{max} 3250, 2969, 2940, 1449, 1364, 1202, 1036 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 3.56 (dt, 1H, $J_{2,1}$ = 5.3 Hz, $J_{2,1}$ = 5.3 Hz, $J_{3,2}$ = 3.9 Hz, H-2), 3.59 (dd, 1H, $J_{4,4}$ = 11.1 Hz, $J_{4,3}$ = 6.5 Hz, H-4), 3.64 (dd, 1H, $J_{4,4}$ = 11.1 Hz, $J_{4,3}$ = 5.1 Hz, H-4), 3.69 (dd, 1H, $J_{1,1}$ = 11.6 Hz, $J_{2,1}$ = 5.4 Hz, H-1), 3.76–3.80 (m, 2H, H-1, H-3), 4.62 (d, 1H, $J_{H,H}$ = 11.5 Hz, OCH_2Ph), 4.73 (d, 1H, $J_{H,H}$ = 11.5 Hz, OCH_2Ph), 7.24–7.40 (m, 5H, Ph); ^{13}C NMR (100 MHz, CD_3OD): δ 62.1 (C-1), 64.1 (C-4), 73.1 (C-3), 74.1 (OCH_2Ph), 81.3 (C-2), 128.7 (CH_{Ph}), 129.1 (2 × CH_{Ph}), 129.3 (2 × CH_{Ph}), 140.1 (C_i). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.21; H, 7.65.

4.1.11. [(4'*S*,5'*S*)-5'-(Benzyloxy)-2',2'-dimethyl-1',3'-dioxan-4'-yl]methanol (16)[30]

*Modification of **15** into **16**:*

K_2CO_3 (24.4 mg, 0.18 mmol) was added to a solution of **15** (0.21 g, 0.59 mmol) in MeOH (6 mL), pre-cooled to 0 °C, and the reaction mixture was stirred at 0 °C for 15 min and then at room temperature for another 4 h. After dilution with Et_2O (18 mL), the solid Na_2SO_4 was added, and salts were removed by filtration. Evaporation of solvent and chromatography of the residue on silica gel (*n*-hexane/ethyl acetate, 1:1) afforded 0.14 g (95%) of compound **16** as white crystals.

*Modification of **18** into **16**:*

To a solution of triol **18** (20.47 g, 96.5 mmol) in dry DMF (235 mL), pre-cooled to –15 °C, were successively added PPTS (1.94 g, 7.72 mmol) and 2-methoxypropene (11.1 mL, 0.12 mol) dissolved in dry DMF (47 mL). The reaction mixture was stirred at –15 °C for 5 h and then at room temperature for another 1 h. The reaction was quenched by neutralization with Et_3N, subsequently diluted with ethyl acetate (100 mL) and washed with a saturated NaCl solution (250 mL). The organic layer was dried over Na_2SO_4, the solvent was evaporated, and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 3:1) to give 5.84 g (24%) of the require alcohol **16**[30] together with a barely separable mixture of compounds: (2*S*)-2-(benzyloxy)-2-[(4'*S*)-2',2'-dimethyl-1',3'-dioxolan-4'-yl]ethanol[30] and (5*S*,6*S*)-6-(benzyloxy)-2,2-dimethyl-1,3-dioxepan-5-ol[30] (16.54 g, 68%). Repeated chromatography on silica gel (*n*-hexane/ethyl acetate, 3:1) afforded both aforementioned derivatives in pure form as analytical samples. Their physical and spectroscopic properties were in agreement with literature data.[30]

Alcohol **16**: mp 60–61 °C (recrystallized from *n*-hexane/ethyl acetate); {$[\alpha]_D^{25}$ +64.7 (*c* 0.30, $CHCl_3$); lit[30] ($[\alpha]_D$ +64.0 (*c* 0.30, temperature and solvent not reporte); lit.[14b] $[\alpha]_D^{23}$ −69.4 (*c* 0.32, $CHCl_3$) for *ent*-**16**}. IR (neat) υ_{max} 3502, 2992, 2960, 2940, 2867, 1455, 1382, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.02 (br s, 1H, OH), 3.30–3.31 (m, 1H, H-5'), 3.60–3.63 (m, 1H, H-1), 3.64 (dd, 1H, $J_{1,1}$ = 11.4 Hz, $J_{4',1}$ = 6.7 Hz, H-1), 3.90 (dd, 1H, $J_{6',6'}$ = 12.9 Hz, $J_{6',5'}$ = 2.2 Hz, H-6'), 3.96 (ddd, 1H, $J_{4',1}$ = 6.8 Hz, $J_{4',1}$ = 4.8 Hz, $J_{5',4'}$ = 2.2 Hz, H-4'), 4.02 (dd, 1H, $J_{6',6'}$ = 12.9 Hz, $J_{6',5'}$ = 2.2 Hz, H-6'), 4.43 (d, 1H, $J_{H,H}$ = 12.3 Hz, OCH_2Ph), 4.75 (d, 1H, $J_{H,H}$ = 12.3 Hz, OCH_2Ph), 7.28–7.35 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1 (CH_3), 28.8 (CH_3), 61.1 (C-6'), 62.8 (C-1), 70.0 (C-5'), 70.7 (OCH_2Ph), 71.6 (C-4'), 98.8 (C_q), 127.9 (3 × CH_{Ph}), 128.4 (2 × CH_{Ph}), 137.8 (C_i). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.61; H, 8.04.

4.1.12. Ethyl (*E*)-3-[(4'*S*,5'*S*)-5'-(benzyloxy)-2',2'-dimethyl-1',3'-dioxan-4'-yl]acrylate [(*E*)-19] and ethyl (*Z*)-3-[(4'*S*,5'*S*)-5'-(benzyloxy)-2',2'-dimethyl-1',3'-dioxan-4'-yl]acrylate [(*Z*)-20]

o-Iodoxybenzoic acid (15.94 g, 56.90 mmol) was added to a solution of **16** (5.74 g, 22.77 mmol) in MeCN (207 mL) and the resulting suspension was stirred and heated to reflux for 1 h. After cooling to room temperature, the insoluble material was filtered off, the solvent was removed, and the crude aldehyde was used immediately in the subsequent reaction without further purification.

To a suspension of NaH (0.74 g, 31 mmol, 60% dispersion in mineral oil) in dry THF (48.50 mL) that was pre-cooled to –10 °C was added dropwise ethyl 2-(diethoxyphosphoryl)acetate (5 mL, 25 mmol), and the mixture was stirred for 25 min at 0 °C. To this mixture, we added a solution of the crude aldehyde (5.70 g, 22.77 mmol) in dry THF (9.80 mL) at 0 °C. After stirring for 1 h at 0 °C, the suspension was poured into a saturated NH_4Cl solution (17.40 mL) and extracted with ethyl acetate (2 × 25 mL). The combined organic layers were dried over Na_2SO_4, the solvent was taken down, and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 5:1) to afford 5.91 g (81%) of (*E*)-**19** and 0.875 g (12%) of (*Z*)-**20**.

Isomer (*E*)-**19**: colourless oil; {$[\alpha]_D^{23}$ −11.4 (*c* 0.36, $CHCl_3$); lit.[14b] $[\alpha]_D^{22}$ +12.3 (*c* 0.26, $CHCl_3$) for *ent*-(*E*)-**19**}. IR (neat) υ_{max} 2988, 2939, 2869, 1714, 1662, 1368, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.30 (t, 3H, J = 7.1 Hz, CH_3), 1.46 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 3.31–3.32 (m, 1H, H-5'), 3.95 (dd, 1H, $J_{6',6'}$ = 12.8 Hz, $J_{6',5'}$ = 2.3 Hz, H-6'), 4.01 (dd, 1H, $J_{6',6'}$ = 12.8 Hz, $J_{6',5'}$ = 2.2 Hz, H-6'), 4.22 (q, 2H, J = 7.1 Hz, CH_2), 4.50 (d, 1H, $J_{H,H}$ = 12.6 Hz, OCH_2Ph), 4.57 (td, 1H, $J_{4',3}$ = 4.3 Hz, $J_{5',4'}$ = 2.1, $J_{4',2}$ = 2.1 Hz, H-4'), 4.70 (d, 1H, $J_{H,H}$ = 12.6 Hz, OCH_2Ph), 6.13 (dd, 1H, $J_{3,2}$ = 15.7 Hz, $J_{4',2}$ = 1.8 Hz, H-2), 6.91 (dd, 1H, $J_{3,2}$ = 15.7 Hz, $J_{4',3}$ = 4.3 Hz, H-3), 7.26–7.32 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3 (CH_3), 19.1 (CH_3), 28.8 (CH_3), 60.3 (CH_2), 61.6 (C-6'), 2 × 70.9 (C-4', C-5'), 71.2 (OCH_2Ph), 99.0 (C_q), 121.8 (C-2), 127.8 (CH_{Ph}), 128.0 (2 × CH_{Ph}), 128.3 (2 × CH_{Ph}), 137.7 (C_i), 144.5 (C-3), 166.2 (C=O). Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.43; H, 7.59.

Isomer (*Z*)-**20**: white crystals, mp 41−42 °C (recrystallized from *n*-hexane/ethyl acetate); {$[\alpha]_D^{23}$ +186.0 (*c* 0.33, $CHCl_3$); lit.[14b] $[\alpha]_D^{22}$ –203.0 (*c* 0.28, $CHCl_3$) for *ent*-(*Z*)-**20**}. IR (neat) υ_{max} 2989, 2958, 2889, 1706, 1645, 1371, 1185 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, 3H, J = 7.1 Hz, CH_3), 1.48 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 3.58–3.60 (m, 1H, H-5'), 3.96 (dd, 1H, $J_{6',6'}$ = 13.0 Hz, $J_{6',5'}$ = 2.1Hz, H-6'), 4.01 (dd, 1H, $J_{6',6'}$ = 12.9 Hz, $J_{6',5'}$ = 2.1 Hz, H-6'), 4.09 (q, 2H, J = 7.1 Hz, CH_2), 4.45 (d, 1H, $J_{H,H}$ = 12.4 Hz, OCH_2Ph), 4.67 (d, 1H, $J_{H,H}$ = 12.4

Hz, OCH_2Ph), 5.50–5.53 (m, 1H, H-4'), 5.80 (dd, 1H, $J_{3,2}$ = 11.8 Hz, $J_{4',2}$ = 1.5 Hz, H-2), 6.39 (dd, 1H, $J_{3,2}$ = 11.8 Hz, $J_{4',3}$ = 6.8 Hz, H-3), 7.23–7.30 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (CH_3), 19.1 (CH_3), 29.2 (CH_3), 60.2 (CH_2), 61.6 (C-6'), 69.4 (C-4'), 71.2 (C-5'), 71.4 (OCH_2Ph), 99.8 (C_q), 119.6 (C-2), 127.6 (CH_{Ph}), 128.1 (4 × CH_{Ph}), 138.0 (C_i), 148.3 (C-3), 165.7 (C=O). Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.53; H, 7.52.

4.1.13. (*E*)-3-[(4'*S*,5'*S*)-5'-(Benzyloxy)-2',2'-dimethyl-1',3'-dioxan-4'-yl]prop-2-en-1-ol (21)

Ester (*E*)-**19** (5.85 g, 18.26 mmol) was dissolved in dry CH_2Cl_2 (82.50 mL), and the resulting solution was cooled to –50 °C. Diisobutylaluminum hydride (45.60 mL, 54.80 mmol, 1.2 M toluene solution) was added dropwise, and the mixture was then stirred for 30 min at –30 °C before quenching with MeOH (18 mL). After warming to room temperature, the mixture was poured into a 30% K/Na tartrate solution (385 mL) with vigorous stirring over 1.5 h at room temperature. The separated aqueous phase was extracted with CH_2Cl_2 (3 × 215 mL). The combined organic layers were dried over Na_2SO_4, stripped of solvent, and the residue was subjected to flash chromatography on silica gel (*n*-hexane/ethyl acetate, 2:1) to furnish 4.73 g (93%) of compound **21** as white crystals; mp 41–43 °C (recrystallized from *n*-hexane/ethyl acetate); {$[\alpha]_D^{26}$ +38.7 (*c* 0.54, $CHCl_3$); lit.[14b] $[\alpha]_D^{23}$ –31.9 (*c* 0.26, $CHCl_3$) for *ent*-**21**}. IR (neat) υ_{max} 3452, 2993, 2866, 1389, 1198, 1065 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.20–3.22 (m, 1H, H-5'), 3.94 (dd, 1H, $J_{6',6'}$ = 12.8 Hz, $J_{6',5'}$ = 2.2 Hz, H-6'), 4.00 (dd, 1H, $J_{6',6'}$ = 12.8 Hz, $J_{6',5'}$ = 2.2 Hz, H-6'), 4.09–4.17 (m, 2H, 2 × H-1), 4.41 (dd, 1H, $J_{4',3}$ = 4.5 Hz, $J_{5',4'}$ = 2.2 Hz, H-4'), 4.50 (d, 1H, $J_{H,H}$ = 12.6 Hz, OCH_2Ph), 4.73 (d, 1H, $J_{H,H}$ = 12.6 Hz, OCH_2Ph), 5.83–5.93 (m, 2H, H-2, H-3),7.26–7.36 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1 (CH_3), 29.1 (CH_3), 61.7 (C-6'), 63.0 (C-1), 71.3 (OCH_2Ph), 71.8 (C-5'), 72.2 (C-4'), 98.8 (C_q), 127.7 (CH_{Ph}), 128.1 (2 × CH_{Ph}), 128.2 (2 × CH_{Ph}), 128.7 (C-2 or C-3), 131.8 (C-2 or C-3), 138.1 (C_i). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.08; H, 7.93.

4.1.14. (4*S*,5*S*)-5-(Benzyloxy)-2,2-dimethyl-4-[(*E*)-3'-thiocyanatoprop-1'-en-1'-yl]-1,3-dioxan (22)

To a solution of **21** (1.81 g, 6.50 mmol) in dry CH_2Cl_2 (78.60 mL) were successively added Et_3N (1.37 mL, 9.75 mmol) and methanesulfonyl chloride (0.75 mL, 9.75 mmol) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C and then for a further 10 min at room

temperature. After evaporating of the solvent, the residue was diluted with Et_2O (20 mL), the insoluble parts were filtered off and washed with Et_2O. Removal of the solvent afforded a mesylate that was used in the next reaction step without purification.

KSCN (1.07 g, 11.05 mmol) was added to a solution of the crude mesylate (2.32 g, 6.50 mmol) in dry MeCN (55.50 mL) at 0 °C. The resulting mixture was stirred for 15 min at 0 °C and then for another 6.5 h at room temperature before evaporating of the solvent. To such residue, Et_2O (20 mL) was added producing salts, which were removed by filtration. The filtrate was concentrated to provide an orange oil, which was chromatographed on silica gel (*n*-hexane/ethyl acetate, 5:1) to give 1.87 g (90%) of compound **22** as white crystals; mp 49–50 °C (recrystallized from *n*-hexane/ethyl acetate); {$[\alpha]_D^{27}$ +42.6 (*c* 0.38, $CHCl_3$); lit.[14b] $[\alpha]_D^{23}$ –49.6 (*c* 0.26, $CHCl_3$) for *ent*-**22**}. IR (neat) υ_{max} 2988, 2940, 2866, 2150, 1453, 1377, 1193, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.47 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.25 (q, 1H, $J_{6,5}$ = 2.2 Hz, $J_{6,5}$ = 2.2 Hz, $J_{5,4}$ = 2.2 Hz, H-5), 3.55 (dd, 1H, $J_{3',3'}$ = 12.7 Hz, $J_{3',2'}$ = 5.5 Hz, H-3'), 3.61 (dd, 1H, $J_{3',3'}$ = 12.9 Hz, $J_{3',2'}$ = 7.3 Hz, H-3'), 3.92 (dd, 1H, $J_{6,6}$ = 12.9 Hz, $J_{6,5}$ = 2.2 Hz, H-6), 3.99 (dd, 1H, $J_{6,6}$ = 12.9 Hz, $J_{6,5}$ = 2.1 Hz, H-6), 4.47 (dd, 1H, $J_{4,1'}$ = 4.8 Hz, $J_{5,4}$ = 2.0 Hz, H-4), 4.54 (d, 1H, $J_{H,H}$ = 12.5 Hz, OCH_2Ph), 4.71 (d, 1H, $J_{H,H}$ = 12.5 Hz, OCH_2Ph), 5.83–5.95 (m, 2H, H-1', H-2'), 7.26–7.36 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1 (CH_3), 29.0 (CH_3), 35.8 (C-3'), 61.5 (C-6), 71.3 (OCH_2Ph), 71.4 (C-4), 71.5 (C-5), 98.9 (C_q), 111.8 (SCN), 124.5 (C-2'), 127.7 (CH_{Ph}), 128.0 (2 × CH_{Ph}), 128.3 (2 × CH_{Ph}), 134.5 (C-1'), 137.9 (C_i). Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39. Found: C, 63.90; H, 6.59; N, 4.43.

4.1.15. (4*S*,5*S*)-5-(Benzyloxy)-4-[(1'*S*)-1'-isothiocyanatoallyl]-2,2-dimethyl-1,3-dioxan (24) and (4*S*,5*S*)-5-(benzyloxy)-4-[(1'*R*)-1'-isothiocyanatoallyl]-2,2-dimethyl-1,3-dioxan (25)

4.1.15.1. Conventional method

A solution of thiocyanate **22** (0.10 g, 0.31 mmol) in *n*-heptane (2.6 mL) was stirred and heated under a nitrogen atmosphere (for the reaction times and temperatures, see Table 1). After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 5:1) to give the corresponding isothiocyanates **24** and **25** as colourless oils (for the combined yields, see Table 1).

Requiring a greater amount of the pure rearranged products **24** and **25**, they were obtained on a multi-gram scale by the conventional method in *n*-heptane at 90 °C.

4.1.15.2. Microwave-assisted synthesis

Thiocyanate **22** (0.10 g, 0.31 mmol) was weighed in a 10-mL glass pressure microwave tube equipped with a magnetic stirbar. *n*-Heptane (2.60 mL) was added, the tube was closed with a silicon septum, and the resulting mixture was subjected to microwave irradiation (for the temperatures and reaction times, see Table 1). Evaporating of the solvent and chromatography on silica gel (*n*-hexane/ethyl acetate, 5:1) gave isothiocyanates **24** and **25** (for the combined yields, see Table 1).

Diastereoisomer **24**: {$[\alpha]_D^{25}$ +63.1 (*c* 0.44, $CHCl_3$); lit.[14b] $[\alpha]_D^{23}$ –61.4 (*c* 0.28, $CHCl_3$) for *ent*-**24**}. IR (neat) υ_{max} 2990, 2870, 2170, 2087, 1454, 1377, 1197 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 3.48–3.49 (m, 1H, H-5), 3.79 (dd, 1H, $J_{4,1'}$ = 9.4 H, $J_{5,4}$ = 2.0 Hz, H-4), 3.89 (dd, 1H, $J_{6,6}$ = 13.1 Hz, $J_{6,5}$ = 2.0 Hz, H-6), 4.07 (dd, 1H, $J_{6,6}$ = 13.1 Hz, $J_{6,5}$ = 2.0 Hz, H-6), 4.59 (d, 1H, $J_{H,H}$ = 11.7 Hz, OCH_2Ph), 4.61–4.65 (m, 1H, H-1'), 4.75 (d, 1H, $J_{H,H}$ = 11.6 Hz, OCH_2Ph), 5.28 (dd, 1H, $J_{3',2'}$ = 10.4 Hz, $J_{3',1'}$ = 1.5 Hz, $J_{3',3'}$ = 0.7 Hz, H-3'$_{cis}$), 5.44 (dd, 1H, $J_{3',2'}$ = 17.0 Hz, $J_{3',1'}$ = 1.7 Hz, $J_{3',3'}$ = 0.7 Hz, H-3'$_{trans}$), 5.95 (dd, 1H, $J_{3',2'}$ = 17.0 Hz, $J_{3',2'}$ = 10.4 Hz, $J_{2',1'}$ = 4.7 Hz, H-2'), 7.29–7.42 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0 (CH_3), 28.8 (CH_3), 58.1 (C-1'), 61.0 (C-6), 69.1 (C-5), 71.4 (OCH_2Ph), 74.0 (C-4), 99.2 (C_q), 117.0 (C-3'), 127.9 (CH_{Ph}), 128.2 (2 × CH_{Ph}), 128.5 (2 × CH_{Ph}), 132.7 (C-2'), 133.9 (NCS), 137.5 (C_i). Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39. Found: C, 63.96; H, 6.59; N, 4.42.

Diastereoisomer **25**: {$[\alpha]_D^{25}$ +42.0 (*c* 0.20, $CHCl_3$); lit.[14b] $[\alpha]_D^{25}$ –41.9 (*c* 0.32, $CHCl_3$) for *ent*-**25**}. IR (neat) υ_{max} 3030, 2990, 2873, 2041, 1454, 1376, 1197, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.49 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 3.25–3.26 (m, 1H, H-5), 3.82 (dd, 1H, $J_{4,1'}$ = 9.1 Hz, $J_{5,4}$ = 2.0 Hz, H-4), 3.87 (dd, 1H, $J_{6,6}$ = 13.2 Hz, $J_{6,5}$ = 2.2 Hz, H-6), 4.11 (dd, 1H, $J_{6,6}$ = 13.2 Hz, $J_{6,5}$ = 2.1 Hz, H-6), 4.37 (d, 1H, $J_{H,H}$ = 11.8 Hz, OCH_2Ph), 4.61–4.65 (m, 1H, H-1'), 4.72 (d, 1H, $J_{H,H}$ = 11.8 Hz, OCH_2Ph), 5.23–5.26 (m, 1H, H-3'$_{cis}$), 5.40–5.45 (m, 1H, H-3'$_{trans}$), 5.53 (ddd, 1H, $J_{3',2'}$ = 16.8 Hz, $J_{3',2'}$ = 9.9 Hz, $J_{2',1'}$ = 5.6 Hz, H-2'), 7.28–7.37 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9 (CH_3), 28.7 (CH_3), 60.5 (C-1'), 60.7 (C-6), 69.2 (C-5), 70.5 (OCH_2Ph), 74.6 (C-4), 99.6 (C_q), 119.6 (C-3'), 127.9 (3 × CH_{Ph}), 128.5 (2 × CH_{Ph}), 130.3 (C-2'), 135.9 (NCS), 137.5 (C_i). Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39. Found: C, 63.88; H, 6.67; N, 4.33.

4.1.16. *N*-{(1'*S*)-1-[(4''*S*,5''*S*)-5''-(Benzyloxy)-2'',2''-dimethyl-1'',3''-dioxan-4''-yl]allyl}-2,2,2-trichloroacetamide (26) and *N*-{(1'*R*)-1-[(4''*S*,5''*S*)-5''-(benzyloxy)-2'',2''-dimethyl-1'',3''-dioxan-4''-yl]allyl}-2,2,2-trichloroacetamide (27)

A solution of **21** (2.72g, 9.77 mmol) in dry THF (15.80 mL) was added to a suspension of NaH (0.52 g, 21.69 mmol, 60% dispersion in mineral oil) in dry THF (15.80 mL) at 0 °C, and the resulting mixture was stirred for 30 min at 0 °C before addition of CCl_3CN (1.20 mL, 11.97 mmol). After stirring for another 30 min at 0 °C, the mixture was warmed to room temperature and filtered through a small pad of Celite. The obtained filtrate was concentrated to furnish trichloroacetimidate **23** that was used without further purification.

4.1.16.1. Conventional procedure

Anhydrous potassium carbonate (37.30 mg, 0.27 mmol) was added to a solution of imidate **23** (0.10 g, 0.24 mmol) in *o*-xylene (3.20 mL) at room temperature. The resulting mixture was heated in a sealed tube for 52 h at 140 °C. After cooling to room temperature, the insoluble parts were filtered off, and the filtrate was concentrated. The residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 3:1) to give trichloroacetamides **26** and **27** both as white crystals (for the combined yield, see Table 2).

4.1.16.2. Microwave-assisted synthesis

Imidate **23** (0.10 g, 0.24 mmol) was weighed into a 10-mL glass pressure microwave tube equipped with a magnetic stirbar. *o*-Xylene (3.20 mL) and anhydrous K_2CO_3 (37.30 mg, 0.27 mmol) were added, the tube was closed with a silicone septum, and the reaction mixture was subjected to microwave irradiation (for the temperatures and reaction times, see Table 2). The mixture was allowed to cool to room temperature, the solid parts were filtered off, and the solvent was evaporated. The residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 3:1) to afford the corresponding amides **26** and **27** (for the combined yields and temperatures, see Table 2).

Requiring a greater amount of the rearranged products **26** and **27**, the aforementioned procedure was repeated at 150 °C using the 80-mL glass pressure microwave tube.

Diastereoisomer **26**: mp 95–96 °C (recrystallized from *n*-hexane/ethyl acetate); {$[\alpha]_D^{26}$ −24.6 (*c* 0.50, $CHCl_3$); lit.[14b] $[\alpha]_D^{24}$ +27.3 (*c* 0.22, $CHCl_3$) for *ent*-**26**}. IR (neat) υ_{max} 3350, 2990, 2876, 1711, 1506, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 3H, CH_3), 1.45 (s, 3H,

CH_3), 3.49–3.50 (m, 1H, H-5''), 3.90 (dd, 1H, $J_{6'',6''}$ = 13.3 Hz, $J_{6'',5''}$ = 1.8 Hz, H-6''), 4.05 (dd, 1H, $J_{4'',1'}$ = 4.9 Hz, $J_{5'',4''}$ = 2.2 Hz, H-4''), 4.15 (dd, 1H, $J_{6'',6''}$ = 13.3 Hz, $J_{6'',5''}$ = 1.9 Hz, H-6''), 4.29 (d, 1H, $J_{H,H}$ = 10.5 Hz, OCH_2Ph), 4.67–4.72 (m, 2H, H-1', OCH_2Ph), 5.26–5.29 (m, 1H, H-3'$_{cis}$), 5.30–5.36 (m, 1H, H-3'$_{trans}$), 5.71 (ddd, 1H, $J_{3',2'}$ = 17.1 Hz, $J_{3',2'}$ = 10.4 Hz, $J_{2',1'}$ = 5.2 Hz, H-2'), 7.32–7.36 (m, 5H, Ph), 8.34 (d, 1H, $J_{NH,1'}$ = 7.2 Hz, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.8 (CH_3), 28.9 (CH_3), 56.1 (C-1'), 60.3 (C-6''), 70.4 (C-4''), 71.1 (OCH_2Ph), 71.7 (C-5''), 92.8 (CCl_3), 98.9 (C_q), 117.8 (C-3'), 128.4 (CH_{Ph}), 128.6 (2 × CH_{Ph}), 128.9 (2 × CH_{Ph}), 131.9 (C-2'), 136.6 (C_i), 162.0 (C=O). Anal. Calcd for $C_{18}H_{22}Cl_3NO_4$: C, 51.14; H, 5.25; N, 3.31. Found: C, 51.18; H, 5.21; N, 3.33.

Diastereoisomer **27**: mp 85–86 °C (recrystallized from *n*-hexane/ethyl acetate); {$[\alpha]_D^{26}$ +30.6 (*c* 0.50, $CHCl_3$); lit.[14b] $[\alpha]_D^{24}$ –28.7 (*c* 0.30, $CHCl_3$) for *ent*-**27**}. IR (neat) υ_{max} 3366, 3242, 2993, 2877, 1692, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 3.33–3.34 (m, 1H, H-5''), 3.86 (dd, 1H, $J_{6'',6''}$ = 13.0 Hz, $J_{6'',5''}$ = 2.2 Hz, H-6''), 4.03 (dd, 1H, $J_{4'',1'}$ = 5.3 Hz, $J_{5'',4''}$ = 2.2 Hz, H-4''), 4.04 (dd, 1H, $J_{6'',6''}$ = 13.0 Hz, $J_{6'',5''}$ = 2.2 Hz, H-6''), 4.44–4.48 (m, 2H, H-1', OCH_2Ph), 4.68 (d, 1H, $J_{H,H}$ = 12.0 Hz, OCH_2Ph), 5.21–5.24 (m, 1H, H-3'$_{cis}$), 5.26–5.30 (m, 1H, H-3'$_{trans}$), 5.81 (ddd, 1H, $J_{3',2'}$ = 17.1 Hz, $J_{3',2'}$ = 10.3 Hz, $J_{2',1'}$ = 6.8 Hz, H-2'), 7.27–7.35 (m, 6H, NH, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1 (CH_3), 28.8 (CH_3), 55.2 (C-1'), 60.9 (C-6''), 70.3 (C-5''), 70.7 (OCH_2Ph), 71.5 (C-4''), 92.9 (CCl_3), 99.3 (C_q), 118.2 (C-3'), 127.9 (CH_{Ph}), 128.1 (2 × CH_{Ph}), 128.5 (2 × CH_{Ph}), 133.4 (C-2'), 137.5 (C_i), 161.1 (C=O). Anal. Calcd for $C_{18}H_{22}Cl_3NO_4$: C, 51.14; H, 5.25; N, 3.31. Found: C, 51.10; H, 5.28; N, 3.34.

4.1.17. Methyl {(1*S*)-1-[(4'*S*,5'*S*)-5'-(benzyloxy)-2',2'-dimethyl-1',3'-dioxan-4'-yl]allyl}carbamate (28)

Sodium methoxide (0.25 g, 4.70 mmol) was added to a solution of **24** (1.25 g, 3.91 mmol) in dry MeOH (38.60 mL) at 0° C. After stirring at 0 °C for 30 min and then at room temperature for 14.5 h, the solvent was evaporated, and the residue was partitioned between CH_2Cl_2 (29 ml) and water (15 mL). The aqueous layer was washed with further portions of CH_2Cl_2 (2 × 29 mL). The combined organic extracts were dried over Na_2SO_4, stripped solvent, and the crude material was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate, 3:1) to provide 1.33 g (97%) of thiocarbamate as a colourless oil {$[\alpha]_D^{25}$ –19.4 (*c* 0.30, $CHCl_3$); lit.[14b] $[\alpha]_D^{23}$ +24.1 (*c* 0.34, $CHCl_3$) for the corresponding antipode}, which was used immediately in the subsequent reaction without spectral characterization.

Mesitylnitrile oxide (0.79 g, 4.92 mmol) was added to a stirring solution of the obtained thiocarbamate (1.33 g, 3.78 mmol) in dry MeCN (37 mL) at room temperature. TLC showed that the reaction was complete after 1.5 h. The solvent was evaporated in vacuo, and the residue was chromatographed through a small column of silica gel (*n*-hexane/ethyl acetate, 2:1) to furnish 1.08 g (85%) of white crystalline compound **28**; mp 88–89 °C (recrystallized from *n*-hexane/ethyl acetate); {$[\alpha]_D^{23}$ −6.0 (*c* 0.30, $CHCl_3$); lit.[14b] $[\alpha]_D^{22}$ +7.3 (*c* 0.30, $CHCl_3$) for *ent*-**28**}. IR (neat) υ_{max} 3299, 2985, 2947, 1691, 1541, 1351, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 3.38–3.39 (m, 1H, H-5'), 3.63 (s, 3H, OCH_3), 3.83 (dd, 1H, $J_{6',6'}$ = 13.0 Hz, $J_{6',5'}$ = 1.8 Hz, H-6'), 3.93 (m, 1H, H-4'), 4.02 (dd, 1H, $J_{6',6'}$ = 13.1 Hz, $J_{6',5'}$ = 2.1 Hz, H-6'), 4.42 (d, 1H, $J_{H,H}$ = 11.8 Hz, OCH_2Ph), 4.44–4.46 (m, 1H, H-1), 4.67 (d, 1H, $J_{H,H}$ = 11.7 Hz, OCH_2Ph), 5.14–5.17 (m, 1H, H-3_{cis}), 5.23–5.27 (m, 1H, H-3_{trans}), 5.74–5.82 (m, 2H, H-2, NH), 7.26–7.36 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9 (CH_3), 28.8 (CH_3), 51.9 (OCH_3), 55.2 (C-1), 61.0 (C-6'), 70.6 (C-5'), 70.8 (OCH_2Ph), 71.3 (C-$_{4'}$), 98.9 (C_q), 116.3 (C-3), 127.9 (CH_{Ph}), 128.1 (2 × CH_{Ph}), 128.4 (2 × CH_{Ph}), 134.9 (C-2), 137.4 (C_i), 156.9 (C=O). Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.50; H, 7.46; N, 4.23.

4.1.18. Methyl {(1*R*)-1-[(4'*S*,5'*S*)-5'-(benzyloxy)-2',2'-dimethyl-1',3'-dioxan-4'-yl]allyl}carbamate (29)

By the similar reaction conditions as described for the preparation **28**, compound **25** (0.24 g, 0.75 mmol) and sodium methoxide (52.80 mg, 0.98 mmol) afforded after flash chromatography on silica gel (*n*-hexane/ethyl acetate, 3:1) 0.256 g (97%) of thiocarbamate as white crystals {mp 119−121 °C; $[\alpha]_D^{24}$ +63.1 (*c* 0.26, $CHCl_3$); lit.[14b] $[\alpha]_D^{23}$ −58.1 (*c* 0.32, $CHCl_3$) for the corresponding enantiomer}, which was used in the subsequent transformation without spectral characterization. Its treatment (0.256 g, 0.73 mmol) with MNO (0.13 g, 0.80 mmol) furnished after flash chromatography on silica gel (*n*-hexane/ethyl acetate, 2:1) 0.227 g (92%) of white crystalline compound **29**; mp 132–133 °C (recrystallized from *n*-hexane/ethyl acetate); {$[\alpha]_D^{24}$ +48.2 (*c* 0.38, $CHCl_3$); lit.[14b] $[\alpha]_D^{23}$ −49.2 (*c* 0.30, $CHCl_3$) for *ent*-**29**}. IR (neat) υ_{max} 3265, 3063, 2982, 2948, 2872, 1706, 1689, 1553, 1359 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.31–3.33 (m, 1H, H-5'), 3.60 (s, 3H, OCH_3), 3.80–3.85 (m, 1H, H-4'), 3.85 (dd, 1H, $J_{6',6'}$ = 13.0 Hz, $J_{6',5'}$ = 2.1 Hz, H-6'), 4.04 (dd, 1H, $J_{6',6'}$ = 13.0 Hz, $J_{6',5'}$ = 2.2 Hz, H-6'), 4.32–4.37 (m, 1H, H-1), 4.43 (d, 1H, $J_{H,H}$ = 11.8 Hz, OCH_2Ph), 4.68 (d, 1H, $J_{H,H}$ = 11.8 Hz, OCH_2Ph), 5.08 (m, 1H, NH), 5.15–5.17 (m, 1H, H-

3_{cis}), 5.23–5.28 (m, 1H, H-3_{trans}), 5.72–5.81 (m, 1H, H-2), 7.26–7.39 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1 (CH_3), 28.8 (CH_3), 51.9 (OCH_3), 54.6 (C-1), 61.2 (C-6'), 70.3 (C-5'), 70.8 (OCH_2Ph), 72.8 (C-4'), 99.2 (C_q), 117.2 (C-3), 127.7 (CH_{Ph}), 127.9 (2 × CH_{Ph}), 128.3 (2 × CH_{Ph}), 135.4 (C-2), 137.8 (C_i), 156.8 (C=O). Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.42; H, 7.55; N, 4.15.

4.1.19. Methyl {(1*S*)-1-[(4'*S*,5'*S*)-5'-(benzyloxy)-2',2'-dimethyl-1',3'-dioxan-4'-yl]-2-hydroxyethyl}carbamate (30)

Ozone was introduced to a solution of **28** (1.01 g, 3.01 mmol) in MeOH (30 mL) at –78 °C for 15 min. After the complete consumption of the starting material (judged by TLC), nitrogen was passed through the cold solution in order to remove excess ozone. Then, $NaBH_4$ (0.51 g, 13.55 mmol) was added in portions, and the reaction mixture was stirred for 30 min at –78 °C. After warming to 0 °C (approximately 20 min), the reaction was quenched by neutralization with a 1 M aqueous HCl solution. The solvent was evaporated in vacuo, and the residue was partitioned between CH_2Cl_2 (56 mL) and water (21 mL), and the aqueous layer was then washed with a further portion of CH_2Cl_2 (56 mL). The combined organic extracts were dried over Na_2SO_4, the solvent was taken down, and the crude product was subjected to flash chromatography on silica gel (*n*-hexane/ethyl acetate, 1:2). This procedure yielded 0.83 g (81%) of derivative **30** as white crystals; mp 125–126 °C (recrystallized from ethyl acetate); {$[\alpha]_D^{27}$ +49.2 (*c* 0.36, $CHCl_3$); lit.[14b] $[\alpha]_D^{23}$ –42.3 (*c* 0.26, $CHCl_3$) for *ent*-**30**}. IR (neat) υ_{max} 3430, 3357, 2993, 2947, 1693, 1525, 1359, 1238 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (br s, 6H, 2 × CH_3), 3.36–3.37 (m, 1H, H-5'), 3.64 (m, 4H, H-2, OCH_3), 3.86 (m, 1H, H-1), 3.88 (dd, 1H, $J_{6',6'}$ = 13.0 Hz, $J_{6',5'}$ = 1.6 Hz, H-6'), 4.00 (m, 1H, H-2), 4.05 (dd, 1H, $J_{6',6'}$ = 13.0 Hz, $J_{6',5'}$ = 1.8 Hz, H-6'), 4.14–4.15 (m, 1H, H-4'), 4.46 (d, 1H, $J_{H,H}$ = 11.9 Hz, OCH_2Ph), 4.72 (d, 1H, $J_{H,H}$ = 11.8 Hz, OCH_2Ph), 5.40–5.42 (m, 1H, NH), 7.29–7.36 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9 (CH_3), 29.0 (CH_3), 52.1 (OCH_3), 53.3 (C-1), 61.1 (C-6'), 62.5 (C-2), 70.2 (C-5'), 70.9 (OCH_2Ph), 71.4 (C-4'), 99.0 (C_q), 127.9 (CH_{Ph}), 128.1 (2 × CH_{Ph}), 128.5 (2 × CH_{Ph}), 137.6 (C_i), 157.1 (C=O). Anal. Calcd for $C_{17}H_{25}NO_6$: C, 60.16; H, 7.42; N, 4.13. Found: C, 60.20; H, 7.38; N, 4.17.

4.1.20. Methyl {(1*R*)-1-[(4'*S*,5'*S*)-5'-(benzyloxy)-2',2'-dimethyl-1',3'-dioxan-4'-yl]-2-hydroxyethyl}carbamate (31)

By the similar reaction conditions as described for the preparation of **30**, ozonolysis of compound **29** (171 mg, 0.83 mmol) in MeOH/CH_2Cl_2 (5:1, 6 mL) followed by $NaBH_4$ (86.80 mg, 2.29 mmol) treatment gave after flash chromatography on silica gel (*n*-hexane/ethyl acetate, 1:2) 151 mg (87%) of derivative **31** as white crystals; mp 126–128 °C (recrystallized from ethyl acetate); {$[\alpha]_D^{23}$ +32.1 (*c* 0.42, $CHCl_3$); lit.[14b] $[\alpha]_D^{23}$ –26.5 (*c* 0.26, $CHCl_3$) for *ent*-**31**}. IR (neat) υ_{max} 3565, 3253, 3093, 2982, 2876, 1705, 1684, 1565, 1269 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 1.38 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.38–3.39 (m, 1H, H-5'), 3.46 (dd, 1H, $J_{2,2}$ = 11.0 Hz, $J_{2,1}$ = 4.1 Hz, H-2), 3.52–3.57 (m, 4H, H-2, OCH_3), 3.83–3.87 (m, 1H, H-1), 3.95 (dd, 1H, $J_{6',6'}$ = 13.1 Hz, $J_{6',5'}$ = 1.7 Hz, H-6'), 4.08 (dd, 1H, $J_{6',6'}$ = 13.1 Hz, $J_{6',5'}$ = 1.9 Hz, H-6'), 4.12–4.15 (m, 1H, H-4'), 4.44 (d, 1H, $J_{H,H}$ = 11.6 Hz, OCH_2Ph), 4.69 (d, 1H, $J_{H,H}$ = 11.6 Hz, OCH_2Ph), 7.26–7.39 (m, 5H, Ph); ^{13}C NMR (100 MHz, CD_3OD): δ 19.1 (CH_3), 29.4 (CH_3), 52.4 (OCH_3), 55.3 (C-1), 61.8 (C-2), 61.9 (C-6'), 70.8 (C-4'), 71.7 (OCH_2Ph), 72.3 (C-5'), 100.4 (C_q), 128.8 (CH_{Ph}), 129.3 (2 × CH_{Ph}), 129.4 (2 × CH_{Ph}), 139.5 (C_i), 159.5 (C=O). Anal. Calcd For $C_{17}H_{25}NO_6$: C, 60.16; H, 7.42; N, 4.13. Found: C, 60.13; H, 7.46; N, 4.09.

4.1.21. (4*S*)-4-[(4'*S*,5'*S*)-5'-(Benzyloxy)-2',2'-dimethyl-1',3'-dioxan-4'-yl]oxazolidin-2-one (32)

*Transformation of alcohol **30** to **32**:*

Sodium hydride (0.18 g, 7.43 mmol, 60% dispersion in mineral oil) was added to a solution of **30** (0.75 g, 2.21 mmol) in dry THF (4.40 mL) at 0 °C, and the resulting mixture was stirred for 10 min at 0 °C and then for another 1 h at room temperature before quenching with MeOH (0.77 mL). The solvent was evaporated in vacuo, and the residue was partitioned between CH_2Cl_2 (14 mL) and a saturated NaCl solution (7.70 mL). The aqueous layer was then washed with further portions of CH_2Cl_2 (2 × 14 mL). The combined organic extracts were dried over Na_2SO_4, stripped of solvent, and the crude product was subjected to flash chromatography on silica gel (*n*-hexane/ethyl acetate, 1:1) to give 0.67 g (99%) of compound **32**.

*Transformation of alcohol **34** to **32**:*

DBU (33.20 µL, 0.22 mmol) was added to a solution of **34** (0.95 g, 2.23 mmol) in dry CH_2Cl_2 (26.60 mL) at 0 °C, and the resulting mixture was stirred for 10 min at 0 °C and then for a further 5 h at room temperature. Evaporation of solvent and chromatography of the residue on silica gel (*n*-hexane/ethyl acetate, 1:2) gave 0.65 g (95%) of **32**.

Oxazolidonone **32**: white crystals, mp 177–179 °C (recrystallized from *n*-hexane/ethyl acetate); {$[\alpha]_D^{25}$ +77.6 (*c* 0.55, $CHCl_3$); lit.[14b] $[\alpha]_D^{23}$ –71.3 (*c* 0.30, $CHCl_3$) for *ent*-**32**}. IR (neat) υ_{max} 3377, 2990, 2879, 1736, 1041, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 3.32–3.33 (m, 1H, H-5'), 3.77 (dd, 1H, $J_{4,4'}$ = 7.9 Hz, $J_{5',4'}$ = 2.3 Hz, H-4'), 3.92 (dd, 1H, $J_{6',6'}$ = 13.1 Hz, $J_{6',5'}$ = 2.2 Hz, H-6'), 3.98–4.03 (m, 1H, H-4), 4.09 (dd, 1H, $J_{6',6'}$ = 13.4 Hz, $J_{6',5'}$ = 2.5 Hz, H-6'), 4.30 (dd, 1H, $J_{5,5}$ = 9.1 Hz, $J_{5,4}$ = 4.7 Hz, H-5), 4.38–4.42 (m, 2H, H-5, OCH_2Ph), 4.77 (d, 1H, $J_{H,H}$ = 12.0 Hz, OCH_2Ph), 5.26 (br s, 1H, NH), 7.35–7.42 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2 (CH_3), 28.6 (CH_3), 51.7 (C-4), 60.5 (C-6'), 67.9 (C-5), 68.1 (C-5'), 70.5 (OCH_2Ph), 72.8 (C-4'), 98.9 (C_q), 128.2 (3 × CH_{Ph}), 128.7 (2 × CH_{Ph}), 137.6 (C_i), 159.6 (C=O). Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.49; H, 6.93; N, 4.53.

4.1.22. (4*R*)-4-[(4'*S*,5'*S*)-5'-(Benzyloxy)-2',2'-dimethyl-1',3'-dioxan-4'-yl]oxazolidin-2-one (33)

*Modification of alcohol **31** into **33**:*

According to the same procedure described for the preparation of **32**, compound **31** (145 mg, 0.43 mmol) and NaH (34.50 mg, 1.44 mmol, 60% dispersion in mineral oil) afforded after flash chromatography on silica gel (*n*-hexane/ethyl acetate, 1:1) 121 mg (92%) of derivative **33**.

*Modification of alcohol **35** into **33**:*

By the similar reaction conditions as described for the transformation of **34** to **32**, compound **35** (0.75 g, 1.76 mmol) and DBU (26.2 µL, 0.18 mmol) afforded after flash chromatography on silica gel (*n*-hexane/ethyl acetate, 1:2) 0.52 g (96%) of oxazolidinone **33**.

Oxazolidinone **33**: colourless oil;{$[\alpha]_D^{25}$ +10.6 (*c* 0.46, $CHCl_3$); lit.[14b] $[\alpha]_D^{23}$ –7.7 (*c* 0.22, $CHCl_3$) for *ent*-**33**}. IR (neat) υ_{max} 3302, 2991, 2872, 1750, 1198, 1083 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 3.29–3.31 (m, 1H, H-5'), 3.76 (dd, 1H, $J_{4,4'}$ = 6.0 Hz, $J_{5',4'}$ = 2.6 Hz, H-4'), 3.85 (dd, 1H, $J_{5,5}$ = 8.6 Hz, $J_{5,4}$ = 5.0 Hz, H-5), 3.90 (dd, 1H, $J_{6',6'}$ = 13.0 Hz, $J_{6',5'}$ = 2.6 Hz, H-6'), 4.00–4.04 (m, 1H, H-4), 4.05 (dd, 1H, $J_{6',6'}$ = 13.0 Hz, $J_{6',5'}$ = 2.6 Hz, H-6'), 4.13 (t, 1H, $J_{5,5}$ = 8.7 Hz, $J_{5,4}$ = 8.7 Hz, H-5), 4.34 (d, 1H, $J_{H,H}$ = 12.1 Hz, OCH_2Ph), 4.75 (d, 1H, $J_{H,H}$ = 12.1 Hz, OCH_2Ph), 5.51 (br s, 1H, NH), 7.27–7.40 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3 (CH_3), 28.3 (CH_3), 53.0 (C-4), 60.3 (C-6'), 65.8 (C-5), 69.2 (C-5'), 70.5 (OCH_2Ph), 72.4 (C-4'), 99.2 (C_q), 128.2 (2 × CH_{Ph}), 128.3 (CH_{Ph}), 128.7

(2 × CH_{Ph}), 137.0 (C_i), 159.1 (C=O). Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.57; H, 6.85; N, 4.52.

4.1.23. *N*-{(1'*S*)-1'-[(4''*S*,5''*S*)-5''-(Benzyloxy)-2'',2''-dimethyl-1'',3''-dioxan-4''-yl]-2'-hydroxyethyl}-2,2,2-trichloroacetamide (34)

Ozone was introduced to a solution of **26** (1.13 g, 2.67 mmol) in MeOH/CH_2Cl_2 (100 mL, 5:1) at –78 °C for 15 min. After the complete consumption of the starting material (judged by TLC), nitrogen was passed through the cold solution in order to remove excess ozone. Then, $NaBH_4$ (0.455 g, 12.03 mmol) was added in portions, and the resulting mixture was stirred for 30 min at –78 °C. After warming to room temperature (approximately 30 min), the reaction was quenched by neutralization with a 1 M aqueous HCl solution. The solvent was evaporated in vacuo, and the residue was partitioned between ethyl acetate (70 mL) and a saturated NH_4Cl solution (35 mL). The aqueous layer was washed with a further portion of ethyl acetate (70 mL). The combined organic extracts were dried over Na_2SO_4, stripped of solvent, and the crude product was chromatographed on silica gel (*n*-hexane/ethyl acetate, 1:1). This procedure yielded 0.98 g (86%) of alcohol **34** as a colourless oil; {$[\alpha]_D^{27}$ +19.3 (*c* 0.42, $CHCl_3$); lit.[14b] $[\alpha]_D^{24}$ –18.0 (*c* 0.30, $CHCl_3$) for *ent*-**34**}. IR (neat) υ_{max} 3344, 2992, 2877, 1701, 1511, 1381, 1236, 1198 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 1.37 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 3.53–3.54 (m, 1H, H-5''), 3.62 (dd, 1H, $J_{2',2'}$ = 11.2 Hz, $J_{2',1'}$ = 5.8 Hz, H-2'), 3.68 (dd, 1H, $J_{2',2'}$ = 11.2 Hz, $J_{2',1'}$ = 5.3 Hz, H-2'), 3.99 (dd, 1H, $J_{6'',6''}$ = 13.3 Hz, $J_{6'',5''}$ = 1.6 Hz, H-6''), 4.13 (dd, 1H, $J_{6'',6''}$ = 13.3 Hz, $J_{6'',5''}$ = 1.8 Hz, H-6''), 4.19–4.23 (m, 1H, H-1'), 4.34 (dd, 1H, $J_{4'',1'}$ = 7.1 Hz, $J_{5'',4''}$ = 1.9 Hz, H-4''), 4.43 (d, 1H, $J_{H,H}$ = 10.7 Hz, OCH_2Ph), 4.66 (d, 1H, $J_{H,H}$ = 10.7 Hz, OCH_2Ph), 7.27–7.43 (m, 5H, Ph); ^{13}C NMR (100 MHz, CD_3OD): δ 19.2 (CH_3), 29.5 (CH_3), 55.6 (C-1'), 61.0 (C-2'), 61.7 (C-6''), 69.9 (C-4''), 72.3 (OCH_2Ph), 72.4 (C-5''), 94.0 (CCl_3), 100.2 (C_q), 129.1 (CH_{Ph}), 129.5 (2 × CH_{Ph}), 130.0 (2 × CH_{Ph}), 139.0 (C_i), 163.9 (C=O). Anal. Calcd for $C_{17}H_{22}Cl_3NO_5$: C, 47.85; H, 5.20; N, 3.28. Found: C, 47.89; H, 5.16; N, 3.31.

4.1.24. *N*-{(1'*R*)-1'-[(4''*S*,5''*S*)-5''-(Benzyloxy)-2'',2''-dimethyl-1'',3''-dioxan-4''-yl]-2'-hydroxyethyl}-2,2,2-trichloroacetamide (35)

By the similar reaction conditions as described for the preparation of **34**, ozonolysis of compound **27** (0.85 g, 2.01 mmol) followed by $NaBH_4$ (0.34 g, 9.05 mmol) treatment furnished after flash chromatography on silica gel (*n*-hexane/ethyl acetate, 1:1) 0.77 g (90%)

of derivative **35** as a colourless oil; {$[\alpha]_D^{23}$ +10.7 (*c* 0.66, $CHCl_3$); lit.[14b] {$[\alpha]_D^{24}$ –10.0 (*c* 0.30, $CHCl_3$) for *ent*-**35**}. IR (neat) υ_{max} 3411, 3348, 2994, 2888, 1691, 1523, 1377, 1200 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 1.38 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 3.38–3.39 (m, 1H, H-5''), 3.53 (dd, 1H, $J_{2',2'}$ = 11.1 Hz, $J_{2',1'}$ = 5.3 Hz, H-2'), 3.57 (dd, 1H, $J_{2',2'}$ = 11.0 Hz, $J_{2',1'}$ = 4.8 Hz, H-2'), 3.97 (dd, 1H, $J_{6'',6''}$ = 13.2 Hz, $J_{6'',5''}$ = 1.8 Hz, H-6''), 4.07–4.12 (m, 2H, H-1', H-6''), 4.31 (dd, 1H, $J_{4'',1'}$ = 6.6 Hz, $J_{5'',4''}$ = 2.0 Hz, H-4''), 4.47 (d, 1H, $J_{H,H}$ = 11.9 Hz, OCH_2Ph), 4.70 (d, 1H, $J_{H,H}$ = 11.9 Hz, OCH_2Ph), 7.26–7.40 (m, 5H, Ph); ^{13}C NMR (100 MHz, CD_3OD): δ 19.4 (CH_3), 29.4 (CH_3), 55.8 (C-1'), 60.6 (C-2'), 61.7 (C-6''), 70.3 (C-4''), 71.6 (OCH_2Ph), 72.0 (C-5''), 94.2 (CCl_3), 100.4 (C_q), 128.9 (CH_{Ph}), 129.4 (2 × CH_{Ph}), 129.5 (2 × CH_{Ph}), 139.4 (C_i), 163.5 (C=O). Anal. Calcd for $C_{17}H_{22}Cl_3NO_5$: C, 47.85; H, 5.20; N, 3.28. Found: C, 47.81; H, 5.23; N, 3.24.

4.1.25. (4*S*)-4-[(1'*S*,2'*S*)-2'-(Benzyloxy)-1',3'-dihydroxypropyl]oxazolidin-2-one (36)

p-Toluenesulfonic acid (40.20 mg, 0.21 mmol) was added to a stirring solution of oxazolidinone **32** (0.65 g, 2.11 mmol) in MeOH (42 mL). TLC showed that the reaction was complete after 1 h. The solvent was removed under reduced pressure, and the solid residue was washed three times with Et_2O. The obtained white crystals were dried on a pump for 10 h at room temperature. This procedure yielded 0.52 g (92%) of compound **36**; mp 122–124 °C (recrystallized from ethyl acetate); {$[\alpha]_D^{24}$ +20.7 (*c* 0.38, MeOH); lit.[14b] $[\alpha]_D^{23}$ –16.7 (*c* 0.24, MeOH) for *ent*-**36**}. IR (neat) υ_{max} 3461, 3294, 2948, 2926, 2874, 1733, 1415, 1087 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 3.50–3.53 (m, 1H, H-2'), 3.73–3.77 (m, 3H, H-1', 2 × H-3'), 3.96–4.01 (m,1H, H-4), 4.35 (t, 1H, $J_{5,5}$ = 8.8 Hz, $J_{5,4}$ = 8.8 Hz, H-5), 4.47 (dd, 1H, $J_{5,5}$ = 8.8 Hz, $J_{5,4}$ = 5.8 Hz, H-5), 4.57 (d, 1H, $J_{H,H}$ = 11.4 Hz, OCH_2Ph), 4.74 (d, 1H, $J_{H,H}$ = 11.4 Hz, OCH_2Ph), 7.28–7.39 (m, 5H, Ph); ^{13}C NMR (100 MHz, CD_3OD): δ 55.9 (C-4), 61.5 (C-3'), 68.4 (C-5), 72.9 (C-1'), 73.8 (OCH_2Ph), 81.1 (C-2'), 128.9 (CH_{Ph}), 129.2 (2 × CH_{Ph}), 129.5 (2 × CH_{Ph}), 139.8 (C_i), 162.5 (C=O). Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.38; H, 6.44; N, 5.27.

4.1.26. (4*R*)-4-[(1'*S*,2'*S*)-2'-(Benzyloxy)-1',3'-dihydroxypropyl]oxazolidin-2-one (37)

To a solution of **33** (0.58 g, 1.89 mmol) in MeOH (37.2 mL) was added *p*-TsOH (36 mg, 0.19 mmol), and the resulting mixture was stirred at room temperature for 1 h before quenching by neutralization with Et_3N. The solvent was evaporated in vacuo, and the residue was flash-chromatographed through a small pad of silica gel (ethyl acetate) to give 0.47 g (93%) of

compound **37** as a colourless oil; {$[\alpha]_D^{26}$ −3.1 (*c* 0.42, MeOH); lit.[14b] $[\alpha]_D^{24}$ +3.2 (*c* 0.36, MeOH) for *ent*-**37**}. IR (neat) υ_{max} 3310, 2918, 1721, 1409, 1241, 1025 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 3.40–3.42 (m, 1H, H-2'), 3.60 (dd, 1H, $J_{4,1'}$ = 5.6 Hz, $J_{2',1'}$ = 3.7 Hz, H-1'), 3.72 (dd, 1H, $J_{3',3'}$ = 11.6 Hz, $J_{3',2'}$ = 4.6 Hz, H-3'), 3.78 (dd, 1H, $J_{3',3'}$ = 11.6 Hz, $J_{3',2'}$ = 5.5 Hz, H-3'), 3.96 (td, 1H, $J_{5,4}$ = 8.9 Hz, $J_{5,4}$ = 5.9 Hz, $J_{4,1'}$ = 5.9 Hz, H-4), 4.10–4.17 (m, 2H, 2 × H-5,), 4.53 (d, 1H, $J_{H,H}$ = 11.6 Hz, OCH_2Ph), 4.72 (d, 1H, $J_{H,H}$ = 11.6 Hz, OCH_2Ph), 7.26–7.39 (m, 5H, Ph); ^{13}C NMR (100 MHz, CD_3OD): δ 55.9 (C-4), 61.1 (C-3'), 68.5 (C-5), 73.3 (C-1'), 73.5 (OCH_2Ph), 80.5 (C-2'), 127.0 (CH_{Ph}), 129.5 (4 × CH_{Ph}), 139.6 (C_i), 162.5 (C=O). Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.48; H, 6.44; N, 5.21.

4.1.27. (4*S*)-4-[(1'*S*,2'*S*)-2'-(Benzyloxy)-1'-hydroxy-3'-(trityloxy)propyl]oxazolidin-2-one (38)

To a solution of **36** (0.50 g, 1.87 mmol) in dry pyridine (18 mL) were successively added trityl chloride (1.56 g, 5.61 mmol) and DMAP (0.23 g, 1.87 mmol). The resulting mixture was stirred and heated to 60 °C for 4.5 h, and then another portion of TrCl (0.52 g, 1.87 mmol) and DMAP (0.23 g, 1.87 mmol) was added. After stirring for a further 17.5 h at 60 °C, the mixture was cooled to room temperature, poured into ice-water (35 mL) and extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, stripped of solvent, and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 1:1). This procedure yielded 0.94 g (99%) of compound **38** as a white foam; {$[\alpha]_D^{24}$ +38.1 (*c* 0.32, $CHCl_3$); lit.[14b]{$[\alpha]_D^{24}$ –33.0 (*c* 0.30, $CHCl_3$) for *ent*-**38**}. IR (neat) υ_{max} 3285, 3029, 1739, 1448, 1231, 1061, 1028 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 3.33–3.37 (m,1H, H-3'), 3.39 (dd, 1H, $J_{3',3'}$ = 10.0 Hz, $J_{3',2'}$ = 5.5 Hz, H-3'), 3.61 (dt, 1H, $J_{3',2'}$ = 5.5 Hz, $J_{3',2'}$ = 5.5 Hz, $J_{2',1'}$ = 2.9 Hz, H-2'), 3.76 (dd, 1H, $J_{4,1'}$ = 4.7 Hz, $J_{2',1'}$ = 2.8 Hz, H-1'), 3.88–3.93 (m,1H, H-4), 4.25 (t, 1H, $J_{5,5}$ = 8.9 Hz, $J_{5,4}$ = 8.9 Hz, H-5), 4.41 (dd, 1H, $J_{5,5}$ = 8.9 Hz, $J_{5,4}$ = 5.8 Hz, H-5), 4.51 (d, 1H, $J_{H,H}$ = 11.5 Hz, OCH_2Ph), 4.65 (d, 1H, $J_{H,H}$ = 11.5 Hz, OCH_2Ph), 7.21–7.45 (m, 20H, Ph); ^{13}C NMR (100 MHz, CD_3OD): δ 56.0 (C-4), 64.5 (C-3'), 68.1 (C-5), 73.1 (C-1'), 74.1 (OCH_2Ph), 80.2 (C-2'), 88.6 (C_q), 128.3 (3 × CH_{Ph}), 128.9 (CH_{Ph}), 128.9 (6 × CH_{Ph}), 129.2 (2 × CH_{Ph}), 129.5 (2 × CH_{Ph}), 129.9 (6 × CH_{Ph}), 139.7 (C_i), 145.3 (3 × C_i), 162.5 (C=O). Anal. Calcd for $C_{32}H_{31}NO_5$: C, 75.42; H, 6.13; N, 2.75. Found: C, 75.46; H, 6.09; N, 2.78.

4.1.28. (4*R*)-4-[(1'*S*,2'*S*)-2'-(Benzyloxy)-1'-hydroxy-3'-(trityloxy)propyl]oxazolidin-2-one (39)

By the similar reaction conditions as described for the preparation of **38**, compound **37** (0.41 g, 1.53 mmol) was converted into derivative **39** (0.72 g, 92%, white foam, *n*-hexane/ethyl acetate, 1:1); {$[\alpha]_D^{27}$ +21.6 (*c* 0.38, $CHCl_3$); lit.[14b] $[\alpha]_D^{24}$ –20.5 (*c* 0.38, $CHCl_3$) for *ent*-**39**}. IR (neat) υ_{max} 3392, 3056, 2875, 1739, 1448, 1217, 1055 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 3.31–3.33 (m, 1H, H-3'), 3.43–3.46 (m, 2H, H-2', H-3'), 3.63 (dd, 1H, $J_{4,1'}$ = 5.0 Hz, $J_{2',1'}$ = 3.7 Hz, H-1'), 3.79 (m, H, H-4), 4.05–4.12 (m, 2H, 2 × H-5), 4.49 (d, 1H, $J_{H,H}$ = 11.6 Hz, OCH_2Ph), 4.65 (d, 1H, $J_{H,H}$ = 11.6 Hz, OCH_2Ph), 7.21–7.44 (m, 20H, Ph); ^{13}C NMR (100 MHz, CD_3OD): δ 55.9 (C-4), 64.2 (C-3'), 68.5 (C-5), 73.6 (C-1'), 73.9 (OCH_2Ph), 79.8 (C-2'), 88.5 (C_q), 128.3 (4 × CH_{Ph}), 129.0 (6 × CH_{Ph}), 129.5 (4 × CH_{Ph}), 129.9 (6 × CH_{Ph}), 139.6 (C_i), 145.3 (3 × C_i), 162.4 (C=O). Anal. Calcd for $C_{32}H_{31}NO_5$: C, 75.42; H, 6.13; N, 2.75. Found: C, 75.39; H, 6.17; N, 2.72.

4.1.29. (4*S*)-3-Benzyl-4-[(1'*S*,2'*S*)-1',2'-bis(benzyloxy)-3'-(trityloxy)propyl]oxazolidin-2-one (40)

Compound **38** (0.91 g, 1.79 mmol) was dissolved in DMF, and to this solution were successively added NaH (0.21 g, 8.93 mmol, 60% dispersion in mineral oil), BnBr (0.51 mL, 4.29 mmol) and TBAI (13.20 mg, 0.036 mmol) at °0 C. The resulting mixture was stirred at 0 °C for 15 min and then another 45 min at room temperature. MeOH (0.20 mL) was added, the mixture was partitioned between water (21 mL) and Et_2O (35 mL), and the aqueous layer was washed with further portions of Et_2O (2 × 25 mL). The combined organic extracts were dried over Na_2SO_4, the solvent was removed, and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 3:1) to afford 1.16 g (94%) of derivative **40** as a white foam; {$[\alpha]_D^{24}$ −15.0 (*c* 0.39, $CHCl_3$); lit.[14b] $[\alpha]_D^{22}$ +13.5 (*c* 0.20, $CHCl_3$) for *ent*-**40**}. IR (neat) υ_{max} 3029, 2873, 1743, 1492, 1448, 1224, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.02 (dd, 1H, $J_{3',3'}$ = 9.1 Hz, $J_{3',2'}$ = 3.2 Hz, H-3'), 3.30–3.37 (m, 2H, H-2', H-3'), 3.48 (dd, 1H, $J_{5,4}$ = 9.3 Hz, $J_{5,4}$ = 5.7 Hz, H-4), 3.54 (d, 1H, $J_{H,H}$ = 15.4 Hz, NCH_2Ph), 3.87 (t, 1H, $J_{5,5}$ = 9.0 Hz, $J_{5,4}$ = 9.0 Hz, H-5), 3.99 (d, 1H, $J_{2',1'}$ = 4.6 Hz, H-1'), 4.32–4.35 (m, 2H, H-5, OCH_2Ph), 4.47 (d, 1H, $J_{H,H}$ = 11.5 Hz, OCH_2Ph), 4.54 (d, 1H, $J_{H,H}$ = 11.4 Hz, OCH_2Ph), 4.56 (d, 1H, $J_{H,H}$ = 15.3 Hz, NCH_2Ph), 4.61 (d, 1H, $J_{H,H}$ = 11.5 Hz, OCH_2Ph), 7.06–7.37 (m, 30H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.6 (NCH_2Ph), 55.9 (C-4), 62.0 (C-3'), 62.9 (C-5), 72.8 (OCH_2Ph), 73.7 (C-1'), 74.0 (OCH_2Ph), 79.1 (C-2'), 87.3 (C_q), 127.2 (3 × CH_{Ph}), 127.8 (CH_{Ph}), 127.9 (10 × CH_{Ph}), 128.1 (3 × CH_{Ph}), 128.4 (2 × CH_{Ph}), 128.5 (8 × CH_{Ph}), 128.7 (3 × CH_{Ph}), 135.7 (C_i),

137.6 (C_i), 137.7 (C_i), 143.6 (3 × C_i), 158.5 (C=O). Anal. Calcd for $C_{46}H_{43}NO_5$: C, 80.09; H, 6.28; N, 2.03. Found: C, 80.05; H, 6.31; N, 2.07.

4.1.29. (4*R*)-3-Benzyl-4-[(1'*S*,2'*S*)-1',2'-bis(benzyloxy)-3'-(trityloxy)propyl]oxazolidin-2-one (41)

By the similar reaction conditions as described for the preparation of **40**, compound **39** (0.68 g, 1.33 mmol) was transformed to derivative **41** (0.89 g, 97%, white foam, *n*-hexane/ethyl acetate, 3:1); {$[\alpha]_D^{24}$ −8.8 (*c* 0.60, $CHCl_3$); lit.[14b] $[\alpha]_D^{22}$ +10.0 (*c* 0.24, $CHCl_3$) for *ent*-**41**}. IR (neat) υ_{max} 3029, 2873, 1745, 1448, 1226, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.28 (dd, 1H, $J_{3',3'}$ = 9.8 Hz, $J_{3',2'}$ = 6.6 Hz, H-3'), 3.33 (dd, 1H, $J_{3',3'}$ = 9.8 Hz, $J_{3',2'}$ = 5.2 Hz, H-3'), 3.49–3.53 (m, 1H, H-2'), 3.55–3.59 (m, 1H, H-4), 3.73 (t, 1H, $J_{5,5}$ = 9.0 Hz, $J_{5,4}$ = 9.0 Hz, H-5), 3.78 (dd, 1H, $J_{4,1'}$ = 7.6 Hz, $J_{2',1'}$ = 2.6 Hz, H-1'), 4.07 (d, 1H, $J_{H,H}$ = 14.8 Hz, NCH_2Ph), 4.24 (dd, 1H, $J_{5,5}$ = 9.0 Hz, $J_{5,4}$ = 4.7 Hz, H-5), 4.32–4.38 (m, 2H, OCH_2Ph, OCH_2Ph), 4.45 (d, 1H, $J_{H,H}$ = 11.5 Hz, OCH_2Ph), 4.51 (d, 1H, $J_{H,H}$ = 11.6 Hz, OCH_2Ph), 4.79 (d, 1H, $J_{H,H}$ = 14.8 Hz, NCH_2Ph), 7.08–7.38 (m, 30H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.7 (NCH_2Ph), 53.7 (C-4), 61.7 (C-3'), 64.7 (C-5), 72.8 (OCH_2Ph), 73.9 (OCH_2Ph), 76.2 (C-2'), 78.6 (C-1'), 87.3 (C_q), 127.2 (3 × CH_{Ph}), 127.7 (CH_{Ph}), 127.9 (6 × CH_{Ph}), 128.0 (2 × CH_{Ph}), 128.2 (2 × CH_{Ph}), 128.3 (4 × CH_{Ph}), 128.4 (7 × CH_{Ph}), 128.5 (3 × CH_{Ph}), 128.7 (2 × CH_{Ph}), 136.0 (C_i), 137.3 (C_i), 137.4 (C_i), 143.6 (3 × C_i), 159.0 (C=O). Anal. Calcd for $C_{46}H_{43}NO_5$: C, 80.09; H, 6.28; N, 2.03. Found: C, 80.12; H, 6.24; N, 2.06.

4.1.30. (4*S*)-3-Benzyl-4-[(1'*S*,2'*S*)-1',2'-bis(benzyloxy)-3'-hydroxypropyl]oxazolidin-2-one (42)

p-Toluenesulfonic acid (0.29 g, 1.52 mmol) was added to a solution of **40** (1.05 g, 1.52 mmol) in CH_2Cl_2/MeOH (2:1, 19.50 mL), and the resulting mixture was stirred for 5 h at room temperature before quenching by neutralization with Et_3N. The solvents were evaporated in vacuo, and the residue was subjected to flash chromatography through a small pad of silica gel (*n*-hexane/ethyl acetate, 1:1) to give 0.635 g (93%) of compound **42** as white crystals; mp 133–134.5 °C (recrystallized from *n*-hexane/ethyl acetate); {$[\alpha]_D^{26}$ −27.4 (*c* 0.34, $CHCl_3$); lit.[14b] $[\alpha]_D^{22}$ +31.7 (*c* 0.18, $CHCl_3$) for *ent*-**42**}. IR (neat) υ_{max} 3354, 3028, 2968, 1705, 1444, 1241, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.41–3.48 (m, 1H, H-2'), 3.53–3.57 (m, 1H, H-3'), 3.65 (d, 1H, $J_{H,H}$ = 15.3 Hz, NCH_2Ph), 3.69–3.72 (m, 1H, H-3'), 3.78 (dd, 1H, $J_{5,4}$ = 9.4 Hz, $J_{5,4}$ = 5.5 Hz, H-4), 3.84 (d, 1H, $J_{2',1'}$ = 5.0 Hz, H-1'), 4.17 (t, 1H, $J_{5,5}$ = 9.1 Hz, $J_{5,4}$ = 9.1

Hz, H-5), 4.44 (d, 1H, $J_{H,H}$ = 11.6 Hz, OCH_2Ph), 4.49 (d, 1H, $J_{H,H}$ = 11.6 Hz, OCH_2Ph), 4.51–4.62 (m, 4H, H-5, NCH_2Ph, OCH_2Ph), 7.17–7.39 (m, 15H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.7 (NCH_2Ph), 55.4 (C-4), 60.2 (C-3'), 63.1 (C-5), 72.5 (OCH_2Ph), 73.4 (C-1'), 73.6 (OCH_2Ph), 78.2 (C-2'), 127.8 (2 × CH_{Ph}), 127.9 (CH_{Ph}), 128.1 (CH_{Ph}), 128.2 (3 × CH_{Ph}), 128.3 (2 × CH_{Ph}), 128.6 (4 × CH_{Ph}), 128.8 (2 × CH_{Ph}), 135.7 (C_i), 137.3 (2 × C_i), 158.6 (C=O). Anal. Calcd for $C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; N, 3.13. Found: C, 72.50; H, 6.49; N, 3.15.

4.1.31. (4*R*)-3-Benzyl-4-[(1'*S*,2'*S*)-1',2'-bis(benzyloxy)-3'-hydroxypropyl]oxazolidin-2-one (43)

By the similar reaction conditions as described for the preparation of **42**, compound **41** (0.65 g, 0.94 mmol) and *p*-TsOH (0.18 g, 0.94 mmol) provided after flash chromatography on silica gel (*n*-hexane/ethyl acetate, 1:1) 0.41 g (97%) of alcohol **43** as a colourless oil; $\{[\alpha]_D^{24}$ −3.5 (*c* 0.46, $CHCl_3$); lit.[14b] $\{[\alpha]_D^{22}$ +5.0 (*c* 0.30, $CHCl_3$) for *ent*-**43**$\}$. IR (neat) υ_{max} 3434, 3030, 2874, 1724, 1422, 1235, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.73 (m, 1H, OH), 3.50–3.58 (m, 2H, H-2', H-3'), 3.66–3.78 (m, 3H, H-1', H-3', H-4), 3.99 (t, 1H, $J_{5,5}$ = 8.6 Hz, $J_{5,4}$ = 8.6 Hz, H-5), 4.23 (d, 1H, $J_{H,H}$ = 14.9 Hz, NCH_2Ph), 4.39 (dd, 1H, $J_{5,5}$ = 9.0 Hz, $J_{5,4}$ = 4.0 Hz, H-5), 4.50 (d, 1H, $J_{H,H}$ = 11.5 Hz, OCH_2Ph), 4.52 (d, 1H, $J_{H,H}$ = 11.1 Hz, OCH_2Ph), 4.53–4.56 (m, 1H, OCH_2Ph), 4.58 (d, 1H, $J_{H,H}$ = 11.6 Hz, OCH_2Ph), 4.80 (d, 1H, $J_{H,H}$ = 14.9 Hz, NCH_2Ph), 7.16–7.37 (m, 15H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.0 (NCH_2Ph), 54.3 (C-4), 60.4 (C-3'), 64.7 (C-5), 72.8 (OCH_2Ph), 73.7 (OCH_2Ph), 77.3 (C-2'), 79.2 (C-1'), 127.8 (CH_{Ph}), 128.2 (5 × CH_{Ph}), 128.3 (3 × CH_{Ph}), 128.6 (4 × CH_{Ph}), 128.7 (2 × CH_{Ph}), 136.2 (C_i), 137.1 (C_i), 137.2 (C_i), 159.1 (C=O). Anal. Calcd for $C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; N, 3.13. Found: C, 72.42; H, 6.49; N, 3.16.

4.1.32. (4*S*)-3-Benzyl-4-[(1'*S*,2'*S*,3'*Z*)-1',2'-bis(benzyloxy)hexadec-3'-en-1'-yl]oxazolidin-2-one [(*Z*)-44] and (4*S*)-3-benzyl-4-[(1'*S*,2'*S*,3'*E*)-1',2'-bis(benzyloxy)hexadec-3'-en-1'-yl]oxazolidin-2-one [(*E*)-44]

To a solution of **42** (0.38 g, 0.85 mmol) in MeCN (4.30 mL) was added IBX (0.48 g, 1.70 mmol) at room temperature, and the resulting suspension was stirred and heated to reflux for 30 min. The insoluble parts were filtered off, the filtrate was concentrated to afford aldehyde, which was used in the subsequent reaction without further purification.

To a solution of 1,1,1,3,3,3-hexamethyldisilazane (0.50 mL, 2.38 mmol) in dry THF (2.50 mL) was added *n*-BuLi (1.49 mL, 2.38 mmol, a 1.6 M solution in *n*-hexane) at room

temperature. The solution of lithium hexamethyldisilazide (LHMDS) thus generated was treated with the known salt $C_{13}H_{27}PPh_3Br$[36] (1.43 g, 2.72 mmol), and the resulting dark mixture was stirred for 5 min at the same temperature. Then, a solution of the obtained aldehyde (0.38 g, 0.85 mmol) in dry THF (2.50 mL) was added. After stirring for 30 min, the mixture was poured into a saturated NH_4Cl solution (16 mL), and the aqueous layer was washed with ethyl acetate (2 × 33 mL). The combined organic extracts were dried over Na_2SO_4, concentrated, and the residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate, 7:1) to afford 0.43 g (83%) of an inseparable mixture of olefins **44** as a colourless oil. Some selected data for major (*Z*)-**44**: ^{1}H NMR (400 MHz, CD_3COCD_3): δ 3.89 (dd, 1H, $J_{5,4}$ = 9.4 Hz, $J_{5,4}$ = 5.6 Hz, H-4), 3.93 (d, 1H, d, $J_{2',1'}$ = 5.3 Hz, H-1'), 3.98 (d, 1H, $J_{H,H}$ = 15.3 Hz, NCH_2Ph), 4.18–4.23 (m, 1H, H-5), 4.35 (d, 1H, $J_{H,H}$ = 11.9 Hz, OCH_2Ph), 4.38–4.41 (m, 1H, H-2'), 4.48–4.58 (m, 4H, OCH_2Ph, NCH_2Ph, H-5), 4.78 (d, 1H, $J_{H,H}$ = 11.6 Hz, OCH_2Ph), 5.24–5.30 (m, 1H, H-3'), 5.72 (td, 1H, $J_{4',3'}$ = 11.2 Hz, $J_{5',4'}$ = 7.4 Hz, $J_{5',4'}$ = 7.4 Hz, H-4'); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 15.4 (CH_3), 29.6 (C-5'), 47.3 (NCH_2Ph), 57.7 (C-4), 64.4 (C-5), 71.7 (OCH_2Ph), 75.5 (OCH_2Ph), 76.8 (C-1'), 78.8 (C-2'), 128.1 (C-3'), 138.1 (C-4'), 160.0 (C=O).

4.1.33. (4*R*)-3-Benzyl-4-[(1'*S*,2'*S*,3'*Z*)-1',2'-bis(benzyloxy)hexadec-3'-en-1'-yl]oxazolidin-2-one [(*Z*)-45] and (4*R*)-3-benzyl-4-[(1'*S*,2'*S*,3'*E*)-1',2'-bis(benzyloxy)hexadec-3'-en-1'-yl]oxazolidin-2-one [(*E*)-45]

By the similar reaction conditions as described for the preparation of **44**, compound **43** (0.37 g, 0.83 mmol) was converted into a mixture of olefins **45** (0.46 g, 91%, *n*-hexane/ethyl acetate, 7:1). Repeated chromatography on silica gel (*n*-hexane/ethyl acetate, 7:1) gave only (*Z*)-**45** in pure form as a colourless oil.

Alkene (*Z*)-**45**: {$[\alpha]_D^{26}$ +11.3 (*c* 0.52, $CHCl_3$); lit.[14b] $[\alpha]_D^{23}$ –12.0 (*c* 0.20, $CHCl_3$) for *ent*-(*Z*)-**45**}. IR (neat) υ_{max} 3030, 2922, 2852, 1750, 1454, 1418, 1229, 1063 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 6.8 Hz, CH_3), 1.26 (m, 20H, 10 × CH_2), 1.87–2.02 (m, 2H, CH_2), 3.64 (dd, 1H, $J_{4,1'}$ = 7.4 Hz, $J_{2',1'}$ = 3.8 Hz, H-1'), 3.69–3.74 (m, 1H, H-4), 4.02 (t, 1H, $J_{5,5}$ = 9.0 Hz, $J_{5,4}$ = 9.0 Hz, H-5), 4.14 (d, 1H, $J_{H,H}$ = 14.9 Hz, NCH_2Ph), 4.26–4.33 (m, 3H, H-2', H-5, OCH_2Ph), 4.48 (d, 1H, $J_{H,H}$ = 11.4 Hz, OCH_2Ph), 4.57 (d, 1H, $J_{H,H}$ = 11.7 Hz, OCH_2Ph), 4.67 (d, 1H, $J_{H,H}$ = 11.4 Hz, OCH_2Ph), 4.81 (d, 1H, $J_{H,H}$ = 14.8 Hz, NCH_2Ph), 5.30–5.35 (m, 1H, H-3'), 5.71 (td, 1H, $J_{4',3'}$ = 11.1 Hz, $J_{5',4'}$ = 7.7 Hz, $J_{5',4'}$ = 7.7 Hz, H-4'), 7.13–7.34 (m, 15H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (CH_3), 22.7 (CH_2), 28.1 (C-5'), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), (3 × CH_2), 29.7 (2 × CH_2), 31.9 (CH_2), 47.7 (NCH_2Ph),

54.2 (C-4), 64.8 (C-5), 70.2 (OCH_2Ph), 73.5 (C-2'), 74.1 (OCH_2Ph), 82.5 (C-1'), 125.5 (C-3'), 127.7 (CH_{Ph}), 127.8 (CH_{Ph}), 128.0 (5 × CH_{Ph}), , 128.4 (6 × CH_{Ph}), 128.6 (2 × CH_{Ph}), 136.1 (C_i), 136.5 (C-4'), 137.4 (C_i), 137.8 (C_i), 158.9 (C=O). Anal. Calcd for $C_{40}H_{53}NO_4$: C, 78.52; H, 8.73; N, 2.29. Found: C, 78.48; H, 8.76; N, 2.31.

4.1.34. (4*S*)-3-Benzyl-4-[(1'*S*,2'*S*)-1',2'-dihydroxyhexadecyl]oxazolidin-2-one (46)

10% Pd/C (29.10 mg) was added to a solution of the mixture of olefins **44** (153 mg, 0.25 mmol) in EtOH (20 mL), and the resulting mixture was stirred at room temperature under an atmosphere of hydrogen. TLC showed that the reaction was complete after 4 h. The catalyst was removed by filtration through a pad of Celite, and the resulting filtrate was concentrated. Purification of the residue by flash chromatography on silica gel (*n*-hexane/ethyl acetate, 1:1) gave 101 mg (93%) of compound **46** as white crystals; mp 91–93 °C (recrystallized from *n*-hexane/ethyl acetate); {$[\alpha]_D^{26}$ −2.8 (*c* 0.40, $CHCl_3$); lit.[14b] $[\alpha]_D^{25}$ +4.4 (*c* 0.52, $CHCl_3$) for *ent*-**46**}. IR (neat) υ_{max} 3294, 2917, 2849, 1721, 1435, 1347 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 0.88 (t, 3H, J = 6.9 Hz, CH_3), 1.27 (m, 24H, 12 × CH_2), 1.40–1.43 (m, 2H, CH_2), 3.31 (m, 1H, H-2'), 3.71 (ddd, 1H, $J_{5,4}$ = 8.8 Hz, $J_{5,4}$ = 6.9 Hz, $J_{4,1'}$ = 1.6 Hz, H-4), 3.75 (dd, 1H, $J_{2',1'}$ = 3.4 Hz, $J_{4,1'}$ = 1.6 Hz, H-1'), 4.15 (d, 1H, $J_{H,H}$ = 15.4 Hz, NCH_2Ph), 4.26 (t, 1H, $J_{5,5}$ = 9.0 Hz, $J_{5,4}$ = 9.0 Hz, H-5), 4.56 (dd, 1H, $J_{5,5}$ = 8.9 Hz, $J_{5,4}$ = 6.9 Hz, H-5), 4.80 (d, 1H, $J_{H,H}$ = 15.4 Hz, NCH_2Ph), 7.27–7.37 (m, 5H, Ph); ^{13}C NMR (100 MHz, CD_3OD): δ 14.5 (CH_3), 23.8 (CH_2), 26.7 (CH_2), 30.5 (CH_2), 30.8 (8 × CH_2), 33.1 (CH_2), 34.7 (CH_2), 46.7 (NCH_2Ph), 59.3 (C-4), 64.7 (C-5), 69.9 (C-1'), 73.4 (C-2'), 129.0 (CH_{Ph}), 129.2 (2 × CH_{Ph}), 130.0 (2 × CH_{Ph}), 137.3 (C_i), 161.4 (C=O). Anal. Calcd for $C_{26}H_{43}NO_4$: C, 72.02; H, 10.00; N, 3.23. Found: C, 71.97; H, 10.04; N, 3.20.

4.1.35. (4*R*)-3-Benzyl-4-[(1'*S*,2'*S*)-1',2'-dihydroxyhexadecyl]oxazolidin-2-one (47)

By the similar reaction conditions as described for the preparation of **46**, the mixture of alkenes **45** (154 mg, 0.25 mmol) and 10% Pd/C (29.20 mg) under an atmosphere of H_2 afforded after flash chromatography on silica gel (*n*-hexane/ethyl acetate, 1:1) 100 mg (92%) of crystalline compound **47**, mp 95–97 °C (recrystallized from *n*-hexane/ethyl acetate); {$[\alpha]_D^{25}$ −4.8 (*c* 0.62, $CHCl_3$); lit.[14b] $[\alpha]_D^{21}$ +6.7 (*c* 0.76, $CHCl_3$) for *ent*-**47**}. IR (neat) υ_{max} 3445, 2916, 2848, 1721, 1441, 1364 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 0.87 (t, 3H, J = 6.8 Hz, CH_3), 1.26 (m, 24H, 12 × CH_2), 1.39–1.46 (m, 2H, CH_2), 3.39–3.42 (m, 1H, H-2'), 3.52 (dd, 1H, $J_{4,1'}$ = 7.1 Hz, $J_{2',1'}$ = 2.2 Hz, H-1'), 3.83–3.89 (m, 1H, H-4), 4.26–4.29 (m, 2H, 2

× H-5), 4.52 (d, 1H, $J_{H,H}$ = 15.1 Hz, NCH_2Ph), 4.73 (d, 1H, $J_{H,H}$ = 15.1 Hz, NCH_2Ph), 7.25–7.33 (m, 5H, Ph); ^{13}C NMR (100 MHz, CD_3OD): δ 14.5 (CH_3), 23.8 (CH_2), 26.9 (CH_2), 30.5 (CH_2), 30.8 (8 × CH_2), 33.1 (CH_2), 34.8 (CH_2), 48.4 (NCH_2Ph), 58.0 (C-4), 66.4 (C-5), 71.7 (C-2'), 76.5 (C-1'), 128.8 (CH_{Ph}), 129.3 (2 × CH_{Ph}), 129.8 (2 × CH_{Ph}), 138.2 (C_i), 161.8 (C=O). Anal. Calcd for $C_{26}H_{43}NO_4$: C, 72.02; H, 10.00; N, 3.23. Found: C, 72.05; H, 9.96; N, 3.27.

(4*S*)-4-[(1'*S*,2'*S*)-1',2'-Dihydroxyhexadecyl]oxazolidin-2-one (48)

To a solution of **46** (95 mg, 0.22 mmol) in EtOH (17.80 mL) was added 10% Pd/C (62.80 mg) and then 35% HCl (0.21 mL) at room temperature. The resulting mixture was stirred at 60 °C under an atmosphere of hydrogen for 3 h. The catalyst was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. Chromatography of the residue on silica gel (*n*-hexane/ethyl acetate, 1:5) provided 66 mg (88%) of white crystalline compound **48**; mp 91–92 °C (recrystallized from ethyl acetate); {$[\alpha]_D^{25}$ −7.1 (*c* 0.58, MeOH); lit.[14b] $[\alpha]_D^{22}$ +8.7 (*c* 0.38, $CHCl_3$) for *ent*-**48**}. IR (neat) υ_{max} 3280, 2916, 2847, 1771, 1720, 1469, 1245 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 0.90 (t, 3H, J = 6.8 Hz, CH_3), 1.29 (m, 24H, 12 × CH_2), 1.50–1.57 (m, 2H, CH_2), 3.43 (dd, 1H, $J_{4,1'}$ = 5.5 Hz, $J_{2',1'}$ = 1.9 Hz, H-1'), 3.50–3.53 (m, 1H, H-2'), 3.98 (td, 1H, $J_{5,4}$ = 8.6 Hz, $J_{5,4}$ = 5.9 Hz, $J_{4,1'}$ = 5.9 Hz, H-4), 4.43 (t, 1H, $J_{5,5}$ = 8.8 Hz, $J_{5,4}$ = 8.8 Hz, H-5), 4.50 (dd, 1H, $J_{5,5}$ = 8.8 Hz, $J_{5,4}$ = 6.1 Hz, H-5); ^{13}C NMR (100 MHz, CD_3OD): δ 14.5 (CH_3), 23.8 (CH_2), 27.0 (CH_2), 30.5 (CH_2), 30.8 (8 × CH_2), 33.1 (CH_2), 34.7 (CH_2), 56.0 (C-4), 68.6 (C-5), 72.5 (C-2'), 75.2 (C-1'), 162.6 (C=O). Anal. Calcd for $C_{19}H_{37}NO_4$: C, 66.43; H, 10.86; N, 4.08. Found: C, 66.39; H, 10.89; N, 4.12.

4.1.36. (4*R*)-4-[(1'*S*,2'*S*)-1',2'-Dihydroxyhexadecyl]oxazolidin-2-one (49)

By the similar reaction conditions as described for the preparation of **48**, compound **47** (93 mg, 0.21 mmol) was transformed to derivative **49** (70 mg, 95%, *n*-hexane/ethyl acetate, 1:5, white crystals); mp 105–107 °C (recrystallized from ethyl acetate); {$[\alpha]_D^{24}$ −22.1 (*c* 0.24, MeOH); lit.[14b] $[\alpha]_D^{22}$ +24.0 (*c* 0.20, $CHCl_3$) for *ent*-**49**}. IR (neat) υ_{max} 3385, 2956, 2918, 2847, 1744, 1709, 1469, 1429 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 0.89 (t, 3H, J = 6.9 Hz, CH_3), 1.28 (m, 24H, 12 × CH_2), 1.48–1.53 (m, 2H, CH_2), 3.34 (dd, 1H, $J_{4,1'}$ = 5.1 Hz, $J_{2',1'}$ = 3.1 Hz, H-1'), 3.47–3.51 (m, 1H, H-2'), 4.02 (ddd, 1H, $J_{5,4}$ = 8.9 Hz, $J_{5,4}$ = 6.2 Hz, $J_{4,1'}$ = 5.2 Hz, H-4), 4.24 (dd, 1H, $J_{5,5}$ = 8.7 Hz, $J_{5,4}$ = 6.2 Hz, H-5), 4.45 (t, 1H, $J_{5,5}$ = 8.8 Hz, $J_{5,4}$ = 8.8 Hz, H-5); ^{13}C NMR (100 MHz, CD_3OD): δ 14.5 (CH_3), 23.8 (CH_2), 26.9 (CH_2), 30.5 (CH_2),

30.8 (7 × CH_2), 30.9 (CH_2), 33.1 (CH_2), 34.7 (CH_2), 56.6 (C-4), 68.8 (C-5), 73.2 (C-2'), 75.5 (C-1'), 162.7 (C=O). Anal. Calcd for $C_{19}H_{37}NO_4$: C, 66.43; H, 10.86; N, 4.08. Found: C, 66.46; H, 10.82; N, 4.11.

4.1.37. (2*S*,3*S*,4*S*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol hydrochloride (1.HCl)

Compound **48** (50 mg, 0.15 mmol) was treated with a 6 M aqueous HCl solution (6.70 mL), and the resulting mixture was stirred and heated at reflux for 3 h. After cooling to room temperature, the solvent was coevaporated three times with toluene, and the residue was diluted with Et_2O. The solid part was filtered off and dried on a pump for 10 h at room temperature. This procedure yielded 43.50 mg (89%) of compound **1.HCl** as a white amorphous solid; {$[\alpha]_D^{23}$ +2.8 (*c* 0.36, MeOH); lit.[37]{$[\alpha]_D^{23}$ +2.6 (*c* 0.38, MeOH); lit.[14b] $[\alpha]_D^{27}$ –2.9 (*c* 0.28, MeOH) for *ent*-**1.HCl**}. IR (neat) υ_{max} 3381, 2953, 2916, 2848, 1589, 1529, 1469, 1042 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 0.90 (t, 3H, J = 6.9 Hz, CH_3), 1.29 (m, 24H, 12 × CH_2), 1.62–1.68 (m, 2H, 2 × H-1'), 3.72 (dt, 1H, $J_{2,1'}$ = 6.7 Hz, $J_{2,1'}$ = 6.7 Hz, $J_{3,2}$ = 3.5 Hz, H-2), 3.80 (dd, 1H, $J_{5,5}$ = 7.9 Hz, $J_{5,4}$ = 4.4 Hz, H-5), 3.87–3.94 (m, 2H, H-4, H-5), 4.25–4.27 (m, 1H, H-3); ^{13}C NMR (100 MHz, CD_3OD): δ 14.5 (CH_3), 23.8 (CH_2), 27.3 (CH_2), 29.8 (CH_2), 30.5 (CH_2), 30.7 (2 × CH_2), 30.8 (5 × CH_2), 30.9 (CH_2), 33.1 (CH_2), 54.4 (C-4), 69.0 (C-5), 70.9 (C-3), 84.4 (C-2). Anal. Calcd for $C_{18}H_{38}ClNO_2$: C, 64.35; H, 11.40; N, 4.17. Found: C, 64.31; H, 11.43; N, 4.14.

4.1.38. (2*S*,3*S*,4*R*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol hydrochloride (5.HCl)

By the similar reaction conditions as described for the preparation of **1.HCl**, compound **49** (51 mg, 0.15 mmol) was transformed to **5.HCl** (49.90 mg, quant, white amorphous solid); {$[\alpha]_D^{24}$ –7.3 (*c* 0.46, MeOH); lit.[14b] $[\alpha]_D^{27}$ +7.5 (*c* 0.52, MeOH) for *ent*-**5.HCl**}. IR (neat) υ_{max} 3383, 2952, 2916, 2848, 1595, 1529, 1470, 1148 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 0.86 (t, 3H, J = 6.7 Hz, CH_3), 1.24 (m, 24H, 12 × CH_2), 1.55–1.59 (m, 2H, 2 × H-1'), 3.54–3.57 (m, 2H, H-4, H-5), 3.83–3.87 (m, 1H, H-2), 4.15–4.19 (m, 2H, H-3, H-5); ^{13}C NMR (100 MHz, CD_3OD): δ 14.4 (CH_3), 23.7 (CH_2), 27.3 (CH_2), 29.4 (CH_2), 30.5 (CH_2), 30.7 (3 × CH_2), 30.8 (5 × CH_2), 33.1 (CH_2), 51.3 (C-4), 69.9 (C-5), 73.4 (C-3), 81.2 (C-2). Anal. Calcd for $C_{18}H_{38}ClNO_2$: C, 64.35; H, 11.40; N, 4.17. Found: C, 64.40; H, 11.36; N, 4.22.

4.1.39. (2*S*,3*S*,4*S*)-4-Acetamido-2-tetradecyltetrahydrofuran-3-yl acetate (50)

To a solution of **1.HCl** (37.50 mg, 0.11 mmol) in dry pyridine (3.60 mL) were successively added Ac_2O (0.21 mL, 2.23 mmol) and DMAP (6.80 mg, 0.056 mmol). The resulting mixture was stirred at room temperature for 17 h, then concentrated and co-evaporated three times with toluene. The obtained residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 1:5) to afford 34.70 mg (81%) of crystalline compound **50**; mp 113–114 °C (recrystallized from ethyl acetate); {$[\alpha]_D^{22}$ −29.2 (*c* 0.24, $CHCl_3$); lit.[18] $[\alpha]_D^{26}$ –24.0 (*c* 0.60, $CHCl_3$); lit.[22a] $[\alpha]_D^{23}$ –23.5 (*c* 0.40, $CHCl_3$); lit.[37] $[\alpha]_D^{23}$ –26.4 (*c* 0.50, $CHCl_3$); lit.[38] $[\alpha]_D^{22}$ –22.6 (*c* 1.00, $CDCl_3$)}. IR (neat) υ_{max} 3213, 3066, 2991, 2946, 2916, 2850, 1747, 1739 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 0.88 (t, 3H, CH_3, J = 6.8 Hz, CH_3), 1.25 (m, 24H, 12 × CH_2), 1.40–1.51 (m, 2H, 2 × H-1'), 1.99 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 3.60 (t, 1H, $J_{5,5}$ = 8.2 Hz, $J_{5,4}$ = 8.2 Hz, H-5), 3.89–3.93 (m, 1H, H-2), 4.08 (t, 1H, $J_{5,5}$ = 8.3 Hz, $J_{5,4}$ = 8.3 Hz, H-5), 4.78–4.85 (m, 1H, H-4), 5.38 (dd, 1H, $J_{4,3}$ = 5.1 Hz, $J_{3,2}$ = 3.4 Hz, H-3), 5.68 (m, 1H, NH); ^{13}C NMR (100 MHz, CD_3OD): δ 14.1 (CH_3), 20.7 (CH_3), 22.7 (CH_2), 23.1 (CH_3), 26.0 (CH_2), 29.3 (2 × CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (6 × CH_2), 31.9 (CH_2), 51.3 (C-4), 69.9 (C-5), 73.5 (C-3), 81.2 (C-2), 169.8 (C=O), 169.8 (C=O). Anal. Calcd for $C_{22}H_{41}NO_4$: C, 68.89; H, 10.77; N, 3.65. Found: C, 68.85; H, 10.80; N, 3.62.

4.1.40. (2*S*,3*S*,4*R*)-4-Acetamido-2-tetradecyltetrahydrofuran-3-yl acetate (51)

By the similar reaction conditions as described for the preparation of **50**, compound **5.HCl** (41.20 mg, 0.11 mmol), Ac_2O (0.23 mL, 2.45 mmol) and DMAP (7.50 mg, 0.061 mmol) in pyridine (3.90 mL) afforded after flash chromatography on silica gel (*n*-hexane/ethyl acetate, 1:5) 37.20 mg (85%) of derivative **51** as white crystals; mp 71–73 °C (recrystallized from CH_2Cl_2/*n*-heptane); {$[\alpha]_D^{23}$ −8.2 (*c* 0.15, $CHCl_3$); lit.[14b] $[\alpha]_D^{23}$ +9.9 (*c* 0.26, $CHCl_3$) for *ent*-**51**}. IR (neat) υ_{max} 3278, 2914, 2848, 1746, 1652, 1552, 1372 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 0.88 (t, 3H, J = 6.7 Hz, CH_3), 1.25 (m, 24H, 12 × CH_2), 1.45–1.55 (m, 2H, 2 × H-1'), 1.99 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 3.52 (dd, 1H, $J_{5,5}$ = 8.3 Hz, $J_{5,4}$ = 3.5 Hz, H-5), 3.91–3.95 (m, 1H, H-2), 4.24–4.31 (m, 2H, H-4, H-5), 5.16–5.17 (m, 1H, H-3), 5.91 (br s 1H, NH); ^{13}C NMR (100 MHz, CD_3OD): δ 14.1 (CH_3), 20.8 (CH_3), 22.7 (CH_2), 23.2 (CH_3), 26.2 (CH_2), 28.7 (CH_2), 29.3 (CH_2), 29.5 (2 × CH_2), 29.6 (3 × CH_2), 29.7 (3 × CH_2), 31.9 (CH_2), 57.0 (C-4), 71.0 (C-5), 78.2 (C-3), 80.2 (C-2), 169.9 (C=O), 170.4 (C=O). Anal. Calcd for $C_{22}H_{41}NO_4$: C, 68.89; H, 10.77; N, 3.65. Found: C, 68.91; H, 10.74; N, 3.69.

4.1.41. X-ray techniques

Single crystal of **28** suitable for X-ray diffraction was obtained from *n*-hexane by slow evaporation at room temperature. The intensities were collected at 173 K on an Oxford Diffraction XCalibur2 CCD diffractometer using Mo Kα radiation (λ = 0.71073 Å). Selected crystallographic and other relevant data for compound **28** are listed in Table 3. The structure was solved by direct methods.[41] All non-hydrogen atoms were refined anisotropically by full-matrix least squares calculations based on F^2.[41] All hydrogen atoms were included in calculated positions as riding atoms, with SHELXL97[41] defaults. The PLATON[42] programme was used for structure analysis and molecular and crystal structure drawings.

4.1.42. Supplementary data

Complete crystallographic data for the structural analysis have been deposit with the Cambridge Crystallographic Data Centre, CCDC No. 980202 for compound **28**. These data can be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

4.2. Antiproliferative/cytotoxic activity

4.2.1. Cell culture

The following human cancer cell lines were used for this study: Jurkat (human acute T-lymphoblastic leukemia), HeLa (cervical carcinoma cells), MDA-MB-231 and MCF-7 (breast cancer cells), HCT-116 (human colon carcinoma), Caco -2 (human colon carcinoma) and non-cancerous cell line NiH 3T3 (mouse fibroblasts). Jurkat, HCT-116, MCF-7, Caco-2 and HeLa cells were maintained in RPMI 1640 medium. MDA-MB-231 and NiH 3T3 cell lines were maintained in growth medium consisting of high glucose Dulbecco's Modified Eagle Medium. Both of these media were supplemented with Glutamax, and with 10% (V/V) foetal calf serum, penicillin (100 IU × mL^{-1}), and streptomycin (100 mg × mL^{-1}) (all from Invitrogen, Carlsbad, CA USA), in the atmosphere of 5% CO_2 in humidified air at 37 ^{o}C. Cell viability, estimated by the trypan blue exclusion, was greater than 95% before each experiment.

4.2.2 Cytotoxicity assay

The cytotoxic effect of the tested compounds was studied using the colorimetric microculture assay with the MTT endpoint.[43] The amount of MTT reduced to formazan was proportional to the number of viable cells. Briefly, 5×10^3 cells were plated per well in 96-well polystyrene microplates (Sarstedt, Germany) in the culture medium containing tested chemicals at final concentrations 10^{-4}–10^{-6} mol × L^{-1}. After 72 h incubation, 10 μL of MTT (5 mg × mL^{-1}) were added into each well. After an additional 4 h, during which insoluble formazan was formed, 100 μL of 10% (m/m) sodium dodecylsulfate were added into each well and another 12 h were allowed for the formazan to be dissolved. The absorbance was measured at 540 nm using the automated uQuant™ Universal Microplate Spectrophotometer (Biotek Instruments Inc., Winooski, VT USA). The blank corrected absorbance of the control wells was taken as 100% and the results were expressed as a percentage of the control.

Acknowledgements

The present work was supported by the Grant Agency (No. 1/0568/12, No. 1/0398/14 and No. 1/0322/14) of the Ministry of Education, Slovak Republic. We wish to thank Dr. Juraj Kuchár (P. J. Šafárik University, Košice) for his assistance in X-ray measurements and Dr. Mária Vilková (P. J. Šafárik University, Košice) for NOE experiments.

References

1. (a) Lorente, A.; Lamariano-Merketegi, J.; Albericio, F.; Álvarez, M. *Chem. Rev.* **2013**, *113*, 4567–4610; (b) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407–2474 and references cited therein.
2. Kuroda, I.; Musman, M.; Ohtani, I. I.; Ichiba, T.; Tanaka, J.; Gravalos, D. G.; Higa, T. *J. Nat. Prod.* **2002**, *65*, 1505–1506.
3. Ledroit, V.; Debitus, C.; Lavaud, C.; Massiot, G. *Tetrahedron Lett.* **2003**, *44*, 225–228.
4. For biological activity of jaspine B and its stereoisomers, see: Refs. 2, 3 and (a) Canals, D.; Mormeneo, D.; Fabriàs, G.; Llebaria, A.; Casas, J.; Delgado, A. *Bioorg. Med. Chem.* **2009**, *17*, 235–241; (b) Ghosal, P.; Ajay, S.; Meena, S.; Sinha, S.; Shaw, A. K. *Tetrahedron: Asymmetry* **2013**, *24*, 903–908; (c) Salma, Y.; Lafont, E.;

Therville, N.; Carpentier, S.; Bonnafé, M.-J.; Levade, T.; Génisson, Y.; Andrieu-Abadie, N. *Biochem. Pharmacol.* **2009**, *78*, 477–485; (d) Jayachitra, G.; Sudhakar, N.; Anchoori, R. K.; Rao, B. V.; Roy, S.; Banerjee, R. *Synthesis* **2010**, 115–119; (e) Xu, J.-M.; Zhang, E.; Shi, X.-J.; Wang, Y.-C.; Yu, B.; Jiao, W.-W.; Guo, Y.-Z.; Liu. H.-M. *Eur. J. Med. Chem.* **2014**, *80*, 593–604; (f) Santos, C.; Fabing, I.; Saffon, N.; Ballereau, S.; Génisson, Y. *Tetrahedron* **2013**, *69*, 7227–7233; (g) Liu, J.; Du, Y.; Dong, X.; Meng, S.; Xiao, J.; Cheng, L. *Carbohydr. Res.* **2006**, *341*, 2653–2657.

5. (a) Wennekes, T.; van den Berg, R. J. B. H. N.; Boot, R. G.; van der Marel, G. A.; Overkleeft, H. S.; Aerts, J. M. F. G. *Angew. Chem. Int. Ed.* **2009**, *48*, 8848–8868, and also see: (b) Delgado, A.; Casas, J.; Llebaria, A.; Abad, J. L.; Fabrias, G. *Biochim. Biophys. Acta* **2006**, *1758*, 1957–1977; (c) Kolter, T.; Sandhoff, K. *Angew. Chem. Int. Ed.* **1999**, *38*, 1532–1568.
6. (a) Yoshimitsu, Y.; Oishi, S.; Miyagaki, J.; Inuki, S.; Ohno, H.; Fujii, N. *Bioorg. Med. Chem.* **2011**, *19*, 5402–5408; (b) Yoshimitsu, Y.; Miyagaki, J.; Oishi, S.; Fuji, N.; Ohno, H. *Tetrahedron* **2013**, *69*, 4211–4220.
7. (a) Salma, Y.; Ballereau, S.; Ladeira, S.; Lepetit, C.; Chauvin, R.; Andrieu-Abadie, N.; Génisson, Y. *Tetrahedron* **2011**, *67*, 4253–4262; (b) Salma, Y.; Ballereau, S.; Maaliki, C.; Ladeira, S.; Andrieu-Abadie, N.; Génisson, Y. *Org. Biomol. Chem.* **2010**, *8*, 3227–3243.
8. For aza-analogue of jaspine B, see: (a) Rives, A.; Ladeira, S.; Levade, T.; Andrieu-Abadie, N.; Génisson, Y. *J. Org. Chem.* **2010**, *75*, 7920–7923. For sulfur and selenium analogues of **1**, see: (a) Jeon, H.; Bae, H.; Baek, D. J. Kwak, Y.-S.; Kim, D.; Kim, S. *Org. Biomol. Chem.* **2011**, *9*, 7237–7242.
9. For recent review on syntheses of (+)-jaspine B and 2-*epi*-jaspine B, see: Abraham, E.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Tetrahedron: Asymmetry* **2008**, *19*, 1027–1047, and also see: Ballereau, S.; Baltas, M.; Génisson, Y. *Curr. Org. Chem.* **2011**, *15*, 953–986.
10. For total syntheses of jaspine B (**1**) from (*S*)-Garner's aldehyde, see: Ref. 4b and (a) Passiniemi, M.; Koskinen, A. M. P. *Tetrahedron Lett.* **2008**, *49*, 980–983; (b) Inuki, S.; Yoshimitsu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2009**, *11*, 4478–4481; (c) Yoshimitsu, Y.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2010**, *75*, 3843–3846; (d) Inuki, S.; Yoshimitsu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2010**, *75*, 3831–3842; (e) Passiniemi, M.; Koskinen, A. M. P. *Org. Biomol. Chem.* **2011**, *9*, 1774–1783; (f) Jana, A. K.; Panda, G. *RSC Adv.* **2013**, *3*, 16795–16801. For total

syntheses of 2-*epi*-jaspine B (**3**) from (*S*)-Garner's aldehyde, see: Refs. 6b, 10c, 10e-f. For total syntheses of 3-*epi*-jaspine B (**4**) and *ent*-**5** from (*S*)-Garner's aldehyde, see: Refs. 6b, 10c, 10e.

11. For total synthesis of *ent*-**1**, *ent*-**3**, *ent*-**4** and **5** from (*R*)-Garner's aldehyde, see Ref. 6a.
12. For total synthesis of *ent*-**3** from D-serine methyl ester, see: (a) Lee, D. *Synlett* **2012**, *23*, 2840–2844.
13. For total synthesis of jaspine B (**1**) from D-glucose, see: (a) Schmiedel, V. M; Stefani, S.; Reissig, H.-U. *Beilstein J. Org. Chem.* **2013**, *9*, 2564–2569. For syntheses of *ent*-**1** from D-glucose, see: Refs. 4d, 13a and (b) Cruz-Gregorio, S.; Espinoza-Rojas, C.; Quintero, L.; Sartillo-Piscil, F. *Tetrahedron Lett.* **2011**, *52*, 6370–6371; (c) Rao, G. S.; Chandrasekhar, B.; Rao, B. V. *Tetrahedron: Asymmetry* **2012**, *23*, 564–569. For total synthesis of **3** and *ent*-**3** from D-glucose, see: Ref. 13a. For total synthesis of *ent*-**5** from D-glucose, see: Ref. 4d.
14. For the formal synthesis of jaspine B (**1**) from D-xylose, see: (a) Zhao, M.-L.; Zhang, E.; Gao, J.; Zhang, Z.; Zhao, Y.-T.; Qu, W.; Liu, H.-M. *Carbohydr. Res.* **2012**, *351*, 126–129. For total synthesis of *ent*-**1** and *ent*-**5** from D-xylose, see: (b) Martinková, M.; Mezeiová, E.; Gonda, J.; Jacková, D.; Pomikalová, K. *Tetrahedron: Asymmetry* **2014**, *25*, 750–766.
15. For total synthesis of **3** from D-ribose, see: (a) Rao, G. S.; Rao, B. V. *Tetrahedron Lett.* **2011**, *52*, 4861–4864.
16. For total synthesis of *ent*-**3** from 3-amino-3-deoxy-D-ribofuranose, see: (a) Sánchez-Eleuterio, A.; Quintero, L.; Sartillo-Piscil, F. *J. Org. Chem.* **2011**, *76*, 5466–5471.
17. For total synthesis of *ent*-**3** and **4** from D-mannose, see: (a) Martinková, M.; Gonda, J.; Pomikalová, K.; Vilková, M. *Tetrahedron* **2013**, *69*, 8228–8244.
18. For total synthesis of **1** from L-ascorbic acid, see: (a) Rao, G. S.; Rao, B. V. *Tetrahedron Lett.* **2011**, *52*, 6076–6079.
19. For the formal synthesis of **4** from D-isoascorbic acid, see: (a) Rao, G. S.; Sudhakar, N.; Rao, B. V.; Basha, S. J. *Tetrahedron: Asymmetry* **2010**, *21*, 1963–1970.
20. For total synthesis of **1** and *ent*-**1** from D-erythronolactone, see: Ref. 4f.
21. For total synthesis of **1** from D-glyceraldehyde, see: (a) Vichare, P.; Chattopadhyay, A. *Tetrahedron: Asymmetry* **2010**, *21*, 1983–1987.
22. For total synthesis of **1** from L-tartaric acid, see: (a) Ichikawa, Y.; Matsunaga, K.; Masuda, T.; Kotsuki, H.; Nakano, K. *Tetrahedron* **2008**, *64*, 11313–11318. For total

synthesis of **3** from diethyl D-tartrate, see: (b) Reddipalli, G.; Venkataiah, M.; Mishra, M. K.; Fadnavis, N. W. *Tetrahedron: Asymmetry* **2009**, *20*, 1802–1805.

23. For total synthesis of *ent*-**1** from L-threitol, see: (a) Prasad, K. R.; Penchalaiah, K. *Tetrahedron: Asymmetry* **2011**, *22*, 1400–1403.
24. For total synthesis of **1** from D-*ribo*-phytosphingosine, see: (a) Bae, H.; Jeon, H.; Baek, D. J.; Lee, D.; Kim, S. *Synthesis* **2012**, *44*, 3609–3612. For total synthesis of **3** from D-*ribo*-phytosphingosine, see: Refs. 4a, 24a.
25. For total synthesis of **1** from (*R*)-2-chlorohept-6-enal, see: (a) Dhand, V.; Chang, S.; Britton, R. *J. Org. Chem.* **2013**, *78*, 8208–8213.
26. For total synthesis of *ent*-**1** and *ent*-**5** from (3*R*,4*R*)-hexa-1,5-diene-3,4-diol, see: (a) Lin, C.-W.; Liu, S.-W.; Hou, D.-R. *Org. Biomol. Chem.* **2013**, *11*, 5292–5299.
27. For total synthesis of **1** from 2,2-dimethyl-1,3-dioxan-5-one, see: (a) Enders, D.; Terteryan V.; Paleček J. *Synthesis* **2008**, 2278–2282.
28. For total synthesis of **1** from (*E*)-4-(benzyloxy)but-2-en-1-ol, see: Ref. 7b.
29. For total synthesis of **1**, **3**, **4** and *ent*-**5** from 2-vinyloxirane, see: (a) Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Eur. J. Org. Chem.* **2011**, 1514–1519.
30. Sánchez-Sancho, F.; Valverde, S.; Herradón, B. *Tetrahedron: Asymmetry* **1996**, *7*, 3209–3246.
31. For the preparation of *ent*-**16**, see: Ref. 14b and (a) Sato, H.; Maeba, T.; Yanase, R.; Yamaji-Hasegawa, A.; Kobayashi, T.; Chida, N. *J. Antibiot.* **2005**, *58*, 37–49.
32. Cabaret, D.; Wakselman, M. *Can. J. Chem.* **1990**, *68*, 2253–2257.
33. (a) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001–3003; (b) Satam, V.; Harad, A.; Rajule, R.; Pati, H. *Tetrahedron* **2010**, *66*, 7659–7706.
34. Ohno, M.; Fujita, K.; Nakai, H.; Kobayashi, S.; Inoue, K.; Nojima, S. *Chem. Pharm. Bull.* **1985**, *33*, 572–582.
35. Nishikawa, T.; Asai, M.; Ohyabu, N.; Isobe, M. *J. Org. Chem.* **1998**, *63*, 188–192.
36. (a) Mettu, R.; Thatikonda, N. R.; Olusegun, O. S.; Vishvakarma, R.; Vaidya, J. R. *ARKIVOC* **2012**, 421–436; (b) Martinková, M.; Pomikalová, K.; Gonda, J. *Chem. Pap.* **2013**, *67*, 84–91; (c) Baskaran, S.; Baig, M. H. A.; Banerjee, S.; Baskaran, C.; Bhanu, K.; Deshpande, S. P.; Trivedi, G. K. *Tetrahedron* **1996**, *52*, 6437–6452.
37. Abraham, E.; Brock, E. A.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Perkins, J. H.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E.

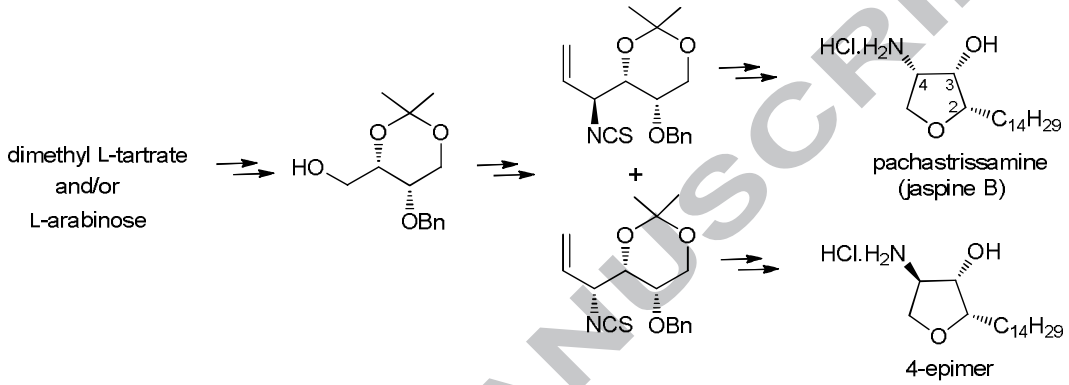
M.; Scott, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 1665–1673.

38. van den Berg, R. J. B. H. N.; Boltje, T. J.; Verhagen, C. P.; Litjens, R. E. J. N.; van der Marel, G. A.; Overkleeft, H. S. *J. Org. Chem.* **2006**, *71*, 836–839.
39. Budovská, M.; Pilátová, M.; Varinská, L.; Mojžiš, J.; Mezencev, R. *Bioorg. Med. Chem.* **2013**, *21*, 6623–6633.
40. Izumi, M.; Tsuruta, O.; Hashimoto, H. *Carbohydr. Res.* **1996**, *280*, 287–302.
41. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112–122.
42. Spek, A. L. *J. Appl. Crystallogr.* **2003**, *36*, 7–13.
43. Mosmann, T. *J. Immunol. Methods* **1983**, *65*, 55–63.

Graphical Abstract

Total synthesis of pachastrissamine together with its 4-*epi*-congener via [3,3]-sigmatropic rearrangements and antiproliferative/cytotoxic evaluation

Miroslava Martinková,* Eva Mezeiová, Milica Fabišíková, Jozef Gonda, Martina Pilátová, Ján Mojžiš



Highlights

- The total synthesis of pachastrissamine and its 4-*epi*-congener was accomplished.
- The cornerstone of this strategy was a [3,3]-heterosigmatropic rearrangement.
- Crystallographic analysis of a key structure was performed.
- A series of synthesized compounds was evaluated for the anticancer activity.