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Total synthesis and antiproliferative/cytotoxic profiling of 2-*epi*-jaspine B

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ABSTRACT

A straightforward access to 2-*epi*-jaspine B (**4**.**HCl**) has been developed. Key to the approach was the use of Overman rearrangement for the instalment of a stereocentre bearing a nitrogen atom. Subsequent rational execution of the stereoselective transformations furnished the functionalized scaffold **38**, whose coupling with a lipophilic segment under Wittig conditions, followed by deprotection and a THF core construction, completed the convergent synthesis of 2-epimer of **1**. The final anhydrophytosphingosine **4**.**HCl** was screened for its antiproliferative/cytotoxic activity employing multiple human cancer cell lines. In vitro evaluation revealed that 2-*epi*-jaspine B exhibited significant antitumour growth inhibitory activity against all used cells.

1. Introduction

Over the past 10 years, anhydrophytosphingosines have emerged on the scene as an attractive and timely target for the total synthesis due to their significant biological activity as well as the architecturally interesting structures. Jaspine B (**1**, also referred as pachastrissamine, Fig. 1) represents such structural archetype that has been isolated independently from two marine sponges[1,2] together with its oxazolidine analogue, jaspine A (**2**, Fig. 1).[2] From the biosynthetic standpoint is highly likely that pachastrissamine would be derived from D-*ribo*-phytosphingosine **3**[3,4] considering the same number of carbon atoms in the backbone as well as the same stereochemical C-2/C-3 amino alcohol motif (used phytosphingosine numbering, see Fig. 1) for both **1** and **3**. Jaspine B has been reported to exhibit significant in vitro cytotoxicity against multiple human cancer cell lines such as A-549,[1,2,5–7] HT-29,[1] MeL-28,[1,8] MCF-7,[6,9–11] KB,[6] HCT-116,[7,11–13] U2OS,[12] MDA-231,[11,13,14] HeLa,[11,14] CNE,[14] MGC-803,[10] EC-9706,[10] PC-3,[7,13] A-375,[15] WM-115,[15] Caco-2,[11] Jurkat,[11] SNU-638[13] and Caki-1[13] with IC_{50} in the micromolar to submicromolar ranges. En passant, this conformationally constrained sphingolipid and all its stereocongeners inhibit both forms of sphingosine kinase (SphK1 and SphK2) with moderate to high activities.[16,17]

Although the first synthesis[18] of anhydrophytosphingosine molecule prior to isolation of jaspine B led ultimately to the production of 2-*epi*-jaspine B (**4**), its structure including relative stereochemistry was confirmed later through the asymmetric synthesis of the truncated derivative **4a**[19–21] (Fig. 1), this compound has attracted less attention. To date, 18 total syntheses of **4** have been reported employing especially chiral-pool approaches, which commenced from D-*ribo*-phytosphingosine **3**,[5,22–25] (*S*)-Garner's aldehyde,[17,26–29] L-serine,[30] diethyl D-tartrate,[31] D-ribose,[32] D-glucose[33] and D-galactal.[34] Further, two specific methods involving the highly diastereoselective conjugate addition of chiral lithium amide to methyl (*E*)-4-(triisopropylsilyloxy)but-2-enoate[35,36] and an enantioselective palladium-catalyzed allylic amination of the racemic 2-vinyloxirane[37] have been used as the key transformations for the construction of 2-*epi*-jaspine B (Fig. 2). On the other hand, a minor synthetic interest in comparison with **4** has been devoted towards *ent*-**4** and only five independent strategies utilizing (*R*)-Garner's aldehyde,[16] D-serine methyl ester,[38] D-mannose,[39] D-glucose[33] and 3-amino-3-deoxy-α-D-ribofuranose[40] have been performed (Fig. 3).

2-*epi*-Jaspine B (**4**) was evaluated for in vitro cytotoxicity against several human cancer cell lines A-549,[5,34] MCF-7,[9,34] DU-145,[34] A-172,[34] PLC/PRF/5,[34] 786-O[34] and DLD-1,[34] its antipode *ent*-**4** (in the form of HCl salt) was assessed for the aforementioned activity on MDA-MB-231,[11] MCF-7,[11] HCT-116,[11] Caco-2,[11] Jurkat[11] and HeLa[11] and compound *ent*-**4**.**HCl** was found to be less active than jaspine B (**1**). Recently, we have accomplished a stereoconvergent synthesis of jaspine B and its five stereoisomers[11,39,41] and revealed that four members of anhydrophytosphingosine family exhibit

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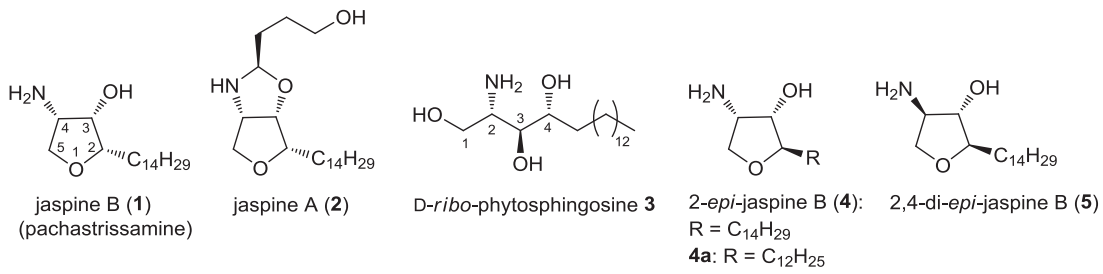


Fig. 1. Structures of various sphingolipids.

interesting antiproliferative/cytotoxic activities.[11] These promising findings as well as our ongoing studies of how the employed chiral allylic templates derived from the simple furanoses can influence the stereochemical outcome of the two types of aza-Claisen rearrangement prompted us to encompass a construction of 2-*epi*-jaspine B (**4**) from L-arabinose utilizing our approach. Moreover, compound **4** was found to show good sphingosine kinase (SphK1) inhibitory activity (IC_{50} = 3.9 μM) comparable to that of the conventional agent N,N-dimethylsphingosine (IC_{50} = 2.8 μM).[16] Pachastrissamine **1** demonstrated lower potency of the aforementioned inhibition (IC_{50} = 4.6 μM).[16]

2. Chemistry

2.1. Results and discussion

As shown in Scheme 1, our investigation began with the construction of the acetonide foldamer **6**. Commencing with the known 1,2-O-isopropylidene-5-O-trityl-β-L-arabinofuranose **7**,[11] the remaining free hydroxyl functionality was bezylated, using standard reaction conditions such as BnBr, NaH in DMF, to afford the fully protected derivative **8** in 95% yield.[42] Following the cleavage of the triphenylmethyl group of **8** (CSA, CH_2Cl_2/MeOH), the liberated primary hydroxyl in **9**[43–46] (81%) was exposed to BzCl in pyridine to provide the corresponding benzoate ester **10**[43,45] in 91% yield (Scheme 1). Removal of the acetonide moiety in **10** with 80% TFA gave a mixture of the anomeric furanoses **11** whose $NaIO_4$-mediated oxidative fragmentation followed by $NaBH_4$ workup furnished diol **12** (94%). A two-step protocol involving protection (2,2-DMP, *p*-TsOH)/deprotection (K_2CO_3, MeOH) manipulations resulted in the formation of the requisite derivative **6** via intermediate **13** in 83% yield starting from **12**.

The next objective was the effective transformation of the alcohol **6** to suitable substrates for the rearrangement reactions. Subsequently realized oxidation/Wittig olefination of **6** provided exclusively (*E*)-α,β-unsaturated ester **14** in 98% yield over two steps (Scheme 2); the (*E*)-geometry within **14** was identified through the vinyl proton coupling constant value (J_{trans} = 15.7 Hz). Exposure of **14** to DIBAl-H generated allylic alcohol **15** in a yield of 97%. After we achieved the construction of the aforementioned substrate **15**, its transformation to the corresponding imidate **16** was accomplished. Its formation proceeded efficiently when **15** was treated with NaH and trichloroacetonitrile. After 30 min, ^{1}H NMR spectrum of the crude reaction mixture showed the complete consumption of the starting alcohol **15**. The Overman rearrangement of imidate **16** was taken place in *o*-xylene and in the presence of K_2CO_3 and furnished the desired products **17** and **18** (**17**:**18** ≈ 50:50 ratio) in high yields (91–97%, Table 1). Column chromatography then allowed the straightforward separation of both products. We also prepared thiocyanate **19** and to accomplish it, the conversion of the **15** into **19** (93%) was carried out via the known two-step procedure[11,41] (Scheme 2). The thermal aza-Claisen rearrangement of **19** was realized either at 70 °C or at 90 °C to afford the corresponding isothiocyanates **20** and **21** in 93% and 90% combined yields, respectively. The stereoselectivities were similar to those observed in the Overman reaction of **16** (**20**:**21** ≈ 50:50 ratio, Scheme 2). Moreover, the resultant rearranged products **20** and **21** were obtained as an inseparable mixture of diastereoisomers and thus we converted only Overman's derivatives **17** and **18** into the required oxazolidinones **24** and **25**, respectively (vide infra). The same cyclic carbamates could be also built up from the isothiocyanates **20** and **21** applying our elaborated protocol.[11,41] Compound **24** allowed then a direct access to the 2-*epi*-jaspine B (Scheme 5). 2,4-Di-*epi*-jaspine B (**5**), which exhibits significant inhibitory activities against SphKs and atypical protein kinase C,[16] could be available from **25**. Our new synthetic approach to **5** and further biological investigations are underway and will be reported in due course.

As we had already prepared amides **17** and **18**, the stage was now set for the confirmation of the newly constructed stereochemistry in these products and for this purpose, chemical correlations of **17**, **18** and the known derivative **26**[11] to the common products were executed (Scheme 4). To reach the requisite oxazolidinones **24** and **25**, a two-step procedure involving ozonolysis (O_3, –78 °C) of both trichloroacetamides **17** and **18** followed by the reductive work up ($NaBH_4$) was performed to furnish the corresponding alcohols **22** and **23** in 98% and 88% yields, respectively. Their DBU treatment

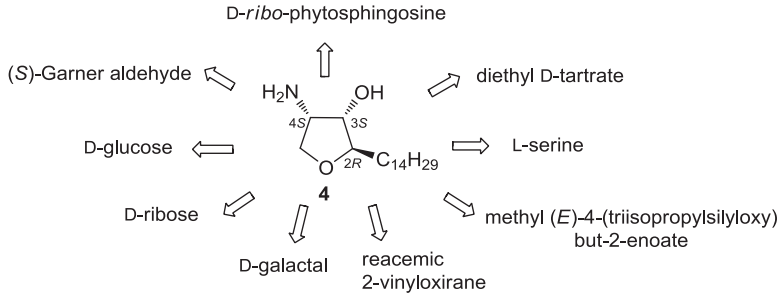


Fig. 2. Reported syntheses of 2-*epi*-jaspine B (2001–2015).

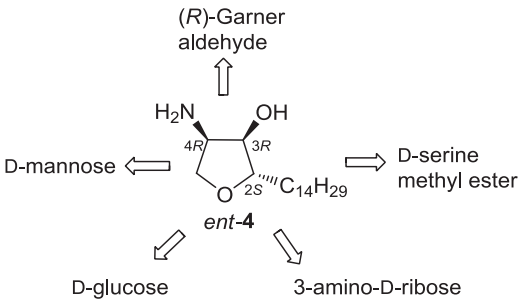


Fig. 3. Published syntheses of *ent*-**4**.

caused an intramolecular cyclization to afford the aforementioned cyclic carbamate **24** (89%) and **25** (85%, Scheme 3). To assign the stereochemistry at the C-4 position in **24** and **25**, our next task was to modify these compounds and also derivative **26**[11] to the common ketones **33** and **34**, and this was effectively accomplished by using the approach illustrated in Scheme 4.

Thus, benzylation of these three derivatives **24**–**26** under standard conditions (BnBr, NaH, DMF) proceeded without problem and afforded the corresponding fully protected structures **27** (92%), **28** (96%) and **29** (91%). The chemoselectivity of the catalytic hydrogenation (H_2, 10% Pd/C) in **27**–**29** secured the formation of the alcohols **30**, **31** and **32** in 97%, 94% and 96% yields, respectively (Scheme 4). Their IBX oxidation successfully led to the desired common ketone **33** (78% from **30** and 81% from **32**) and **34** (89%).

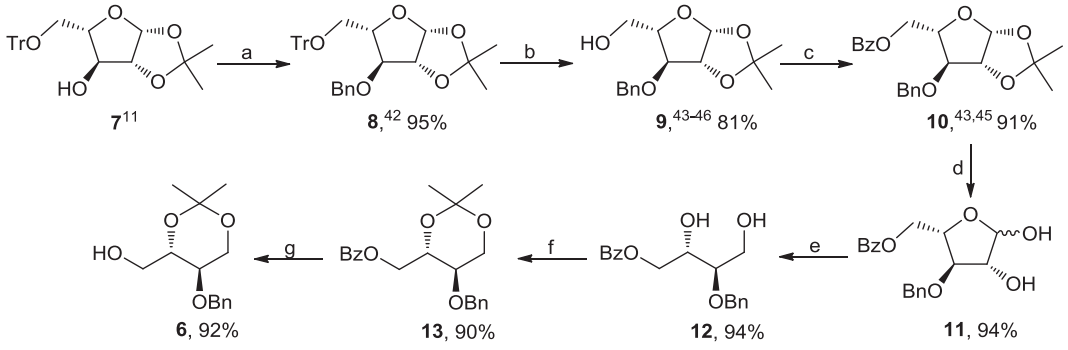
Table 1
Overman rearrangement of imidate **16**

Entry	Imidate	Conditions[a]	Time (h)	Ratio[b] **17**:**18**	Yield[c] (%)
1	**16**	MW, 130 °C	2	52:48	91
2	**16**	MW, 150 °C	0.5	51:49	97

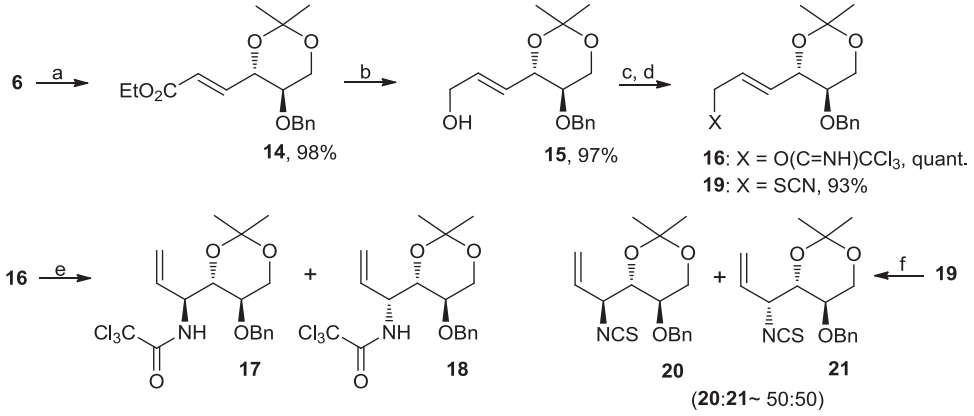
[a] In *o*-xylene, in the presence of K_2CO_3.
[b] Ratio in the crude reaction mixtures. Determined by ^1H NMR spectroscopy.
[c] Isolated combined yields.

The obtained derivative **33**, prepared independently from two diastereoisomers **24** and **26**, had the same spectroscopic data, melting point and specific rotation, revealing that oxazolidinone **24** is (4*S*)-configured. Consequently, the corresponding congener **25** must be (4*R*)-isomer.

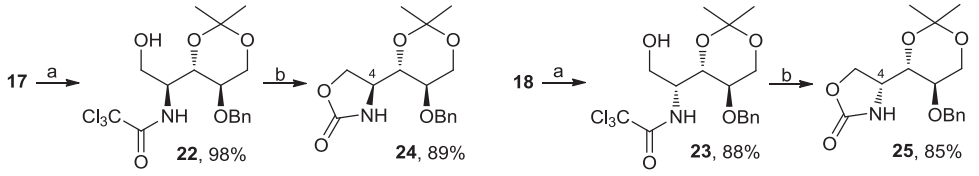
Having unambiguously determined the stereochemistry in both cycles **24** and **25**, our remaining task was to complete the synthesis of **4** as depicted in Scheme 5. Thus, the acetonide moiety of **24** was removed by treatment with *p*-TsOH in MeOH to produce the corresponding diol **35** (92%), wherein the liberated primary hydroxyl group was protected as the triphenymethyl ether **36** in 95% yield. The obtained product **36** was further benzylated (BnBr, NaH, TBAI), furnishing the protected compound **37** in 94% yield (Scheme 5). Exposure of **37** to *p*-TsOH in MeOH/CH_2Cl_2 resulted in the formation of alcohol **38** (92%). To achieve the coupling between a crude aldehyde derived from previously prepared **38** and the phosphonium salt, $C_{13}H_{27}PPh_3Br$,[39,47] the well-established Wittig reaction was executed to afford the (*Z*)-olefin **39** exclusively in 71% yield. The corresponding alkene **39** was reduced by the catalytic



Scheme 1. Reagents and conditions: (a) BnBr, NaH, TBAI, DMF, 0 °C→rt; (b) CSA, CH_2Cl_2/MeOH (2:1), rt; (c) BzCl, pyridine, DMAP, 0 °C→rt; (d) 80% TFA, 0 °C; (e) (i) $NaIO_4$, MeOH/H_2O (1:1), rt; (ii) $NaBH_4$, MeOH/CH_2Cl_2 (4:1), 0 °C→rt; (f) 2,2-DMP, *p*-TsOH, CH_2Cl_2, rt; (g) K_2CO_3, MeOH, 0 °C→rt.



Scheme 2. Reagents and conditions: (a) (i) IBX, MeCN, reflux; (ii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt; (b) DIBAL-H, CH_2Cl_2, –50 °C→rt; (c) NaH, CCl_3CN, THF, 0 °C→rt, **16**; (d) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C→rt; (ii) KSCN, MeCN, 5 °C→rt, **19**; (e) Table 1; (f) Δ, *n*-heptane, 70 °C (23 h, 93%) and 90 °C (15 h, 90%).



Scheme 3. Reagents and conditions: (a) (i) O_3, MeOH/CH_2Cl_2 (5:1), –78 °C; (ii) $NaBH_4$, –78 °C→0 °C; (b) DBU, CH_2Cl_2, 0 °C→rt.

hydrogenation on 10% Pd/C to provide the saturated derivative **40** (89%). Finally, N-debenzylation of **40** (H_2, 10% Pd/C, 35% HCl) and subsequent treatment of the resulting protected phytosphingosine **41** {69%, $[\alpha]_D^{23} = +7.9$ (*c* 0.24, MeOH)} with 6 M HCl furnished **4**.**HCl** in 89% yield {$[\alpha]_D^{26} = +25.0$ (*c* 0.16, MeOH), lit.[36] {$[\alpha]_D^{21} = +15.5$ (*c* 0.9, MeOH)} (Scheme 5). The NMR data and also magnitude of the optical rotation were in accord with those reported for the corresponding enantiomers *ent*-**41** {lit.[39] $[\alpha]_D^{25} = -5.0$ (*c* 0.22, MeOH)} and *ent*-**4**.**HCl** {lit.[39] $[\alpha]_D^{22} = -29.6$ (*c* 0.48, MeOH)}. As a further confirmation of structure, we converted salt **4**.**HCl** into the acetylated products **42**[23,32,36] (75%). Again, the spectroscopic data and the specific rotation (both sign and magnitude) for **42** {$[\alpha]_D^{27} = -13.3$ (*c* 0.18, $CHCl_3$)} nicely matched the values published in the literature for the same product {lit.[23] $[\alpha]_D^{22} = -15.4$ (*c* 1.0, $CHCl_3$), lit.[32] $[\alpha]_D^{26} = -15.1$ (*c* 1.2, $CHCl_3$), lit.[36] $[\alpha]_D^{21} = -14.6$ (*c* 0.5, $CHCl_3$)}. As an additional determination of the stereochemistry, ^{1}H NMR NOE analyses on the N,O-acetylated derivative **42** have been carried out. As seen in Fig. 4, NOE experiments of **42** revealed *trans* relationship between protons H-2 and H-3 on the tetrahydrofuran skeleton. On the other hand, enhancements between H-3 and H-4 protons proved their *cis* orientation on the aforementioned ring.

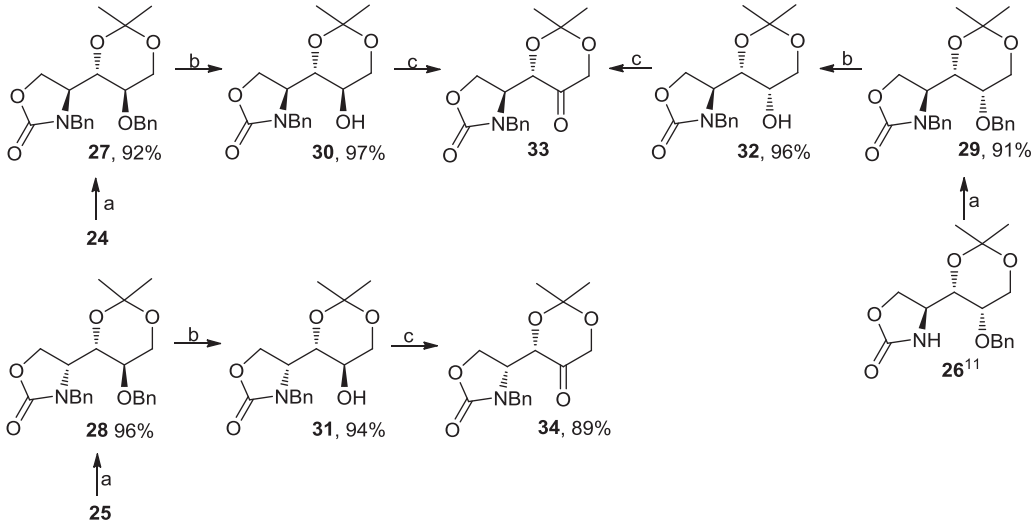
2.2. Antiproliferative/cytotoxic activity

The final 2-*epi*-jaspine B (**4**.**HCl**) was in vitro screened for its antiproliferative/cytotoxic activities against six different human cancer cell lines MDA-MB-231 (mammary gland adenocarcinoma), MCF-7 (mammary gland adenocarcinoma), HCT-116 (colon carcinoma), Caco-2 (colon carcinoma), Jurkat (acute T-lymphoblastic leukaemia), HeLa (cervical adenocarcinoma), and a non-malignant cell line NiH 3T3 (mouse fibroblasts) using the MTT assay. The obtained results are summarized in Table 2 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[48] (Table 2), on HCT-116, Caco-2 and NiH 3T3 cell lines they were not tested. Table 2 also includes the known IC_{50} values for the HCl salts of jaspine B (**1**.**HCl**) and *ent*-**4**.**HCl**.[11]

To allow comparison, most recently, Shaw and co-workers[34] reported in vitro anticancer activity for 2-*epi*-jaspine B (**4**) against seven cancer cell lines (A549: $IC_{50} = 4.8$ μM, DU-145: $IC_{50} = 2$ μM, MCF-7: $IC_{50} = 4.04$ μM, A-172: $IC_{50} = 4.59$ μM, PLC/PFR/5: $IC_{50} = 1.36$ μM, 786-O: $IC_{50} = 1.08$ μM, DLD-1: $IC_{50} = 0.5$ μM). As shown in Table 2, 2-*epi*-jaspine B (**4**.**HCl**) displayed higher or comparable antiproliferative/cytotoxic activities than conventional anticancer agents such as cisplatin, etoposide and doxorubicin. Compound **4**.**HCl** demonstrated remarkable in vitro potency on both leukaemia and solid tumour cell lines. Moreover, this compound was found to be more active on MDA-MB-231 and HCT-116 cells than natural jaspine B (**1**.**HCl**), whose IC_{50} values on these lines were at least 4× higher. On the other hand, the cytotoxicity of *ent*-**4**.**HCl** was significantly reduced, especially on MDA-MB-231 and HeLa cells.

3. Conclusions

In conclusion, the convergent total synthesis of cytotoxic 2-*epi*-jaspine B (**4**.**HCl**) has been performed from the commercially available and inexpensive L-arabinose. Key steps in the developed route are construction of the oxazolidinone **24** employing the Overman rearrangement to establish the stereocentre bearing the amino group and the Wittig transformation to build up the long hydrocarbon side chain. The final 2-epimer of the natural jaspine B demonstrated significant antiproliferative/cytotoxic activities against all tested cancer cell lines. This makes compound **4**.**HCl** an appropriate candidate for further screening and evaluation.



Scheme 4. Reagents and conditions: (a) BnBr, NaH, TBAI, 0 °C→rt; (b) H_2, 10% Pd/C, EtOH, rt; (c), IBX, MeCN, reflux, **33** (78% from **30**, 81% from **32**).

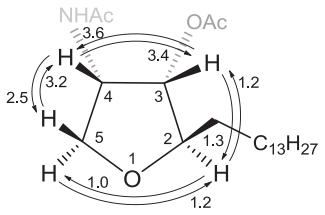
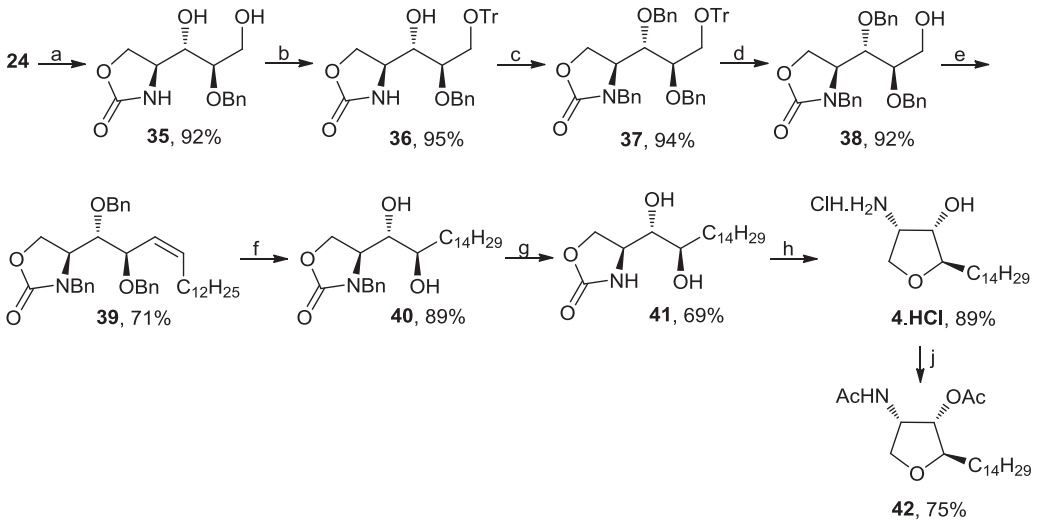


Fig. 4. Some selected NOE enhancements for **42**.

4. Experimental

4.1. Chemistry

All commercial reagents were used in the highest available purity from Aldrich, Merck and 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 chromatography (*n*-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 100.6 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 ($\delta = 0.0$), CD_3OD ($\delta = 4.84$) and C_6D_6 ($\delta = 7.15$) and for ^{13}C relative to $CDCl_3$ ($\delta = 77.0$), CD_3OD ($\delta = 49.05$) and C_6D_6 ($\delta = 128.02$). 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 *v* 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



Scheme 5. Reagents and conditions: (a) *p*-TsOH, MeOH, rt; (b) TrCl, pyridine, DMAP, 60 °C; (c) BnBr, NaH, TBAI, DMF, 0 °C→rt; (d) *p*-TsOH, MeOH/CH_2Cl_2, rt; (e) (i) IBX, MeCN, reflux; (ii) $C_{13}H_{27}PPh_3Br$, LHMDS, 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, 120 °C; (j) Ac_2O, pyridine, DMAP, rt.

Table 2
Antiproliferative activity of 2-*epi*-jaspine B 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
4.HCl	0.55 ± 0.08	0.7 ± 0.3	0.47 ± 0.25	0.35 ± 0.35	0.4 ± 0.14	0.45 ± 0.2	6.2 ± 0.7
ent-**4.HCl**[b]	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
1.HCl[b]	2.35 ± 1.20	0.41 ± 0.09	2.59 ± 1.02	0.35 ± 0.11	0.50 ± 0.27	0.61 ± 0.27	4.60 ± 0.90
Cisplatin[c]	14.7 ± 2.7	11.4 ± 2.4	NT	NT	12 ± 1.8	7.7 ± 2.3	NT
Etoposide[c]	21.2 ± 4.2	10.9 ± 2.1	NT	NT	1.2 ± 1.5	3.9 ± 2.3	NT
Doxorubicin[c]	0.2 ± 0.8	0.5 ± 0.024	NT	NT	0.078 ± 0.02	0.2 ± 0.06	NT

NT, not tested.
[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 Section 4.2).
[b] Values for the HCl salt of jaspine B (**1.HCl**) and *ent*-**4.HCl** were reported in Ref. 11 and were utilized from the same source.
[c] Values for the clinically available anticancer drugs were reported in Ref. 48 and were utilized from the same source.

(Hamilton). All reactions were performed under an atmosphere of nitrogen, unless otherwise noted.

4.1.1. 3-O-Benzyl-1,2-O-isopropylidene-5-O-trityl-β-L-arabinofuranose (**8**)[42]

To a solution of the known furanose **7**[11] (15.4 g, 35.6 mmol) in dry DMF (93 mL) that had been pre-cooled to 0 °C was added NaH (2.14 g, 53 mmol, 60% dispersion in mineral oil). After 5 min, TBAI (0.26 g, 0.71 mmol) was added, followed by dropwise addition of BnBr (5.1 mL, 43 mmol). The resulting mixture was stirred for 10 min at 0 °C and then at room temperature for another 30 min. The excess hydride was decomposed by the cautious addition of MeOH (1.1 mL). The mixture was then poured into ice-water (130 mL) and extracted with Et_2O (2 × 140 mL). The combined organic extracts were dried over Na_2SO_4, the solvent was evaporated, and the residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate, 9:1) to furnish 17.68 g (95%) of compound **8** as a colourless foam {$[\alpha]_D^{26}$ +1.1 (*c* 0.51, $CHCl_3$), lit.[42] $[\alpha]_D^{22}$ –55.2 (*c* 1.5, $CHCl_3$)}. IR (neat) υ_{max} 3058, 3031, 2935, 1448, 1209, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.18 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 3.23 (dd, 1H, *J* = 9.3 Hz, *J* = 7.9 Hz, H-5), 3.38 (dd, 1H, *J* = 9.3 Hz, *J* = 5.4 Hz, H-5), 4.11 (m, 1H, H-3), 4.31 (ddd, 1H, *J* = 7.7 Hz, *J* = 5.4 Hz, *J* = 2.3 Hz, H-4), 4.58–4.64 (m, 3H, H-2, OCH_2Ph), 5.87 (d, 1H, *J* = 4.0 Hz, H-1), 7.19–7.43 (m, 20H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1 (CH_3), 26.7 (CH_3), 63.6 (C-5), 71.5 (OCH_2Ph), 83.0 (C-3), 84.1 (C-4), 84.9 (C-2), 86.7 (C_{qTr}), 105.7 (C-1), 112.4 (C_q), 127.0 (3 × CH_{Ph}), 127.7 (2 × CH_{Ph}), 127.8 (7 × CH_{Ph}), 128.5 (2 × CH_{Ph}), 128.7 (6 × CH_{Ph}), 137.4 (C_i), 143.8 (3 × C_i). Anal. calcd for $C_{34}H_{34}O_5$: C, 78.14; H, 6.56. Found: C, 78.09; H, 6.61.

4.1.2. 3-O-Benzyl-1,2-O-isopropylidene-β-L-arabinofuranose (**9**)[43,44,46]

To a solution of **8** (17.45 g, 33 mmol) in CH_2Cl_2/MeOH (339 mL, 2:1) was added CSA (0.39 g, 1.7 mmol), and the resulting mixture was stirred at room temperature. After 5 h, the reaction was quenched by neutralization with Et_3N, solvents were removed in vacuo, and the crude product was flash-chromatographed through a short column of silica gel (*n*-hexane/ethyl acetate, 3:1) to afford 7.58 g (81%) of derivative **9** as white crystals; mp 73–74 °C (recrystallized from *n*-hexane/ethyl acetate); $[\alpha]_D^{26}$ –31.6 (*c* 0.23, $CHCl_3$) {lit.[43] mp 73–77 °C, $[\alpha]_D^{20}$ –22.4 (concentration and solvent not reported), lit.[44] mp 80–82 °C, $[\alpha]_D$ not reported, lit.[46] mp 77–78 °C, $[\alpha]_D^{20}$ –19.2 (*c* 1.7, $CHCl_3$)}. IR (neat) υ_{max} 3489, 2977, 2940, 2908, 2889, 1379, 1211, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 3.73–3.74 (m, 2H, 2 × H-5), 3.98 (d, 1H, *J* = 3.2 Hz, H-3), 4.20 (dt, 1H, *J* = 5.4 Hz, *J* = 5.4 Hz, *J* = 3.5 Hz, H-4), 4.56 (d, 1H, *J* = 11.7 Hz, OCH_2Ph), 4.65 (d, 1H, *J* = 11.7 Hz, OCH_2Ph), 4.68 (d, 1H, *J* = 4.1 Hz, H-2), 5.92 (d, 1H, *J* = 4.1 Hz, H-1), 7.26–7.38 (m, 5H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3 (CH_3), 27.1 (CH_3), 62.6 (C-5), 71.9 (OCH_2Ph), 82.7 (C-3), 85.2 (C-2), 85.5 (C-4), 105.6 (C-1), 112.9 (C_q), 127.7 (2 × CH_{Ph}), 128.0 (CH_{Ph}), 128.5 (2 × CH_{Ph}), 137.1 (C_i). Anal. calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.22; H, 7.23.

4.1.3. 5-O-Benzoyl-3-O-benzyl-1,2-O-isopropylidene-β-L-arabinofuranose (**10**)[43,45]

To a solution of **9** (7.41 g, 26.4 mmol) in dry pyridine (119 mL) that was cooled to 0 °C were successively added BzCl (3.7 mL, 32 mmol) and DMAP (0.32 g, 2.6 mmol). The resulting mixture was stirred for 10 min at 0 °C and then at room temperature for another 1.5 h. The mixture was concentrated and co-evaporated three times with toluene (3 × 20 mL). The residue was dissolved in EtOAc (132 mL) and washed with water (66 mL). The organic layer was dried over Na_2SO_4, the solvent was removed in vacuo, and the crude product was chromatographed on silica gel (*n*-hexane/ethyl acetate, 9:1) to give 9.25 g (91%) of compound **10** in the form of white crystals; mp 79–80 °C (recrystallized from *n*-hexane/ethyl acetate); $[\alpha]_D^{23}$ –19.9 (*c* 0.45, $CHCl_3$) {lits.[43,45] $[\alpha]_D$ and melting point not reported}. IR υ_{max} 2995, 2857, 1722, 1450, 1378, 1276, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 4.08 (d, 1H, *J* = 2.8 Hz, H-3), 4.39–4.43 (m, 2H, H-4), 4.48–4.50 (m, 2H, 2 × H-5), 4.58 (d, 1H, *J* = 11.9 Hz, OCH_2Ph), 4.65 (d, 1H, *J* = 11.9 Hz, OCH_2Ph), 4.69 (d, 1H, *J* = 3.9 Hz, H-2), 5.95 (d, 1H, *J* = 3.9 Hz, H-1), 7.25–7.31 (m, 5H, Ph), 7.40–7.44 (m, 2H, Ph), 7.53–7.58 (m, 1H, Ph), 7.99–8.01 (m, 2H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3 (CH_3), 27.2 (CH_3), 64.4 (C-5), 71.8 (OCH_2Ph), 82.3 (C-4), 82.7 (C-3), 84.8 (C-2), 105.8 (C-1), 113.1 (C_q), 127.8 (2 × CH_{Ph}), 128.0 (CH_{Ph}), 128.3 (2 × CH_{Ph}), 128.5 (2 × CH_{Ph}), 129.7 (2 × CH_{Ph}), 129.8 (C_i), 133.1 (CH_{Ph}), 137.0 (C_i), 166.1 (C═O). Anal. calcd for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29. Found: C, 68.79; H, 6.24.

4.1.4. (2S,3R)-3-(Benzyloxy)-2,4-dihydroxybutyl benzoate (**12**)

A solution of **10** (9.05 g, 23.5 mmol) in TFA/H_2O (4:1, 42 mL) was stirred at room temperature for 1.5 h. Then, EtOAc (92 mL) and water (83 mL) were added, and the resulting mixture was neutralized with solid $NaHCO_3$ (~38.7 g). The insoluble material was filtered off, and the filtrate was washed with the further portions of EtOAc (2 × 85 mL). The combined organic extracts were dried over Na_2SO_4, the solvent was evaporated, and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 1:1) to afford 7.62 g (94%) of compound **11** (mixture of anomers) as a colourless oil, which was used immediately to the next reaction without spectral characterization.

To a solution of **11** (7.62 g, 22.1 mmol) in MeOH/H_2O (1:1, 52 mL) was added $NaIO_4$ (5.58 g, 26 mmol), and the resulting suspension was stirred at room temperature. After 1.5 h, the solid parts were removed by filtration and the filtrate was concentrated in vacuo. The residue obtained was diluted with a saturated $NaHCO_3$ solution (55 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over Na_2SO_4, stripped of solvent, and the crude product was immediately used to the next reaction.

A solution of the prepared crude aldehyde (7.57 g, 22.1 mmol) in MeOH/CH_2Cl_2 (4:1, 90 mL) was cooled to 0 °C and treated with $NaBH_4$ (0.835 g, 22.1 mmol). The resulting mixture was stirred for 10 min at 0 °C and then at room temperature for the further 50 min. After neutralization with Amberlite IR-120 (H^+ form), the insoluble material was filtered off, the filtrate was concentrated in vacuo, and the residue was flash-chromatographed through a short column of silica gel (*n*-hexane/ethyl acetate, 1:1). This procedure yielded 6.58 g (94%) of crystalline compound **12**; mp 59–60 °C (recrystallized from *n*-hexane/ethyl acetate); $[\alpha]_D^{23}$ –40.2 (*c* 0.50, $CHCl_3$). IR υ_{max} 3498, 3392, 3062, 3032, 2918, 2892, 1705, 1601, 1583, 1431, 1371, 1276 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 3.55–3.59 (m, 1H, H-3), 3.77 (dd, 1H, *J* = 11.9 Hz, *J* = 4.4 Hz, H-4), 3.92 (dd, 1H, *J* = 11.9 Hz, *J* = 3.6 Hz, H-4), 4.05 (ddd, 1H, *J* = 7.4 Hz, *J* = 5.7 Hz, *J* = 3.0 Hz, H-2), 4.38 (dd, 1H, *J* = 11.5 Hz, *J* = 5.7 Hz, H-1), 4.48 (dd, 1H, *J* = 11.5 Hz, *J* = 3.1 Hz, H-1), 4.56 (d, 1H, *J* = 11.5 Hz, OCH_2Ph), 4.73 (d, 1H, *J* = 11.5 Hz, OCH_2Ph), 7.15–7.33 (m, 5H, Ph), 7.42–7.46 (m, 2H, Ph), 7.55–7.60 (m, 1H, Ph), 7.99–8.01 (m, 2H, Ph); ^{13}C NMR (100 MHz, CD_3OD): δ 61.5 (C-4), 67.6 (C-1), 70.0 (C-2), 73.3 (OCH_2Ph), 80.9 (C-3), 128.7 (CH_{Ph}), 129.2 (2 × CH_{Ph}), 129.4 (2 × CH_{Ph}), 129.5 (2 × CH_{Ph}), 130.7 (2 × CH_{Ph}), 131.5 (C_i), 134.3 (CH_{Ph}), 139.7 (C_i), 168.2 (C═O). Anal. calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.29; H, 6.41.

4.1.5. [(4′S,5′R)-5-(Benzyloxy)-2′,2′-dimethyl-1′,3′-dioxan-4′-yl]methyl benzoate (**13**)

To a solution of **12** (6.49 g, 20.5 mmol) in dry CH_2Cl_2 (113 mL) were successively added 2,2-DMP (7.6 mL, 61.5 mmol) and catalytic amounts of *p*-TsOH (160 mg, 0.82 mmol). The resulting solution was stirred at room temperature. After 2 h, no starting material was identified in the mixture (judged by TLC), which was then washed with a saturated $NaHCO_3$ solution (2 × 110 mL). The organic layer was dried over Na_2SO_4, the solvent was evaporated in vacuo, and

the residue was subjected to flash chromatography on silica gel (*n*-hexane/ethyl acetate, 5:1) to give 6.58 g (90%) of derivative **13** as a colourless oil; $[\alpha]_D^{24}$ –56.5 (*c* 0.63, $CHCl_3$). IR υ_{max} 2992, 2942, 2871, 1717, 1602, 1452, 1371, 1269, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 3.61 (ddd, 1H, *J* = 9.2 Hz, *J* = 8.8 Hz, *J* = 5.2 Hz, H-5′), 3.75 (dd, 1H, *J* = 11.4 Hz, *J* = 8.8 Hz, H-6′), 3.99 (dd, 1H, *J* = 11.4 Hz, *J* = 5.2 Hz, H-6′), 4.05 (ddd, 1H, *J* = 9.1 Hz, *J* = 4.6 Hz, *J* = 2.7 Hz, H-4′), 4.43–4.52 (m, 3H, 2 × H-1, OCH_2Ph), 4.57 (d, 1H, *J* = 11.5 Hz, OCH_2Ph), 7.21–7.28 (m, 5H, Ph), 7.41–7.45 (m, 2H, Ph), 7.54–7.56 (m, 1H, Ph), 8.00–8.02 (m, 2H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5 (CH_3), 28.2 (CH_3), 62.5 (C-6′), 64.2 (C-1), 70.3 (C-5′), 71.1 (C-4′), 72.1 (OCH_2Ph), 99.0 (C_q), 127.9 (2 × CH_{Ph}), 128.0 (CH_{Ph}), 128.3 (2 × CH_{Ph}), 128.5 (2 × CH_{Ph}), 129.7 (2 × CH_{Ph}), 130.1 (C_i), 132.9 (CH_{Ph}), 137.5 (C_i), 166.4 (C═O). Anal. calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.83; H, 6.75.

*4.1.6. [(4′S,5′R)-5′-(Benzyloxy)-2′,2′-dimethyl-1′,3′-dioxan-4′-yl]methanol (**6**)*

A solution of **13** (6.5 g, 18.2 mmol) in dry MeOH (190 mL) was cooled to 0 °C and then treated with solid K_2CO_3 (0.76 g, 5.5 mmol). The resulting mixture was stirred for 15 min at 0 °C, and then at room temperature for another 4.5 h before dilution with Et_2O (255 mL). The solid Na_2SO_4 wad added, the insoluble material was removed by filtration, the filtrate was concentrated, and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 3:1) to furnish 4.23 g (92%) of compound **6** as a colourless oil; $[\alpha]_D^{24}$ –55.9 (*c* 0.57, $CHCl_3$). IR υ_{max} 3464, 3031, 2992, 2872, 1455, 1372, 1199, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.01 (br s, 1H, OH), 3.56 (dt, 1H, *J* = 9.1 Hz, *J* = 9.1 Hz, *J* = 5.3 Hz, H-5′), 3.66–3.72 (m, 2H, H-1, H-6′), 3.76–3.80 (m, 2H, H-1, H-4′), 3.92 (dd, 1H, *J* = 11.3 Hz, *J* = 5.3 Hz, H-6′), 4.53 (d, 1H, *J* = 11.6 Hz, OCH_2Ph), 4.58 (d, 1H, *J* = 11.6 Hz, OCH_2Ph), 7.27–7.37 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6 (CH_3), 28.4 (CH_3), 62.4 (C-6′), 62.5 (C-1), 70.2 (C-5′), 72.3 (OCH_2Ph), 72.9 (C-4′), 98.8 (C_q), 127.9 (2 × CH_{Ph}), 128.0 (CH_{Ph}), 128.5 (2 × CH_{Ph}), 137.8 (C_i). Anal. calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.60; H, 7.94.

*4.1.7. Ethyl (2E)-3-[(4′S,5′R)-5′-(benzyloxy)-2′,2′-dimethyl-1′,3′-dioxan-4′-yl]acrylate (**14**)*

IBX (11.16 g, 40.0 mmol) was added to a solution of alcohol **6** (4.02 g, 15.8 mmol) in acetonitrile (143 mL), and the resulting mixture was stirred and heated to reflux for 30 min. Then, the insoluble parts were removed by filtration and the filtrate was concentrated in vacuo. The obtained crude product was used immediately in subsequent reaction without chromatographic purification.

To a solution of the crude aldehyde (3.95 g, 15.8 mmol) in dry CH_2Cl_2 (158 mL) was added stabilized ylide (Ph_3P═$CHCO_2Et$, 6.05 g, 17.4 mmol), and the resulting mixture was stirred at room temperature for 30 min before evaporating of dichloromethane. The obtained residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate, 9:1) to afford 5.01 g (98%) of compound **14** as a colourless oil; $[\alpha]_D^{27}$ –53.7 (*c* 0.38, $CHCl_3$). IR υ_{max} 2991, 2939, 2871, 1717, 1660, 1367, 1301, 1259, 1159, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.30 (t, 3H, *J* = 7.1 Hz, CH_3), 1.41 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.32 (dt, 1H, *J* = 9.2 Hz, *J* = 9.2 Hz, *J* = 5.3 Hz, H-5′), 3.71 (dd, 1H, *J* = 11.5 Hz, *J* = 9.0 Hz, H-6′), 3.91 (dd, 1H, *J* = 11.5 Hz, *J* = 5.3 Hz, H-6′), 4.21 (q, 2H, *J* = 7.1 Hz, CH_2), 4.34 (ddd, 1H, *J* = 9.5 Hz, *J* = 4.4 Hz, *J* = 1.7 Hz, H-4′), 4.53 (m, 2H, OCH_2Ph), 6.13 (dd, 1H, *J* = 15.7 Hz, *J* = 1.7 Hz, H-2), 7.07 (dd, 1H, *J* = 15.7 Hz, *J* = 4.4 Hz, H-3), 7.27–7.37 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (CH_3), 19.4 (CH_3), 28.3 (CH_3), 60.4 (CH_2), 62.7 (C-6′), 71.5 (C-4′), 72.5 (OCH_2Ph), 74.1 (C-5′), 98.9 (C_q), 121.7 (C-2), 127.9 (2 × CH_{Ph}), 128.0 (CH_{Ph}), 128.5 (2 × CH_{Ph}), 137.5 (C_i), 144.5 (C-3), 166.5 (C═O). Anal. calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.42; H, 7.59.

*4.1.8. (2E)-3-[(4′S,5′R)-5′-(Benzyloxy)-2′,2′-dimethyl-1′,3′-dioxan-4′-yl]prop-2-en-1-ol (**15**)*

To a solution of **14** (4.92 g, 15.4 mmol) in dry CH_2Cl_2 (116 mL) that had been pre-cooled to –50 °C was added DIBAl-H (38.4 mL, 46 mmol, ~1.2 M solution in toluene) dropwise, and the resulting solution was stirred at –50 °C for 30 min. The excess hydride was decomposed by the cautious addition of MeOH (15.1 mL). After warming to room temperature, the mixture was poured into a 30% aqueous solution of K/Na tartrate (323 mL) and stirred at room temperature for 1.5 h. The aqueous phase was then extracted with CH_2Cl_2 (2 × 180 mL). The combined organic extracts were 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 4.15 g (97%) of compound **15** as a colourless oil; $[\alpha]_D^{27}$ –44.0 (*c* 0.48, $CHCl_3$). IR υ_{max} 3412, 2992, 2869, 1497, 1370, 1262, 1198 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 3.32 (dt, 1H, *J* = 9.3 Hz, *J* = 9.3 Hz, *J* = 5.4 Hz, H-5′), 3.70 (dd, 1H, *J* = 11.4 Hz, *J* = 9.3 Hz, H-6′), 3.92 (dd, 1H, *J* = 11.4 Hz, *J* = 5.4 Hz, H-6′), 4.14–4.15 (m, 2H, 2 × H-1), 4.20 (dd, 1H, *J* = 9.0 Hz, *J* = 6.6 Hz, H-4′), 4.51 (d, 1H, *J* = 11.7 Hz, OCH_2Ph), 4.55 (d, 1H, *J* = 11.7 Hz, OCH_2Ph), 5.75 (tdd, 1H, *J* = 15.6 Hz, *J* = 6.3 Hz, *J* = 1.5 Hz, *J* = 1.5 Hz, H-3), 5.99 (td, 1H, *J* = 15.6 Hz, *J* = 5.2 Hz, *J* = 5.2 Hz, H-2), 7.26–7.36 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4 (CH_3), 28.5 (CH_3), 62.6 (C-6′), 62.9 (C-1), 72.5 (OCH_2Ph), 73.0 (C-4′), 74.3 (C-5′), 98.7 (C_q), 127.9 (3 × CH_{Ph}), 128.4 (2 × CH_{Ph}), 128.7 (C-3), 132.7 (C-2), 137.8 (C_i). Anal. calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.08; H, 7.92.

*4.1.9. N-{(1′S)-1-[(4″S,5″R)-5″-(Benzyloxy)-2″,2″-dimethyl-1″,3″-dioxan-4″-yl] allyl}-2,2,2-trichloroacetamide (**17**) and N-{(1′R)-1-[(4″S,5″R)-5″-(benzyloxy)-2″,2″-dimethyl-1″,3″-dioxan-4″-yl] allyl}-2,2,2-trichloroacetamide (**18**)*

To a suspension of NaH (0.38 g, 15.8 mmol, 60% dispersion in mineral oil) in dry THF (11.5 mL) that had been pre-cooled to 0 °C was added a solution of **15** (1.98 g, 7.11 mmol) in dry THF (11.5 mL). The resulting mixture was stirred at 0 °C for 30 min and then was treated with CCl_3CN (0.86 mL, 8.64 mmol). After stirring at the same temperature for 30 min, the mixture was filtered through a small pad of Celite, the filtrate was concentrated in vacuo, and the crude imidate **16** (quant) was used in subsequent Overman rearrangement without further purification.

Imidate **16** (0.10 g, 0.24 mmol) was weighed into a 10-mL glass pressure microwave tube equipped with a magnetic stirbar. *o*-Xylene (3.2 mL) and anhydrous K_2CO_3 (37.3 mg, 0.27 mmol) were then added. The tube was closed with a silicon septum and the reaction mixture was subjected to the microwave irradiation (for the temperatures and the reaction times, see Table 1). Removal of the solvent and chromatography on silica gel (*n*-hexane/ethyl acetate, 3:1) gave the corresponding trichloroacetamides **17** and **18** as colourless oils (for the combined yields, see Table 1). Requiring a greater amount of the rearranged products **17** and **18**, the aforementioned procedure was repeated several times at 130 °C using 0.25 g of the starting imidate **16**.

Diastereoisomer **17**: $[\alpha]_D^{27}$ –50.2 (*c* 0.95, $CHCl_3$). IR υ_{max} 3421, 2992, 2875, 1717, 1500, 1226, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.48 (dt, 1H, *J* = 8.8 Hz, *J* = 8.8 Hz, *J* = 5.2 Hz, H-5″), 3.68 (dd, 1H, *J* = 11.5 Hz, *J* = 8.4 Hz, H-6″), 3.89–3.95 (m, 2H, H-4″, H-6″), 4.47 (d, 1H, *J* = 11.6 Hz, OCH_2Ph), 4.55 (d, 1H, *J* = 11.6 Hz, OCH_2Ph), 4.71 (dt, 1H, *J* = 8.4 Hz, *J* = 8.4 Hz, *J* = 3.1 Hz, H-1′), 5.23–5.29 (m, 2H, 2 × H-3′), 5.79 (ddd, 1H, *J* = 17.3 Hz, *J* = 10.3 Hz, *J* = 8.2 Hz, H-2′), 7.13 (d, 1H, *J* = 8.3 Hz, NH), 7.26–7.38 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7 (CH_3), 27.9 (CH_3), 54.1 (C-1′), 62.2 (C-6″), 70.6 (C-5″), 71.6 (OCH_2Ph), 73.4 (C-4″), 92.7 (CCl_3), 99.3 (C_q), 120.4 (C-3′), 127.9 (2 × CH_{Ph}), 128.1 (CH_{Ph}), 128.5 (2 × CH_{Ph}), 131.4 (C-2′), 137.5 (C_i), 160.7 (C═O). Anal. calcd for $C_{18}H_{22}Cl_3NO_4$: C, 51.14; H, 5.25; N, 3.31. Found: C, 51.19; H, 5.20; N, 3.36.

Diastereoisomer **18**: $[\alpha]_D^{28}$ –3.1 (*c* 0.83, $CHCl_3$). IR υ_{max} 3422, 2992, 2874, 1716, 1455, 1284, 1225, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 3.43 (dt, 1H, *J* = 9.5 Hz, *J* = 9.5 Hz, *J* = 5.4 Hz, H-5″), 3.68 (dd, 1H, *J* = 11.2 Hz, *J* = 9.7 Hz, H-6″), 3.87 (dd, 1H, *J* = 9.5 Hz, *J* = 1.5 Hz, H-4″), 3.91 (dd, 1H, *J* = 11.3 Hz, *J* = 5.4 Hz, H-6″), 4.51 (m, 2H, OCH_2Ph), 4.81–4.85 (m, 1H, H-1′), 5.24–5.31 (m, 2H, 2 × H-3′), 5.86 (ddd, 1H, *J* = 17.2 Hz, *J* = 10.5 Hz, *J* = 5.1 Hz, H-2′), 7.26–7.37 (m, 6H, Ph, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1 (CH_3), 28.5 (CH_3), 52.5 (C-1′), 62.3 (C-6″), 70.4 (C-5″), 72.7 (OCH_2Ph), 73.6 (C-4″), 92.7 (CCl_3), 99.1 (C_q), 117.0 (C-3′), 128.3 (CH_{Ph}), 128.5 (2 × CH_{Ph}), 128.6 (2 × CH_{Ph}), 133.9 (C-2′), 137.1 (C_i), 161.5 (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, 5.30; N, 3.26.

4.1.10. (4*S*,5R)-5-(Benzyloxy)-2,2-dimethyl-4-[(1′*E*)-3′-thiocyanatoprop-1′-en-1′-yl]-1,3-dioxane (**19**)

A solution of compound **15** (0.195 g, 0.70 mmol) in dry CH_2Cl_2 (6 mL) was cooled to 0 °C and then successively treated with Et_3N (0.148 mL, 1.05 mmol) and MsCl (0.08 mL, 1.05 mmol). The resulting mixture was stirred for 15 min at 0 °C and then at room temperature for another 20 min. After evaporation of the solvent, the residue was diluted with Et_2O, the insoluble material was filtered off, washed with Et_2O, and the solvent was evaporated. The obtained crude product was used in the next reaction without further purification.

To a solution of the crude mesylate (0.25 g, 0.70 mmol) in dry acetonitrile (6 mL) that had been pre-cooled to 5 °C was added KSCN (0.116 g, 1.19 mmol), and the resulting mixture was then stirred at room temperature for 6.5 h before evaporating of the solvent. To the obtained residue, Et_2O was added to give salts, which were removed by filtration. The filtrate was concentrated to provide a pale yellow oil, which was subjected to the flash chromatography on silica gel (*n*-hexane/ethyl acetate, 7:1) to yield 0.208 g (93%) of compound **19** as white crystals; mp 48.5–50 °C (recrystallized from *n*-hexane/ethyl acetate); $[\alpha]_D^{27}$ –24.6 (*c* 0.41, $CHCl_3$). IR υ_{max} 2992, 2939, 2871, 2154, 1455, 1379, 1261, 1199, 1083 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.34 (dt, 1H, *J* = 9.3 Hz, *J* = 9.3 Hz, *J* = 5.4 Hz, H-5), 3.56–3.57 (m, 2H, 2 × H-3′), 3.69 (dd, 1H, *J* = 11.4 Hz, *J* = 9.3 Hz, H-6), 3.90 (dd, 1H, *J* = 11.4 Hz, *J* = 5.4 Hz, H-6), 4.23 (dd, 1H, *J* = 9.3 Hz, *J* = 3.8 Hz, H-4), 4.54 (d, 1H, *J* = 11.6 Hz, OCH_2Ph), 4.58 (d, 1H, *J* = 11.6 Hz, OCH_2Ph), 5.88–5.99 (m, 2H, H-1′, H-2′), 7.27–7.36 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4 (CH_3), 28.5 (CH_3), 35.9 (C-3′), 62.7 (C-6), 72.0 (C-4), 72.6 (OCH_2Ph), 74.6 (C-5), 98.9 (C_q), 111.8 (SCN), 124.2 (C-2′), 127.9 (CH_{Ph}), 128.0 (2 × CH_{Ph}), 128.4 (2 × CH_{Ph}), 135.1 (C-1′), 137.8 (C_i). Anal. calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39. Found: C, 63.97; H, 6.59; N, 4.35.

The corresponding rearrangements of **19** were realized according to our procedures reported in the literature.[11,41]

4.1.11. *N*-{(1′*S*)-1-[(4″*S*,5″*R*)-5′-(Benzyloxy)-2″,2″-dimethyl-1″,3″-dioxan-4″-yl]-2′-hydroxyethyl}-2,2,2-trichloroacetamide (**22**)

Ozone was introduced to a solution of **17** (1.33 g, 3.15 mmol) in CH_2Cl_2/MeOH (120 mL, 1:5) at –78 °C for 15 min. After the complete consumption of the starting material (judged by TLC), nitrogen was passed through the cold solution for 5 min in order to remove the excess ozone. Then $NaHB_4$ (0.535 g, 14.2 mmol) was added in portions, and the resulting mixture was stirred for 30 min at –78 °C and then at 0 °C for another 30 min. The reaction was quenched by the neutralization with a 1 M aqueous HCl solution, the solvent was removed, and the residue was partitioned between EtOAc (92 mL) and a saturated NH_4Cl solution (46 mL). The aqueous layer was then washed with the further portion of EtOAc (92 mL). The combined organic extracts were dried over Na_2SO_4, stripped solvent, and the residue was chromatographed through a short column of silica gel (*n*-hexane/ethyl acetate, 4:1) to give 1.275 g (95%) of compound **22** as a colourless oil; $[\alpha]_D^{26}$ –2.5 (*c* 1.12, $CHCl_3$). IR υ_{max} 3399, 2886, 1693, 1511, 1454, 1208, 1058 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.50 (br s, 1H, OH), 3.53–3.59 (m, 2H, H-2′, H-5″), 3.70 (dd, 1H, *J* = 11.5 Hz, *J* = 8.3 Hz, H-6″), 3.79 (1H, dd, *J* = 12.1 Hz, *J* = 2.5 Hz, H-2′), 3.98 (dd, 1H, *J* = 11.5 Hz, *J* = 5.0 Hz, H-6″), 4.06 (dd, 1H, *J* = 9.5 Hz, *J* = 3.3 Hz, H-4″), 4.15–4.20 (m, 1H, H-1′), 4.47 (d, 1H, *J* = 11.9 Hz, OCH_2Ph), 4.62 (d, 1H, *J* = 11.9 Hz, OCH_2Ph), 7.29–7.38 (m, 5H, Ph), 7.45 (d, 1H, *J* = 7.9 Hz, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4 (CH_3), 28.0 (CH_3), 51.7 (C-1′), 60.5 (C-2′), 62.2 (C-6″), 70.5 (C-5″), 71.4 (OCH_2Ph), 74.1 (C-4″), 92.5 (CCl_3), 99.6 (C_q), 128.0 (2 × CH_{Ph}), 128.2 (CH_{Ph}), 128.6 (2 × CH_{Ph}), 137.2 (C_i), 161.6 (C═O). Anal. calcd for $C_{17}H_{22}Cl_3NO_5$: C, 47.85; H, 5.20; N, 3.28. Found: C, 47.80; H, 5.24; N, 3.33.

4.1.12. *N*-{(1′*R*)-1-[(4″*S*,5″*R*)-5′-(Benzyloxy)-2″,2″-dimethyl-1″,3″-dioxan-4″-yl]-2′-hydroxyethyl}-2,2,2-trichloroacetamide (**23**)

According to the same procedure described for the preparation of **22**, compound **18** (1.39 g, 3.29 mmol) afforded after ozonolysis and the reductive workup ($NaHB_4$, 0.56 g, 14.8 mmol) the residue, which was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate, 3:1). This procedure yielded 1.23 g (88%) of derivative **23** as a colourless oil; $[\alpha]_D^{26}$ –27.0 (*c* 0.43, $CHCl_3$). IR υ_{max} 3416, 2992, 2877, 1713, 1505, 1455, 1227, 1164 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 1.35 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 3.37 (dt, 1H, *J* = 9.2 Hz, *J* = 9.2 Hz, *J* = 5.3 Hz, H-5″), 3.58–3.67 (m, 2H, 2 × H-2′), 3.68 (dd, 1H, *J* = 11.3 Hz, *J* = 9.1 Hz, H-6″), 3.90 (dd, 1H, *J* = 11.4 Hz, *J* = 5.3 Hz, H-6″), 4.02 (dd, 1H, *J* = 9.5 Hz, *J* = 1.2 Hz, H-4″), 4.34–4.37 (m, 1H, H-1′), 4.50 (d, 1H, *J* = 11.1 Hz, OCH_2Ph), 4.54 (d, 1H, *J* = 11.1 Hz, OCH_2Ph), 7.25–7.36 (m, 5H, Ph); ^{13}C NMR (100 MHz, CD_3OD): δ 19.8 (CH_3), 28.7 (CH_3), 53.5 (C-1′), 61.2 (C-2′), 63.5 (C-6″), 71.6 (C-4″, C-5″), 73.4 (OCH_2Ph), 94.0 (CCl_3), 100.4 (C_q), 129.0 (CH_{Ph}), 129.5 (4 × CH_{Ph}), 139.3 (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, 5.18; N, 3.24.

4.1.13. (4*S*)-4-[(4′*S*,5′*R*)-5′-(Benzyloxy)-2′,2′-dimethyl-1′,3′-dioxan-4′-yl]oxazolidin-2-one (**24**)

A solution of **22** (0.92 g, 2.16 mmol) in dry CH_2Cl_2 (25.7 mL) was cooled to 0 °C and then treated with DBU (32 μL, 0.22 mmol). The resulting solution was stirred for 10 min at 0 °C and then for room temperature for another 6 h. After evaporating of the solvent, the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 1:2) to afford 0.59 g (89%) of oxazolidinone **24** as a colourless oil; $[\alpha]_D^{26}$ –40.7 (*c* 0.34, $CHCl_3$). IR υ_{max} 3288, 2991, 2874, 1747, 1455, 1265, 1168, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.47 (dt, 1H, *J* = 9.0 Hz, *J* = 9.0 Hz, *J* = 5.0 Hz, H-5′), 3.69 (m, 2H, H-4′, H-6′), 3.87 (td, 1H, *J* = 8.6 Hz, *J* = 5.7 Hz, *J* = 5.7 Hz, H-4), 3.99 (dd, 1H, *J* = 11.5 Hz, *J* = 5.0 Hz, H-6′), 4.27 (t, 1H, *J* = 8.8 Hz, H-5), 4.34 (dd, 1H, *J* = 8.9 Hz, *J* = 5.6 Hz, H-5), 4.44 (d, 1H, *J* = 11.5 Hz, OCH_2Ph), 4.60 (d, 1H, *J* = 11.5 Hz, OCH_2Ph), 5.38 (br s, 1H, NH), 7.27–7.41 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4 (CH_3), 28.1 (CH_3), 54.7 (C-4), 61.9 (C-6′), 66.3 (C-5), 71.5 (OCH_2Ph), 72.6 (C-5′), 72.7 (C-4′), 99.3 (C_q), 128.1 (2 × CH_{Ph}), 128.4 (CH_{Ph}), 128.8 (2 × CH_{Ph}), 136.9 (C_i), 159.2 (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, 6.92; N, 4.52.

4.1.14. (4*R*)-4-[(4′*S*,5′*R*)-5′-(Benzyloxy)-2′,2′-dimethyl-1′,3′-dioxan-4′-yl]oxazolidin-2-one (**25**)

Similar to the preceding procedure, compound **23** (1.15 g, 2.7 mmol) was treated with DBU (40 μL, 0.27 mmol) at 0 °C. After stirring (6 h) at room temperature, the flash chromatography (silica gel, *n*-hexane/ethyl acetate, 2:1) of the residue gave 0.705 g (85%) of crystalline compound **25**; mp 99–101 °C (recrystallized from *n*-hexane/ethyl acetate); $[\alpha]_D^{26}$ –87.6 (*c* 0.36, $CHCl_3$). IR υ_{max} 3221, 2922, 1753, 1418, 1304, 1265, 1162, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.41 (dt, 1H, *J* = 8.9 Hz, *J* = 8.9 Hz, *J* = 5.1 Hz, H-5′), 3.62–3.72 (m, 2H, H-4′, H-6′), 3.89 (m,

1H, H-4), 3.98 (dd, 1H, *J* = 11.4 Hz, *J* = 5.1 Hz, H-6′), 4.31–4.38 (m, 2H, 2 × H-5), 4.41 (d, 1H, *J* = 11.5 Hz, OCH_2Ph), 4.57 (d, 1H, *J* = 11.5 Hz, OCH_2Ph), 5.59–5.61 (m, 1H, NH), 7.26–7.40 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5 (CH_3), 28.1 (CH_3), 54.7 (C-4), 61.9 (C-6′), 68.8 (C-5), 71.6 (OCH_2Ph), 72.1 (C-5′), 73.2 (C-4′), 99.3 (C_q), 128.1 (2 × CH_{Ph}), 128.4 (CH_{Ph}), 128.7 (2 × CH_{Ph}), 137.0 (C_i), 159.2 (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, 6.84; N, 4.61.

4.1.15. (4S)-3-Benzyl-4-[(4′S,5′R)-5′-(benzyloxy)-2′,2′-dimethyl-1′,3′-dioxan-4′-yl]oxazolidin-2-one (**27**)

A solution of **24** (95 mg, 0.31 mmol) in dry DMF (0.5 mL) was cooled to 0 °C and then treated with NaH (18.5 mg, 0.77 mmol, 60% dispersion in mineral oil). Next, benzyl bromide (44.5 μL, 0.37 mmol) and TBAI (1.1 mg, 3.1 μmol) were successively added. The resulting mixture was stirred for 10 min at 0 °C and then at room temperature for 30 min. The excess hydride was removed by the cautious addition of MeOH (0.1 mL), the mixture was poured into ice-water (2 mL) and extracted with Et_2O (2 × 5 mL). The combined organic extracts were dried over Na_2SO_4, the solvent was evaporated, and the residue was subjected to flash chromatography on silica gel (*n*-hexane/ethyl acetate, 5:1) to furnish 113 mg (92%) of compound **27** as white crystals; mp 81–82 °C (recrystallized from *n*-hexane/ethyl acetate); $[\alpha]_D^{27}$ –29.1 (*c* 0.32, $CHCl_3$). IR υ_{max} 2995, 2920, 1736, 1482, 1426, 1369, 1291, 1268, 1169 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.28 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 3.24 (dt, 1H, *J* = 8.9 Hz, *J* = 8.9 Hz, *J* = 5.3 Hz, H-5′), 3.65 (dd, 1H, *J* = 11.5 Hz, *J* = 8.6 Hz, H-6′), 3.77–3.85 (m, 3H, H-4, H-4′, H-5), 3.93 (dd, 1H, *J* = 11.5 Hz, *J* = 5.2 Hz, H-6′), 4.22 (d, 1H, *J* = 15.2 Hz, NCH_2Ph), 4.28 (dd, 1H, *J* = 7.1 Hz, *J* = 4.4 Hz, H-5), 4.30 (d, 1H, *J* = 11.7 Hz, OCH_2Ph), 4.51 (d, 1H, *J* = 11.7 Hz, OCH_2Ph), 4.72 (d, 1H, *J* = 15.2 Hz, NCH_2Ph), 7.15–7.16 (m, 2H, Ph), 7.31–7.36 (m, 8H, Ph); ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.0 (CH_3), 28.0 (CH_3), 46.5 (NCH_2Ph), 54.9 (C-4), 62.0 (C-6′), 62.3 (C-5), 69.2 (C-4′), 69.3 (C-5′), 71.7 (OCH_2Ph), 99.2 (C_q), 127.8 (CH_{Ph}), 128.1 (2 × CH_{Ph}), 128.3 (3 × CH_{Ph}), 128.6 (2 × CH_{Ph}), 128.7 (2 × CH_{Ph}), 136.1 (C_i), 136.9 (C_i), 158.8 (C═O). Anal. calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.45; H, 6.89; N, 3.56.

4.1.16. (4R)-3-Benzyl-4-[(4′S,5′R)-5′-(benzyloxy)-2′,2′-dimethyl-1′,3′-dioxan-4′-yl]oxazolidin-2-one (**28**)

Using the same procedure as described for the preparation of **27**, compound **25** (0.10 g, 0.325 mmol) was converted into crystalline derivative **28** (124 mg, 96%, *n*-hexane/ethyl acetate, 5:1); mp 77–78 °C (recrystallized from *n*-hexane/ethyl acetate); $[\alpha]_D^{27}$ –34.2 (*c* 0.26, $CHCl_3$). IR υ_{max} 2906, 2878, 1732, 1454, 1395, 1271, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 3.45–3.50 (m, 1H, H-5′), 3.66 (dd, 1H, *J* = 11.5 Hz, *J* = 7.5 Hz, H-6′), 3.71–3.76 (m, 1H, H-4), 3.87–3.90 (m, 2H, H-4′, H-6′), 4.18 (t, 1H, *J* = 9.0 Hz, H-5), 4.31–4.35 (m, 3H, H-5, NCH_2Ph, OCH_2Ph), 4.44 (d, 1H, *J* = 11.1 Hz, OCH_2Ph), 4.79 (d, 1H, *J* = 15.2 Hz, NCH_2Ph), 7.28–7.34 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8 (CH_3), 27.4 (CH_3), 47.8 (NCH_2Ph), 56.3 (C-4), 61.9 (C-6′), 64.4 (C-5), 71.7 (OCH_2Ph), 72.7 (C-4′), 72.8 (C-5′), 99.3 (C_q), 127.6 (CH_{Ph}), 127.9 (2 × CH_{Ph}), 128.2 (3 × CH_{Ph}), 128.6 (4 × CH_{Ph}), 136.5 (C_i), 137.0 (C_i), 158.9 (C═O). Anal. calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.54; H, 6.81; N, 3.57.

4.1.17. (4S)-3-Benzyl-4-[(4′S,5′S)-5′-(benzyloxy)-2′,2′-dimethyl-1′,3′-dioxan-4′-yl]oxazolidin-2-one (**29**)

According to the same experiment described for the preparation of **27** and **28**, the known compound **26**[11] (90 mg, 0.29 mmol) was transformed to the crystalline derivative **29** (106 mg, 91%, *n*-hexane/ethyl acetate, 1:2); mp 78–79 °C (recrystallized from *n*-hexane/ethyl acetate); $[\alpha]_D^{26}$ +36.2 (*c* 0.50, $CHCl_3$). IR υ_{max} 2871, 1743, 1728, 1496, 1423, 1322, 1264, 1198, 1144 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.20 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.15 (q, 1H, *J* = 2.5 Hz, H-5′), 3.65 (ddd, 1H, *J* = 8.9 Hz, *J* = 6.7 Hz, *J* = 2.0 Hz, H-4), 3.82 (dd, 1H, *J* = 13.1 Hz, *J* = 2.5 Hz, H-6′), 3.98 (dd, 1H, *J* = 13.1 Hz, *J* = 2.4 Hz, H-6′), 4.03 (t, 1H, *J* = 2.3 Hz, H-4′), 4.20–4.27 (m, 3H, H-5, NCH_2Ph, OCH_2Ph), 4.61 (d, 1H, *J* = 15.5 Hz, NCH_2Ph), 4.64 (d, 1H, *J* = 12.3 Hz, OCH_2Ph), 4.68 (dd, 1H, *J* = 9.4 Hz, *J* = 6.9 Hz, H-5), 7.22–7.35 (m, 10H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.8 (CH_3), 28.4 (CH_3), 46.5 (NCH_2Ph) 57.5 (C-4), 60.2 (C-6′), 63.9 (C-5), 67.4 (C-4′), 70.6 (OCH_2Ph), 71.0 (C-5′), 99.0 (C_q), 127.7 (4 × CH_{Ph}), 127.8 (CH_{Ph}), 128.0 (CH_{Ph}), 128.5 (2 × CH_{Ph}), 128.8 (2 × CH_{Ph}), 136.2 (C_i), 137.2 (C_i), 158.9 (C═O). Anal. calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.45; H, 6.88; N, 3.58.

4.1.18. (4S)-3-Benzyl-4-[(4′S,5′R)-5′-hydroxy-2′,2′-dimethyl-1′,3′-dioxan-4′-yl]oxazolidin-2-one (**30**)

A solution of **27** (70 mg, 0.18 mmol) in dry EtOH (6.8 mL) was treated with 10% Pd/C (6.1 mg) under an atmosphere of hydrogen, and the resulting suspension was stirred for 7 h at room temperature. After filtration of the mixture through a small pad of Celite, the filtrate was concentrated, and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 1:1) to afford 52.5 mg (97%) of compound **30** as white crystals; mp 127–128 °C (recrystallized from *n*-hexane/ethyl acetate); $[\alpha]_D^{27}$ –5.7 (*c* 0.30, $CHCl_3$). IR υ_{max} 3434, 1728, 1713, 1474, 1374, 1265, 1164 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.28 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 3.05 (d, 1H, *J* = 5.8 Hz, OH), 3.52 (m, 1H, H-5′), 3.59 (dd, 1H, *J* = 11.2 Hz, *J* = 9.2 Hz, H-6′), 3.79 (dd, 1H, *J* = 9.5 Hz, *J* = 1.6 Hz, H-4′), 3.84 (dd, 1H, *J* = 11.2 Hz, *J* = 5.4 Hz, H-6′), 4.04 (ddd, 1H, *J* = 9.5 Hz, *J* = 5.6 Hz, *J* = 1.6 Hz, H-4), 4.23 (dd, 1H, *J* = 9.5 Hz, *J* = 8.6 Hz, H-5), 4.27 (d, 1H, *J* = 15.3 Hz, NCH_2Ph), 4.47 (dd, 1H, *J* = 8.4 Hz, *J* = 5.7 Hz, H-5), 4.66 (d, 1H, *J* = 15.3 Hz, NCH_2Ph), 7.27–7.34 (m, 5H, Ph); ^{13}C NMR (150 MHz, $CDCl_3$): δ 18.7 (CH_3), 28.3 (CH_3), 46.6 (NCH_2Ph), 55.3 (C-4), 62.8 (C-5′), 62.9 (C-5), 64.5 (C-6′), 71.2 (C-4′), 99.0 (C_q), 127.9 (CH_{Ph}), 128.1 (2 × CH_{Ph}), 128.7 (2 × CH_{Ph}), 135.1 (C_i), 159.3 (C═O). Anal. calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.59; H, 6.84; N, 4.61.

4.1.19. (4R)-3-Benzyl-4-[(4′S,5′R)-5′-hydroxy-2′,2′-dimethyl-1′,3′-dioxan-4′-yl]oxazolidin-2-one (**31**)

By the similar procedure as described for the preparation of **30**, compound **28** (97 mg, 0.244 mmol) and 10% Pd/C (8.4 mg) afforded after stirring for 28 h under an atmosphere of hydrogen and chromatography on silica gel (*n*-hexane/ethyl acetate, 1:1) 70.7 mg (94%) of alcohol **31** in the form of white crystals; mp 115–116 °C (recrystallized from *n*-hexane/ethyl acetate); $[\alpha]_D^{26}$ –8.5 (*c* 0.26, $CHCl_3$). IR υ_{max} 3369, 2917, 2851, 1731, 1498, 1430, 1336, 1256 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.33 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 3.20 (d, 1H, *J* = 6.0 Hz, OH), 3.60 (dd, 1H, *J* = 11.4 Hz, *J* = 8.4 Hz, H-6′), 3.65–3.70 (m, 1H, H-5′), 3.76 (td, 1H, *J* = 8.8 Hz, *J* = 6.0 Hz, *J* = 6.0 Hz, H-4), 3.84 (dd, 1H, *J* = 11.2 Hz, *J* = 5.0 Hz, H-6′), 3.86 (dd, 1H, *J* = 8.8 Hz, *J* = 6.2 Hz, H-4′), 4.28 (t, 1H, *J* = 9.2 Hz, H-5), 4.38 (d, 1H, *J* = 15.2 Hz, NCH_2Ph), 4.46 (dd, 1H, *J* = 9.5 Hz, *J* = 5.8 Hz, H-5), 4.78 (d, 1H, *J* = 15.2 Hz, NCH_2Ph), 7.26–7.35 (m, 5H, Ph); ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.4 (CH_3), 27.9 (CH_3), 47.8 (NCH_2Ph), 56.8 (C-4), 64.6 (C-5), 64.7 (C-5′, C-6′), 74.0 (C-4′), 98.9 (C_q), 127.7 (CH_{Ph}), 127.9 (2 × CH_{Ph}), 128.7 (2 × CH_{Ph}), 136.4 (C_i), 159.4 (C═O). Anal. calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.48; H, 6.85; N, 4.60.

4.1.20. (4S)-3-Benzyl-4-[(4′S,5′S)-5′-hydroxy-2′,2′-dimethyl-1′,3′-dioxan-4′-yl]oxazolidin-2-one (**32**)

Using the same procedure as described for the preparation of **30** and **31**, compound **29** (101 mg, 0.256 mmol) was converted into derivative **32** (3 h, 75 mg, 96% (*n*-hexane/ethyl acetate, 1:1, white amorphous compound); $[\alpha]_D^{26}$ –5.0 (*c* 0.48, $CHCl_3$). IR υ_{max} 3573, 2991, 1736, 1478, 1428, 1334, 1266, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 2.77–2.79 (m, 1H, OH), 3.36–3.38 (m, 1H, H-5′), 3.74–3.80 (m, 2H, H-4, H-6′), 3.93–3.94 (m, 1H, H-4′), 4.00–4.04 (m, 1H, H-6′), 4.25–4.30 (m, 2H, H-5′, NCH_2Ph), 4.47

(dd, 1H, J = 9.0 Hz, J = 6.0 Hz, H-5), 4.70 (d, 1H, J = 15.4 Hz, NCH_2Ph), 7.28–7.36 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.0 (CH_3), 29.1 (CH_3), 47.0 (NCH_2Ph) 56.6 (C-4), 64.1 (C-5′), 64.4 (C-5), 65.4 (C-6′), 69.6 (C-4′), 99.3 (C_q), 127.8 (3 × CH_{Ph}), 128.7 (2 × CH_{Ph}), 136.2 (C_i), 159.0 (C═O). Anal. calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.58; H, 6.85; N, 4.52.

4.1.21. (4S)-3-Benzyl-4-[(4′S)-2′,2′-dimethyl-5′-oxo-1′, 3′-dioxan-4′-yl]oxazolidin-2-one (**33**)

*4.1.21.1. Modification of **30** into ketone **33**.* To a solution of **30** (30 mg, 0.1 mmol) in acetonitrile (0.9 mL) wad added IBX (55 mg, 0.2 mmol), and the resulting suspension was stirred and heated to reflux for 2 h. After cooling of the mixture to room temperature, the insoluble parts were filtered off, the filtrate was concentrated in vacuo, and the residue was chromatographed through a small pad of silica gel (*n*-hexane/ethyl acetate, 2:1) to furnish 23.2 mg (78%) of crystalline compound **33**.

*4.1.21.2. Modification of **32** into **33**.* Similar to the preceding experiment, compound **32** (69 mg, 0.22 mmol) was converted into derivative **33** (55.5 mg, 81%, *n*-hexane/ethyl acetate, 2:1).

Diastereoisomer **33**: mp 130–131 °C (recrystallized from *n*-hexane/ethyl acetate); $[\alpha]_D^{26}$ –213.8 (*c* 0.26, $CHCl_3$). IR υ_{max} 1748, 1731, 1483, 1426, 1361, 1253, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 4.01 (d, 1H, J = 17.6 Hz, H-6′), 4.12–4.23 (m, 4H, H-4, H-5, H-6′, NCH_2Ph), 4.27–4.31 (m, 1H, H-5), 4.45 (m, 1H, H-4′), 4.80 (d, 1H, J = 15.4 Hz, NCH_2Ph), 7.27–7.38 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4 (CH_3), 23.6 (CH_3), 46.5 (NCH_2Ph), 53.8 (C-4), 62.9 (C-5), 66.8 (C-6′), 71.2 (C-4′), 101.5 (C_q), 128.0 (2 × CH_{Ph}), 128.1 (CH_{Ph}), 129.0 (2 × CH_{Ph}), 135.4 (C_i), 158.4 (C═O), 207.5 (C═O). Anal. calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.89; H, 6.32; N, 4.63.

4.1.22. (4R)-3-Benzyl-4-[(4′S)-2′,2′-dimethyl-5′-oxo-1′, 3′-dioxan-4′-yl]oxazolidin-2-one (**34**)

According to the same procedure described for the preparation of **33**, compound **31** (35 mg, 0.11 mmol) and IBX (64 mg, 0.23 mmol) gave 31 mg (89%) of ketone **34** as a colourless oil (*n*-hexane/ethyl acetate, 2:1); $[\alpha]_D^{26}$ –54.3 (*c* 0.42, $CHCl_3$). IR υ_{max} 2987, 1736, 1496, 1376, 1222, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.41 (br s, 6H, 2 × CH_3), 3.88–3.93 (m, 2H, 2 × H-6′), 3.98–4.03 (m, 1H, H-4), 4.14 (dd, 1H, J = 9.4 Hz, J = 6.0 Hz, H-5), 4.30–4.31 (m, 1H, H-4′), 4.41 (d, 1H, J = 15.2 Hz, NCH_2Ph), 4.49 (t, 1H, J = 9.3 Hz, H-5), 4.63 (d, 1H, J = 15.1 Hz, NCH_2Ph), 7.25–7.35 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4 (CH_3), 23.5 (CH_3), 48.2 (NCH_2Ph), 53.6 (C-4), 64.7 (C-5), 66.4 (C-6′), 76.5 (C-4′), 101.5 (C_q), 127.8 (CH_{Ph}), 128.3 (2 × CH_{Ph}), 128.6 (2 × CH_{Ph}), 136.1 (C_i), 159.0 (C═O), 206.8 (C═O). Anal. calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.99; H, 6.21; N, 4.55.

4.1.23. (4S)-4-[(1′S,2′R)-2′-(Benzyloxy)-1′, 3′-dihydroxypropyl]oxazolidin-2-one (**35**)

A solution of **24** (0.28 g, 0.91 mmol) in MeOH (17.5 mL) was treated with *p*-TsOH (17.3 mg, 0.09 mmol) and the resulting mixture was stirred at room temperature for 4 h. Following complete consumption of the starting material (TLC monitoring), the reaction was stopped, the solvent was evaporated in vacuo, and the residue was then chromatographed on silica gel (ethyl acetate) to give 0.225 g (92%) of compound **35** as white crystals; mp 101–103 °C (recrystallized from ethyl acetate); $[\alpha]_D^{24}$ –43.8 (*c* 0.60, MeOH). IR υ_{max} 3437, 3316, 2921, 2883, 1721, 1426, 1244, 1051 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 3.38 (td, 1H, J = 7.6 Hz, J = 4.0 Hz, J = 4.0 Hz, H-2′), 3.71 (dd, 1H, J = 12.0 Hz, J = 4.0 Hz, H-3′), 3.74–3.77 (m, 1H, H-1′), 3.88 (dd, 1H, J = 12.0 Hz, J = 3.9 Hz, H-3′), 4.03–4.12 (m, 2H, H-4, H-5), 4.32 (1H, dd, J = 7.6 Hz, J = 4.6 Hz, H-5), 4.51 (d, 1H, J = 11.6 Hz, OCH_2Ph), 4.72 (d, 1H, J = 11.6 Hz, OCH_2Ph), 7.28–7.38 (m, 5H, Ph); ^{13}C NMR (100 MHz, CD_3OD): δ 55.3 (C-4), 61.2 (C-3′), 67.0 (C-5), 71.5 (C-1′), 73.1 (OCH_2Ph), 81.1 (C-2′), 129.0 (CH_{Ph}), 129.5 (4 × CH_{Ph}), 139.5 (C_i), 162.6 (C═O). Anal. calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.36; H, 6.45; N, 5.30.

4.1.24. (4S)-4-[(1′S,2′R)-2′-(Benzyloxy)-1′-hydroxy-3′-(trityloxy)propyl]oxazolidin-2-one (**36**)

To a solution of **35** (0.20 g, 0.75 mmol) in dry pyridine (7.3 mL) were successively added trityl chloride (0.625 g, 2.24 mmol) and DMAP (91.5 mg, 0.75 mmol), and the resulting solution was stirred and heated at 60 °C. After 8 h, another portion of TrCl (0.2 g, 0.75 mmol) and DMAP (91.5 mg, 0.75 mmol) was added, and the mixture was stirred at 60 °C for further 15 h. After cooling to room temperature, the mixture was poured into ice-water (4.5 mL) and extracted with Et_2O (3 × 9 mL). The combined organic extracts were dried over Na_2SO_4, the solvent was evaporated, and the residue was chromatographed through a short column of silica gel (*n*-hexane/ethyl acetate, 1:1) to furnish 0.36 g (95%) of compound **36** as a white foam; $[\alpha]_D^{23}$ –21.8 (*c* 0.23, $CHCl_3$). IR υ_{max} 3306, 3058, 3030, 2921, 2873, 1732, 1448, 1219, 1062 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 3.27–3.30 (m, 1H, H-3′), 3.41 (dd, 1H, J = 10.3 Hz, J = 3.5 Hz, H-3′), 3.50–3.54 (m, 1H, H-2′), 3.85 (dd, 1H, J = 6.6 Hz, J = 3.0 Hz, H-1′), 4.00–4.04 (m, 1H, H-4), 4.07–4.11 (m, 1H, H-5), 4.31 (dd, 1H, J = 8.3 Hz, J = 5.4 Hz, H-5), 4.44 (d, 1H, J = 11.5 Hz, OCH_2Ph), 4.63 (d, 1H, J = 11.5 Hz, OCH_2Ph), 7.20–7.47 (m, 20H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4 (C-4), 64.1 (C-3′), 66.9 (C-5), 71.9 (C-1′), 73.5 (OCH_2Ph), 80.5 (C-2′), 88.3 (C_{qTr}), 128.2 (3 × CH_{Ph}), 128.9 (7 × CH_{Ph}), 129.3 (2 × CH_{Ph}), 129.5 (2 × CH_{Ph}), 130.0 (6 × CH_{Ph}), 139.5 (C_i), 145.4 (3 × C_i), 162.6 (C═O). Anal. calcd for $C_{32}H_{31}NO_5$: C, 75.42; H, 6.13; N, 2.75. Found: C, 75.35; H, 6.18; N, 2.70.

4.1.25. (4S)-3-Benzyl-4-[(1′S,2′R)-1′,2′-bis(benzyloxy)-3′-(trityloxy)propyl]oxazolidin-2-one (**37**)

To a solution of **36** (0.34 g, 0.67 mmol) in dry DMF (1.6 mL) that had been pre-cooled to 0 C were successively added NaH (80.1 mg, 3.34 mmol, 60% dispersion in mineral oil), BnBr (0.19 mL, 1.6 mmol) and TBAI (4.9 mg, 0.013 mmol). The resulting mixture was stirred for 15 min at 0 °C, and then at room temperature for another 45 min. The excess hydride was decomposed by the cautious addition of MeOH. The mixture was poured into ice-water (8 mL) and extracted with E_2O (2 × 16 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated in vacuo, and the residue was subjected to flash chromatography on silica gel (*n*-hexane/ethyl acetate, 3:1) to afford 0.434 g (94%) of compound **37** as white crystals; mp 145–147 °C (recrystallized from *n*-hexane/ethyl acetate); $[\alpha]_D^{23}$ –33.9 (*c* 0.39, $CHCl_3$). IR υ_{max} 3027, 2927, 2871, 1743, 1494, 1478, 1447, 1430, 1360, 1321, 1246, 1201 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.06 (dd, 1H, J = 10.4 Hz, J = 5.9 Hz, H-3′), 3.19 (dd, 1H, J = 10.4 Hz, J = 4.8 Hz, H-3′), 3.54–3.58 (m, 1H, H-2′), 3.63 (d, 1H, J = 15.4 Hz, NCH_2Ph), 3.74 (dd, 1H, J = 9.4 Hz, J = 6.2 Hz, H-4), 3.90–3.96 (m, 2H, H-1′, H-5), 4.21 (d, 1H, J = 11.6 Hz, OCH_2Ph), 4.34 (d, 1H, J = 11.8 Hz, OCH_2Ph), 4.42 (d, 1H, J = 11.6 Hz, OCH_2Ph), 4.48 (dd, 1H, J = 8.7 Hz, J = 6.1 Hz, H-5), 4.52 (d, 1H, J = 15.4 Hz, NCH_2Ph), 4.53 (d, 1H, J = 11.7 Hz, OCH_2Ph), 7.08–7.37 (m, 30H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.8 (NCH_2Ph), 54.9 (C-4), 62.5 (C-3′), 63.1 (C-5), 72.1 (OCH_2Ph), 72.7 (OCH_2Ph), 73.4 (C-1′), 76.8 (C-2′), 87.2 (C_{qTr}), 127.2 (2 × CH_{Ph}), 127.7 (CH_{Ph}), 127.8 (2 × CH_{Ph}), 127.9 (7 × CH_{Ph}), 128.0 (CH_{Ph}), 128.1 (2 × CH_{Ph}), 128.3 (2 × CH_{Ph}), 128.4 (2 × CH_{Ph}), 128.5 (9 × CH_{Ph}), 128.7 (2 × CH_{Ph}), 136.0 (C_i), 137.5 (2 × C_i), 143.6 (3 × C_i), 158.8 (C═O). Anal. calcd for $C_{46}H_{43}NO_5$: C, 80.09; H, 6.28; N, 2.03. Found: C, 80.15; H, 6.23; N, 1.97.

4.1.26. (4S)-3-Benzyl-4-[(1′S,2′R)-1′,2′-bis(benzyloxy)-3′-hydroxypropyl]oxazolidin-2-one (**38**)

A solution of **37** (0.42 g, 0.61 mmol) in CH_2Cl_2/MeOH (7.8 mL, 2:1) was treated with *p*-TsOH (116 mg, 0.61 mmol), and the resulting

mixture was stirred at room temperature for 4 h before neutralization with Et_3N. Removal of the solvent and chromatography of the residue on silica gel (*n*-hexane/ethyl acetate, 2:1) gave 0.25 g (92%) of compound **38** as a colourless oil; $[\alpha]_D^{24}$ –22.5 (*c* 0.91, $CHCl_3$). IR υ_{max} 3421, 3030, 2921, 1717, 1604, 1454, 1243, 1058 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.40 (m, 1H, H-2′), 3.59–3.64 (m, 2H, 2 × H-3′), 3.65 (d, 1H, *J* = 15.1 Hz, NCH_2Ph), 3.75–3.79 (m, 2H, H-1′, H-4), 3.86 (dd, 1H, *J* = 9.4 Hz, *J* = 8.3 Hz, H-5), 4.39 (dd, 1H, *J* = 8.3 Hz, *J* = 5.5 Hz, H-5), 4.40 (d, 1H, *J* = 11.9 Hz, OCH_2Ph), 4.46 (d, 1H, *J* = 11.3 Hz, OCH_2Ph), 4.56 (d, 1H, *J* = 11.7 Hz, OCH_2Ph), 4.60 (d, 1H, *J* = 11.3 Hz, OCH_2Ph), 4.67 (d, 1H, *J* = 15.1 Hz, NCH_2Ph), 7.11–7.39 (m, 15H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.9 (NCH_2Ph), 54.9 (C-4), 60.2 (C-3′), 62.7 (C-5), 72.4 (OCH_2Ph), 73.2 (OCH_2Ph), 73.6 (C-1′), 77.6 (C-2′), 128.0 (CH_{Ph}), 128.1 (2 × CH_{Ph}), 128.2 (2 × CH_{Ph}), 128.4 (4 × CH_{Ph}), 128.6 (4 × CH_{Ph}), 128.8 (2 × CH_{Ph}), 135.7 (C_i), 137.0 (C_i), 137.3 (C_i), 158.7 (C═O). Anal. calcd for Pre $C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; 3.13. Found: C, 72.50; H, 6.48; N, 3.07.

*4.1.27. (4S)-3-Benzyl-4-[(1′S,2′R,3′Z)-1′,2′-bis(benzyloxy)hexadec-3′-en-1′-yl]oxazolidin-2-one (**39**)*

IBX (0.11 g, 0.40 mmol) was added to a solution of **38** (88 mg, 0.30 mmol) in acetonitrile (1.0 mL), and the resulting mixture was stirred at reflux. After 30 min, the insoluble parts were removed by filtration, the solvent was evaporated in vacuo, and the residue was immediately used in the next reaction without further purification.

To a solution of 1,1,1,3,3,3-hexamethyldisilazane (0.12 mL, 0.56 mmol) in dry THF (0.58 mL) was added *n*-BuLi (0.35 mL, 0.56 mmol, a 1.6 M solution in *n*-hexane) at room temperature. The solution of hexamethyldisilazide (LHMDS) such generated was treated with the salt $C_{13}H_{27}PPh_3Br$ (0.336 g, 0.64 mmol), and the resulting dark mixture was stirred for 5 min at the same temperature. Next, a solution of the obtained crude aldehyde (87.6 mg, 0.20 mmol) in dry THF (0.6 mL) was added. After stirring for 1 h, the mixture was diluted with EtOAc (10 mL) and poured into a saturated NH_4Cl solution (5 mL). The aqueous phase was washed with further portions of EtOAc (2 × 5 mL). The combined organic layers were dried over Na_2SO_4, the solvent was removed in vacuo, and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 7:1) to give 86 mg (71%) of a waxy compound **39**; $[\alpha]_D^{23}$ –73.1 (*c* 0.36, $CHCl_3$). IR υ_{max} 2919, 2850, 1736, 1478, 1453, 1435, 1421, 1364, 1259, 1201, 1177, 1089, 1067, 1047, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 6.4 Hz, CH_3), 1.26–1.32 (m, 20H, 10 × CH_2), 1.84–1.96 (m, 2H, 2 × H-5′), 3.50–3.51 (m, 1H, H-1′), 3.58 (d, 1H, *J* = 15.2 Hz, NCH_2Ph), 3.79 (dd, 1H, *J* = 9.3 Hz, *J* = 6.2 Hz, H-4), 4.10 (t, 1H, *J* = 9.1 Hz, H-5), 4.21–4.26 (m, 2H, H-2′, OCH_2Ph), 4.31 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 4.51 (d, 1H, *J* = 12.1 Hz, OCH_2Ph), 4.55–4.58 (m, 2H, OCH_2Ph, NCH_2Ph), 4.61–4.65 (m, 1H, H-5), 5.12–5.17 (m, 1H, H-3′), 5.61 (dt, *J* = 10.7 Hz, *J* = 7.6 Hz, *J* = 7.6 Hz, H-4′), 7.14–7.37 (m, 15H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (CH_3), 22.6 (CH_2), 27.9 (C-5′), 29.3 (2 × CH_2), 29.5 (2 × CH_2), 29.6 (4 × CH_2), 31.9 (CH_2), 45.9 (NCH_2Ph), 55.1 (C-4), 63.2 (C-5), 70.3 (OCH_2Ph), 72.2 (OCH_2Ph), 73.6 (C-2′), 76.4 (C-1′), 126.7 (C-3′), 127.5 (2 × CH_{Ph}), 127.6 (CH_{Ph}), 127.8 (CH_{Ph}), 127.9 (CH_{Ph}), 128.1 (2 × CH_{Ph}), 128.3 (2 × CH_{Ph}), 128.4 (4 × CH_{Ph}), 128.6 (2 × CH_{Ph}), 135.8 (C_i), 135.9 (C-4′), 137.6 (C_i), 137.9 (C_i), 158.8 (C═O). Anal. calcd for $C_{40}H_{53}NO_4$: C, 78.52; H, 8.73; N, 2.29. Found: C, 78.63; H, 8.80; N, 2.34.

*4.1.28. (4S)-3-Benzyl-4-[(1′S,2′R)-1′,2′-dihydroxyhexadecyl]oxazolidin-2-one (**40**)*

A solution of **39** (102 mg, 0.17 mmol) in dry EtOH (13 mL) was treated with 10% Pd/C (17.5 mg), and the resulting suspension was stirred at room temperature under an atmosphere of hydrogen. After 3 h, the catalyst was filtered through a small pad of Celite, the filtrate was concentrated, and the residue was subjected to flash chromatography on silica gel (*n*-hexane/ethyl acetate, 1:1) to give 64 mg (89%) of compound **40** in the form of white crystals; mp 130–132 °C (recrystallized from *n*-hexane/ethyl acetate); $[\alpha]_D^{24}$ +3.7 (*c* 0.35, $CHCl_3$). IR υ_{max} 3333, 2916, 2848, 1745, 1708, 1470, 1427, 1243, 1085, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 6.8 Hz, CH_3), 1.14–1.35 (m, 26H, 13 × CH_2), 2.35 (br s, 1H, OH), 3.42 (br s, 1H, OH), 3.63–3.65 (m, 1H, H-2′), 3.75–3.76 (m, 1H, H-1′), 3.86–3.90 (m, 1H, H-4), 4.21(d, 1H, *J* = 15.3 Hz, NCH_2Ph), 4.27 (t, 1H, *J* = 9.1 Hz, H-5), 4.54 (dd, 1H, *J* = 8.8 Hz, *J* = 7.4 Hz, H-5), 4.76 (d, 1H, *J* = 15.3 Hz, NCH_2Ph), 7.29–7.38 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (CH_3), 22.7 (CH_2), 25.6 (CH_2), 29.3 (CH_2), 29.5 (2 × CH_2), 29.6 (2 × CH_2), 29.7 (2 × CH_2), 29.8 (2 × CH_2), 31.9 (CH_2), 33.5 (CH_2), 46.2 (NCH_2Ph), 55.8 (C-4), 62.9 (C-5), 69.3 (C-1′), 72.7 (C-2′), 128.1 (3 × CH_{Ph}), 129.0 (2 × CH_{Ph}), 135.7 (C_i), 159.6 (C═O). Anal. calcd for $C_{26}H_{43}NO_4$: C, 72.02; H, 10.00; N, 3.23. Found: C, 72.10; H, 9.94; N, 3.28.

*4.1.29. (4S)-4-[(1′S,2′R)-1′,2′-Dihydroxyhexadecyl]oxazolidin-2-one (**41**)*

To a solution of **40** (59 mg, 0.14 mmol) in dry EtOH (11 mL) were successively added 10% Pd/C (39 mg) and 35% HCl (0.14 mL), and the resulting mixture was stirred and heated at 60 °C for 5.5 h. After cooling to room temperature, the catalyst was removed by filtration through a small pad of Celite, the solvent was evaporated, and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 1:2) to afford 32 mg (69%) of compound **41** as a white solid; mp 122–123 °C (recrystallized from *n*-hexane/ethyl acetate), lit.[39] mp = 118–120 °C for *ent*-**41**; {$[\alpha]_D^{23}$ +7.9 (*c* 0.24, MeOH), lit.[39] $[\alpha]_D^{25}$ = –5.0 (*c* 0.22, MeOH) for *ent*-**41**}. IR υ_{max} 3288, 2956, 2915, 2848, 1737, 1724, 1688, 1470, 1418, 1076, 1014 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 0.88 (t, 3H, *J* = 6.7 Hz, CH_3), 1.09–1.57 (m, 25H, H-3′, 12 × CH_2), 1.61–1.69 (m, 1H, H-3′), 3.39 (m, 2H, H-1′, H-2′), 4.07–4.11 (m, 1H, H-4), 4.35–4.39 (m, 1H, H-5), 4.44 (dd, 1H, *J* = 8.6 Hz, *J* = 6.0 Hz, H-5); ^{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 (7 × CH_2), 30.9 (CH_2), 33.1 (CH_2), 34.8 (C-3′), 55.5 (C-4), 67.3 (C-5), 73.7 (C-2′), 75.7 (C-1′), 162.8 (C═O). Anal. calcd for $C_{19}H_{37}NO_4$: C, 66.43; H, 10.86; N, 4.08. Found: C, 66.51; H, 10.90; N, 4.12.

*4.1.30. (2R,3S,4S)-4-Amino-2-tetradecyltetrahydrofuran-3-ol hydrochloride (**4.HCl**)*

Compound **41** (29 mg, 0.08 mmol) was treated with a 6 M aqueous HCl solution (3.8 mL), and the resulting mixture was stirred and heated at 120 °C for 2.5 h. After cooling to room temperature, the solvent was evaporated in vacuo, and the residue was diluted with Et_2O. The solid part was filtered off and dried on a pump for 10 h. This procedure yielded 25 mg (89%) of compound **4**.**HCl** as a white amorphous solid {$[\alpha]_D^{26}$ = +25.0 (*c* 0.16, MeOH), lit.[36] {$[\alpha]_D^{21}$ = +15.5 (*c* 0.9, MeOH), lit.[39] $[\alpha]_D^{22}$ = –29.6 (*c* 0.48, MeOH) for *ent*-**4**.**HCl**}. IR υ_{max} 3297, 3057, 2915, 2849, 2360, 2341, 1583, 1505, 1469, 1051, 1022 cm^{-1}; ^1H NMR (600 MHz, CD_3OD): δ 0.89 (t, 3H, *J* = 6.9 Hz, CH_3), 1.28–1.39 (m, 23H, 11 × CH_2, *H*-CH), 1.44–1.54 (m, 2H, H-1′, *H*-CH), 1.59–1.65 (m, 1H, H-1′), 3.68–3.75 (m, 3H, H-2, H-4, H-5), 4.02–4.04 (m, 1H, H-3), 4.12–4.16 (m, 1H, H-5); ^{13}C NMR (CD_3OD, 150 MHz): δ 14.5 (CH_3), 23.8 (CH_2), 26.9 (CH_2), 30.5 (CH_2), 30.7 (3 × CH_2), 30.8 (5 × CH_2), 33.1 (CH_2), 34.1 (C-1′), 53.7 (C-4), 69.4 (C-5), 74.4 (C-3), 85.2 (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, 11.45; N, 4.20.

*4.1.31. (2R,3S,4S)-4-Acetamido-2-tetradecyltetrahydrofuran-3-yl acetate (**42**)*

To a solution of **4**.**HCl** (20 mg, 0.06 mmol) in pyridine (1.8 mL) were successively added Ac_2O (0.11 mL, 1.2 mmol) and DMAP (3.7 mg, 0.03 mmol), and the resulting mixture was stirred at room temperature for 1 h before evaporating of the solvent. The residue was subjected to flash chromatography on silica gel (*n*-hexane/ethyl acetate, 1:2) to furnish 17 mg (75%) of compound **42** as white

crystals; mp 75–76 °C (recrystallized from *n*-hexane/ethyl acetate), lit.[23] mp 72–73 °C, lit.[32] mp not reported, lit.[36] mp 65–67 °C, lit.[39] mp 75–76 °C for *ent*-**42** {$[\alpha]_D^{27}$ –13.3 (*c* 0.18, $CHCl_3$, lit.[23] $[\alpha]_D^{22} = -15.4$ (*c* 1.0, $CHCl_3$), lit.[32] $[\alpha]_D^{26} = -15.1$ (*c* 1.2, $CHCl_3$), lit.[36] $[\alpha]_D^{21} = -14.6$ (*c* 0.5, $CHCl_3$), lit.[39] $[\alpha]_D^{24} = +17.7$ (*c* 0.13, $CHCl_3$) for *ent*-**42**}. IR υ_{max} 3290, 2914, 2846, 2362, 2342, 1733, 1650, 1563, 1459, 1375, 1300, 1231, 1104, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, $J = 6.7$ Hz, CH_3), 1.25–1.45 (m, 24H, $12 \times CH_2$), 1.49–1.67 (m, 2H, $2 \times$ H-1′), 2.01 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 3.52 (t, 1H, $J = 8.6$ Hz, $J = 8.6$ Hz, H-5), 3.86 (ddd, 1H, $J = 7.8$ Hz, $J = 5.4$ Hz, $J = 2.6$ Hz, H-2), 4.16–4.19 (m, 1H, H-5), 4.62–4.69 (m, 1H, H-4), 4.91 (dd, 1H, $J = 5.9$ Hz, $J = 2.6$ Hz, H-3), 5.65 (br d, 1H, $J = 8.3$ Hz, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (CH_3), 21.0 (CH_3), 22.7 (CH_3), 23.3 (CH_2), 25.5 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 ($4 \times CH_2$), 29.7 ($2 \times CH_2$), 31.9 (CH_2), 33.5 (C-1′), 49.8 (C-4), 69.8 (C-5), 76.7 (C-3), 84.1 (C-2), 169.8 (C═O), 169.9 (C═O). Anal. calcd for $C_{22}H_{41}NO_4$: C, 68.89; H, 10.77; N, 3.65. Found: C, 68.95; H, 10.85; N, 3.67.

4.2. Antiproliferative/cytotoxic activity

4.2.1. Cell culture

The following human cancer cell lines were used for this study: MCF-7 and MDA-MB-231 (breast cancer cells), HeLa (human cervical adenocarcinoma), Jurkat (human acute T-lymphoblastic leukaemia), HCT-116 and Caco-2 (human colon carcinoma cells) and non-cancerous cell line NiH 3T3 (mouse fibroblasts). MCF-7, HCT-116, Caco-2, HeLa and Jurkat 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's Medium. Both of these media were supplemented with Glutamax, and with 10% (V/V) foetal calf serum, penicillin ($100\ IU \times mL^{-1}$), and streptomycin ($100\ mg \times mL^{-1}$) (all from Invitrogen, Carlsbad, CA, USA), in the atmosphere of 5% CO_2 in humidified air at 37 °C. Cell viability, estimated by the tryptan 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.[49,50] 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}–$10^{-6}\ mol \times L^{-1}$. After 72 h incubation, 10 µL of MTT ($5\ mg \times mL^{-1}$) was added into each well. After an additional 4 h, during which insoluble formazan was formed, 100 µL of 10% (m/m) sodium dodecylsulfate was added into each well and another 12 h was 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.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.carres.2016.01.011.

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