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New approach to carbamoyl-polyoxamic acid derivatives through an oxazolidinone synthon

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Abstract—A key oxazolidinone synthon was obtained through condensation of vinyl magnesium with an epoxyimine, followed by a carbonation/cyclisation reaction in the presence of ammonium carbonate. Oxidative ozonolysis after protection and carbamolylation (optional) afforded the (5-*O*-carbamoyl-)polyoxamic derivatives in 9% (or 14%) total yield in six (or four) steps.

1. Introduction

Fungal infections of humans range from superficial to invasive and often lethal ones. Over the past two decades, the number of life threatening infections has increased dramatically.[1] Factors contributing to these phenomena include the growth of immunocompromised populations of patients with AIDS, more aggressive medical procedures and treatment with broad spectrum antibiotics creating resistance.[2] Therapy for systemic mycoses began with the discovery of amphotericin B and 5-fluorocytosine in the 1950s, followed by azoles in the 1960s and lipopeptides in the 1970s. Resistance against many of these compounds is still emerging.

The fungal cell wall is a structure, that is, both essential for the fungus and absent from the mammalian host, consequently it presents an attractive target for pharmaceutical (but also agricultural) pathogen management. Chitin and glucan are two main components of the cell wall unique to the fungi and thus a priori good drug target.[3]

Polyoxins form an important class of peptidyl nucleosidic antibiotics isolated from the culture broths of *Streptomyces cacoi var. asoensis* by Isono et al.[4] They are known antifungal agents that selectively and competitively inhibit membrane-bound enzyme chitin synthase from yeasts and other fungi.[5] Polyoxin D is used as an antifungal agent to treat rice sheath blight and pear black spot with no side effects.[6] They are also therapeutically useful against *Candida albicans*, a fungal pathogen that affects humans. However, polyoxins are only weakly active against whole cells of pathogenic fungi as presumably due to their hydrolytic instability and/or inefficient transport into the cell.[7] All members of the polyoxin family comprise a nucleosidic aminoacid moiety connected by a peptide linkage to the unnatural aminoacid 5-*O*-carbamoyl polyoxamic acid (except for polyoxins E and G, Fig. 1).

Polyoxamic acid **1** and its 5-*O*-carbamoyl derivative **2** (Fig. 2) have been the subject of many synthetic studies and a variety of chemical syntheses have been reported, most of which are based on carbohydrate chemistry or on the use of chiral auxiliaries.[8] Conversely, a very few number of de novo asymmetric syntheses have been reported. Trost et al.[9] have described one using a Pd-based opening of a vinyl epoxide by phthalamide in the presence of a chiral ligand. More recently, Pepper et al.[10] used a stereoselective cycloaddition of acyl nitroso compounds to cyclic dienes followed by an oxidative ring cleavage of the cycloadducts as a new approach to the synthesis of polyoxamic acid.

Over the course of our ongoing research program directed towards the use of α,β-epoxyaldehydes for the elaboration of natural products and analogues possessing a 1,2,3-polyol or aminodiol pattern, we have described the convergent synthesis of thymine polyoxin[11] C and the 5-*O*-carbamoyl

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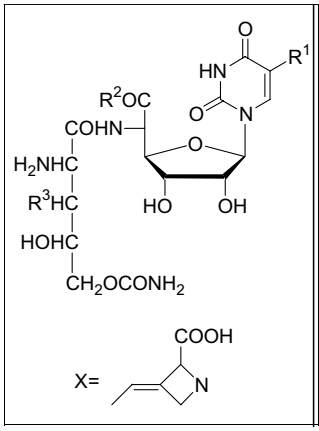

Polyoxines	R^1	R^2	R^3
A	CH_2OH	X	HO
B	CH_2OH	HO	HO
D	COOH	HO	HO
E	COOH	HO	H
F	COOH	X	HO
G	CH_2OH	HO	H
H	CH_3	X	HO
J	CH_3	HO	HO
K	H	X	HO
L	H	HO	HO

Figure 1. List of polyoxins from A to L.

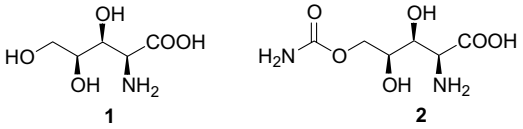

Figure 2. Polyoxamic acid **1** and its 5-*O*-carbamoyl polyoxamic derivative **2**.

polyoxamic acid.[12] In the latter case, our methodology was based on four steps, that is (a) Sharpless asymmetric epoxidation; (b) homologation of the epoxyaldehyde; (c) stereo- and regioselective opening of the oxirane; and (d) epimerisation of the C-2 carbon atom.

We have recently developed[13] a flexible and stereoselective approach to 1,2,3-aminodiol systems possessing a terminal vinyl group and made use for the synthesis of various iminosugars. Herein we report the use of this methodology for a new access to 5-*O*-carbamoyl polyoxamic derivatives.

2. Results and discussion

The key synthon of the methodology presented here is vinylic oxazolidinone **6**, the synthesis of which is presented in Figure 3. The suitably chosen epoxyimine **4** is reacted under conditions inspired by Procter's methodology[14] with vinylmagnesium bromide in the presence of the Lewis acid chelator $Et_2O{\cdot}BF_3$, to afford compound **5**. Its stereochemical assignment has already been established by chemical correlation.[15]

Compound **5** possesses the right C-2 and C-4 stereogenic centres of the polyoxamic acid and a reverse one at the C-3 position. Opening of the oxirane moiety at the C-3 position was then accomplished by our recently elaborated intramolecular cyclisation sequence[16] affording oxazolidinone **6** as the sole product of the reaction in 90% yield after silica-gel purification.

Having in hand oxazolidinone **6**, we explored two pathways for the synthesis of 5-*O*-carbamoyl polyoxamic acid derivatives (Fig. 4). The first resides on cleavage of the oxazolidinone moiety prior to further group manipulations, while the second maintains the oxazolidinone moiety until the end of the synthetic pathway.

Cleavage of the cyclic carbamate was performed via a saponification reaction (Fig. 5). Compound **6**, when treated with lithium hydroxide under reflux conditions, afforded aminotriol **7** in 65% yield after silica gel purification. The

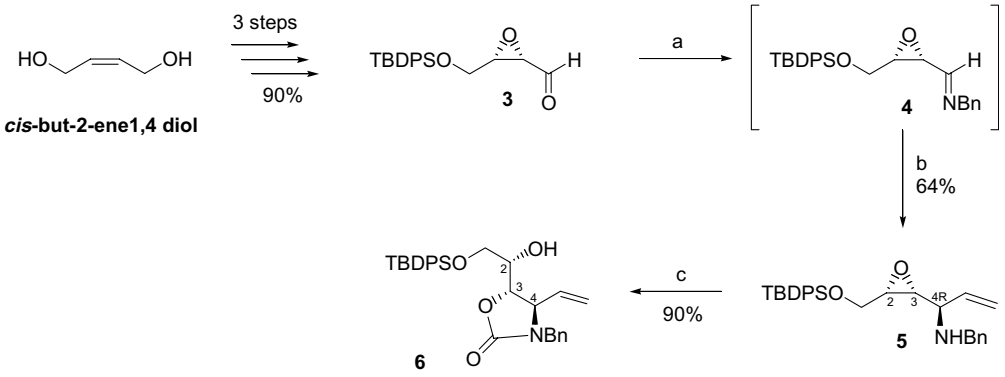

Figure 3. Reagents and conditions: (a) $PhCH_2NH_2$, MS 4 Å, Et_2O, rt, 3 h; (b) $Et_2O{\cdot}BF_3$, C_2H_3MgBr, Et_2O, −78 °C, 64%; (c) $(NH_4)_2CO_3$, THF/H_2O (4/1), rt, 90%.

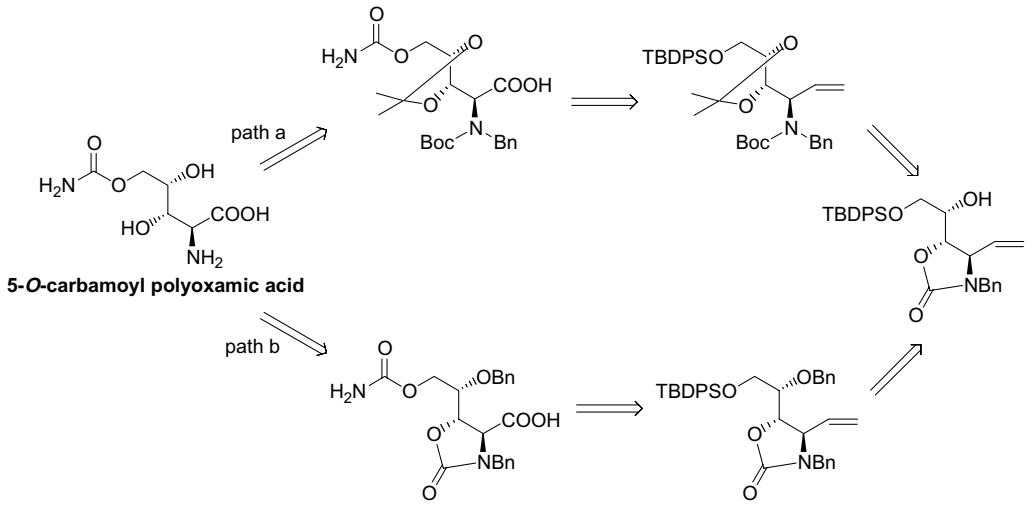

Figure 4. Retrosynthetic pathways.

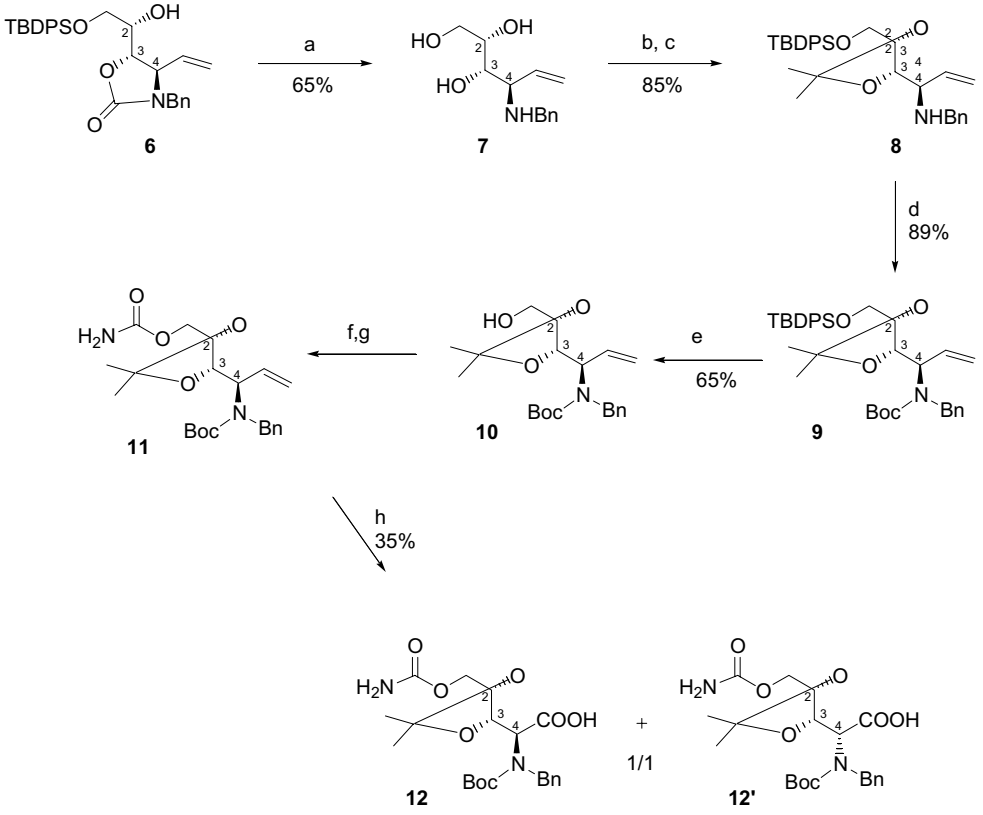

Figure 5. Reagents and conditions: (a) $LiOH{\cdot}H_2O$, dioxane/H_2O (3/1), reflux, 4 h, 65%; (b) TBDPSCl, Et_3N, DMAP (cat), CH_2Cl_2, rt, 20 h, 85%; (c) CSA, dimethoxypropane, rt, 24 h, quant.; (d) Boc_2O, Et_3N, CH_2Cl_2, rt, 48 h, 89%; (e) TBAF/SiO_2, THF, rt, 20 h, 85%; (f) *p*-nitrophenylchloroformate, pyridine, rt 30 min; (g) NH_3 in MeOH (7 N), 0 °C, 1 h, 77%; (h) O_3, AcOEt, −78 °C, then H_2O_2 (30% in H_2O), 50 °C, 5 min, 35%.

tert-butyldiphenyl silyl group had also been eliminated. Other basic conditions reactions used gave the same result. Protection of the aminotriol at the primary position, and subsequent formation of the five membered acetonide yielded compound **8** in 85% yield for the two steps sequence. *tert*-Butyloxy carbonyl protection of the secondary amine afforded the completely protected aminopolyol **9**. Elimination of the silyl group was followed by carbamoylation of primary alcohol **10** via a two-step procedure using *p*-nitrophenylchloroformate in pyridine and treatment of the primary carbamate intermediate at 0 °C with methanolic ammonia. The 5-*O*-carbamoyl moiety was thus installed in 65% yield (three steps). An ozonolysis reaction at low temperature followed by the immediate treatment

of the ozonide with hydrogen peroxide for 5 min at 50 °C afforded the protected 5-*O*-carbamoyl polyoxamic acid **12** and its aminoacid epimer **12′** in 35% yield and in a 1:1 ratio.

With regards to the second pathway, the ozonolysis reaction of the vinylic group (Fig. 6) was also explored. Protection of the secondary hydroxyl group (NaH, BnBr, *n*-Bu_4NI) led to oxazolidinone **13** in 70% yield.

Since the oxidative ozonolysis reaction at rt gave a mixture of non-acid compounds (not characterised), we studied the reaction conditions at different temperatures. In all cases, the ozonolysis reaction started at −78 °C in ethylacetate, after which the reaction mixture was dropped in a 30% aqueous H_2O_2 solution heated at two different temperatures, 50 °C and 80 °C.

When the reaction mixture was heated for 30 min at 50 °C, two compounds were isolated after quenching, extraction and silica-gel purification. They were identified to be derivatives **15** and **16** (35% yield, 3:2 ratio of **15**:**16**). The latter was obtained through an additional oxidative process of the benzyloxy group. Primary methyl ethers (RCH_2OCH_3) have already been reported as latent carbomethoxy groups in ruthenium tetraoxide catalysed oxidations.[17] To the best of our knowledge, this is the first time that this transformation has occurred in such functionalised systems.

One dimensional (^1H, ^{13}C) and two dimensional (HSQC, HMBC) NMR spectroscopy was performed for compound **15**. Concerning the ^1H NMR spectra, we can find a straightforwad AB system for the N–CH_2–Ph hydrogen atoms ($\Delta\delta H_A - \delta H_B = 148$ Hz) and small coupling constants for J_{H3-H2} and J_{H3-H4} (both equal to $J = 1.8$ Hz). These small values are indicative of a *trans* relationship of the oxazolidinone system. Analogous coupling values and chemical shifts have been reported in the literature.[18] Concerning the ^{13}C NMR spectra, two C=O chemical shifts were observed at $\delta = 160.1$ ppm (COOH) and at $\delta = 156.9$ (NCOO), the latter being in agreement with the literature data.[18] Finally, the IR spectra showed two carbonyl absorption bands at 1775 $\nu\,cm^{-1}$ (NCOO) and 1727 cm^{-1} (COOH).

The reaction mixture of the ozonolysis reaction on compound **13** was also allowed to react at 80 °C for 5 min. After quenching, extraction and silica-gel purification, a sole product could be obtained different from compounds **15** and **16**. It is noteworthy that the same new compound was also obtained when the H_2O_2 treatment was conducted at 50 °C for 40 h. After a careful analysis of its spectroscopic characteristics (^1H, ^{13}C, HSQC, HMBC, IR), we assigned the structure to compound **14**, obtained in 35% yield. Some marked differences appear between compounds **14** and **15**. First, the N–CH_2–Ph AB system in **14** has a different chemical shift and is much less split ($\Delta\delta HA - HB = 69$ Hz, vs 148 Hz), suggesting a less constrained environment for the corresponding methylene. The H-4 chemical shift has moved downfield for compound **14**, $\delta = 5.01$ versus $\delta = 5.90$ for compound **15**, while the coupling constants remain small. Concerning the ^{13}C NMR spectra, we observed only one chemical shift for the C=O functions ($\delta = 157.9$ ppm) and in the IR spectra a unique carbonyl band absorption at $\nu = 1739\ cm^{-1}$. Relative data are scarce in the literature. It is noteworthy that an unsubstituted analogous compound reported recently by Martin[19] shows a sole ^{13}C carbonyl chemical shift.

A mechanism for this transformation is tentatively presented below (Fig. 7). The process might be initiated from intermediate **15** by the reversible intramolecular attack of the carboxylate onto the oxazolidinone carbonyl. The unstable cyclic entity thus formed might then rapidly evolve, either through cleavage of the C–N or the C–O

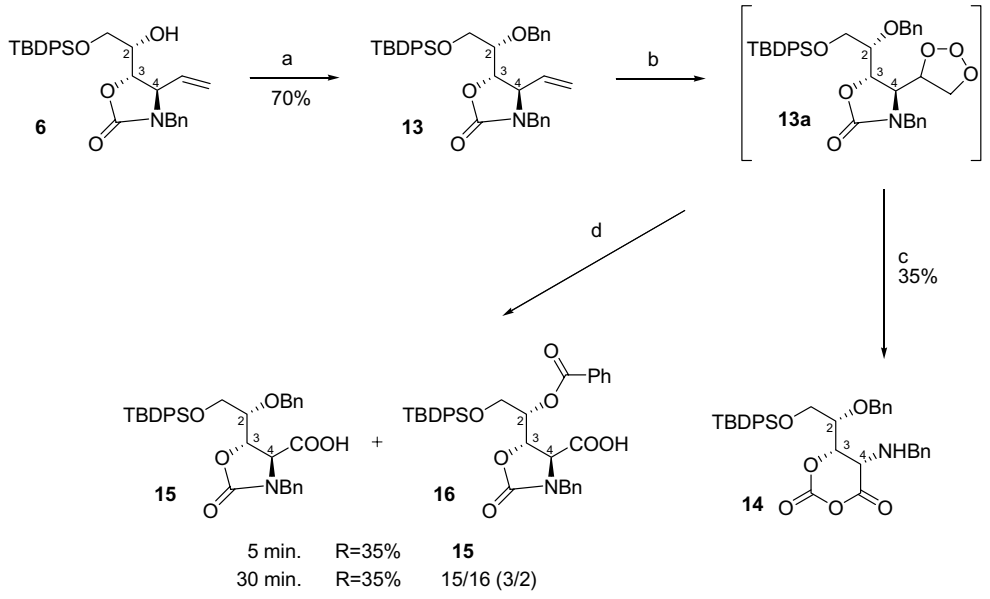

Figure 6. Reagents and conditions: (a) NaH, BnBr, *n*-Bu_4NI, THF, rt, 70%; (b) O_3, AcOEt, −78 °C, 20 mn; (c) H_2O_2 (30% in H_2O), 80 °C, 5 min, 35%; (d) H_2O_2 (30% in H_2O), 50 °C, 5 or 30 min.

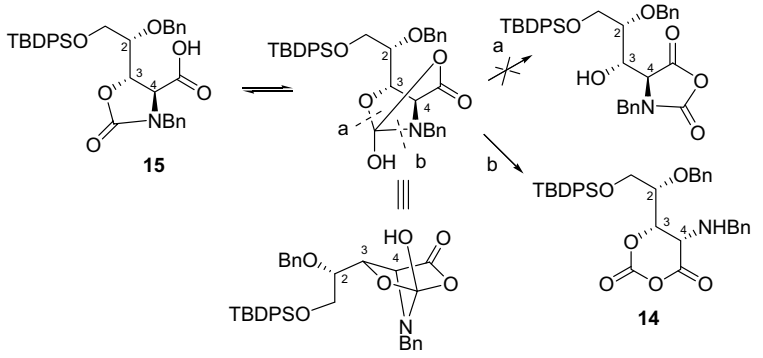

Figure 7. Proposed mechanism for the formation of cyclic mixed anhydride **14**.

bond. The former possibility would lead to the formation of an *N*-carboxyanhydride that can be ruled out on the basis of the characterisation of compound **14**. On the other hand, in the latter case, an intramolecular mixed anhydride would be generated. Such a structure would be in agreement with the spectral data of derivative **14**.

In order to proceed with the synthesis of the carbamoylated derivatives, oxazolidinone **13** was desilylated smoothly ($TBAF/SiO_2$, THF rt 83%) and the carbamoylation was conducted as previously to afford compound **18** in 90% yield (Fig. 8). The oxidative (5 min, 50 °C) ozonolysis reaction performed as before yielded the corresponding acid **19** in 30% yield.

3. Conclusion

In conclusion, based on the use of a suitably chosen epoxyalcohol, our methodology on the region- and stereocontrolled opening of the oxirane ring of the vinylic epoxyamines and on the direct oxidative ozonolyses reactions can lead to the formal synthesis of 5-*O*-carbamoyl polyoxamic acid and its protected derivatives.

Following the first methodology, the carbamoylated ethylenic intermediate **11** was obtained in eight steps starting from epoxyaldehyde **3** and 18.4% total yield. Nevertheless, the transformation of the ethylenic functionality to the acid remains problematic under ozonolysis conditions due essentially to low yield and epimerisation.

Following the second approach, protected polyoxamic acid **15** was obtained in 24.5% total yield from oxazolidinone **6** and 14.1% yield from epoxyaldehyde **3** (four steps). Finally, the protected 5-*O*-carbamoyl-polyoxamic acid derivative **19** was obtained in 15.8% yield (from **6**) and 9% from **3** (six steps).

4. Experimental

4.1. General methods

Dry solvents were distilled prior to use: CH_2Cl_2, Et_3N and DMSO from CaH_2, and THF from sodium/benzophenone. Chromatographic purifications were performed by Medium-pressure liquid chromatography with a Jobin-Yvon apparatus using Merck 15–40 μm silica gel, flash column chromatography was carried out with SDS 35–70 μm silica gel, and preparative HPLC column chromatography was carried out using Merck 12 μm silica gel. ^1H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on Brucker AC 250 and AC400 spectrometers at 20 °C, using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded on a Perkin–Elmer FT-IR 883 spectrometer using NaCl plates. Mass spectrometry (MS) data were obtained on a NERMAG R10-10 spectrometer. Optical rotations were measured on a Perkin–Elmer model 141 polarimeter. High resolution mass spectra (HRMS) were performed on a ThermoFinnigan MAT 95 XL spectrometer (DCI). Enantiomeric excesses were determined by HPLC using a chiral analytic column CHIRACEL OD.

4.2. (4*R*,5*S*)-3-Benzyl-5-((1*S*)-2-*tert*-butyldiphenylsilyloxy-1-hydroxyethyl)-4-vinyl-1,3-oxazolan-2-one 6

To a solution of epoxyamine **5** (3.73 g, 8.16 mmol) in a mixture of THF/H_2O 4:1 (20 mL/mmol) was added ammo-

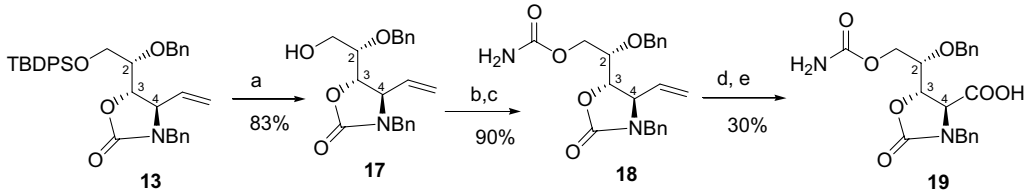

Figure 8. Reagents and conditions: (a) $TBAF/SiO_2$, THF, rt, 20 h, 83%; (b) *p*-nitrophenylchloroformate, pyridine, rt 30 mn; (c) NH_3 in MeOH (7 M), 0 °C, 1 h, 90%; (d) O_3, AcOEt, −78 °C, 20 min; (e) H_2O_2 (30% in H_2O), 50 °C, 5 min, 30%.

nium carbonate (6.30 g, 65.30 mmol). After 24 h, the mixture was concentrated and 150 mL of water was added. The aqueous phase was extracted three times with Et_2O, and the combined organic layers were successively washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was then purified by medium-pressure chromatography on silica gel (petroleum ether/EtOAc 85:15) to give starting materials **5** (0.25 g, 0.55 mmol), which has not reacted, and **6** (3.68 g, 7.34 mmol, 90% yield): $R_f = 0.11$ (petroleum ether/EtOAc 85:15); $[\alpha]_D^{25} = +30.2$ (*c* 1.06, $CHCl_3$); IR (film) 3405, 3074, 1726, 1426, 1064 cm^{-1}; ^1H NMR δ ppm (400 MHz, $CDCl_3$) 7.65–7.60 (4H, m, phenyl), 7.46–7.39 (6H, m, phenyl), 7.32–7.26 (5H, m, phenyl), 5.68 (1H, ddd, $^3J H_5/H_4 = 9.2$ Hz, $^3J H_5/H_{6a} = 10.4$ Hz and $^3J H_5/H_{6b} = 17.0$ Hz, H5), 5.35 (1H, d, $^3J H_{6a}/H_5 = 10.4$ Hz, H6a), 5.24 (1H, d, $^3J H_{6b}/H_5 = 17.0$ Hz, H6b), 4.77 and 4.05 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 288$ Hz, $^2J_{gem} = 15.2$ Hz, N*CH*$_2$Ph), 4.27 (1H, dd, $^3J H_3/H_2 = 2.4$ Hz and $^3J H_3/H_4 = 7.2$ Hz, H3), 4.07 (1H, dd, $^3J H_4/H_3 = 7.2$ Hz and $^3J H_4/H_5 = 9.2$ Hz, H4), 3.77 and 3.72 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 21$ Hz, $^3J H_{1a}/H_2 = 7.0$ Hz, $^3J H_{1b}/H_2 = 5.8$ Hz, $^2J H_{1a}/H_{1b} = 10.2$ Hz, H1), 3.65 (1H, ddd, $^3J H_2/H_{1a} = 7.0$ Hz, $^3J H_2/H_{1b} = 5.8$ Hz and $^3J H_2/H_3 = 2.4$ Hz, H2), 2.39–2.21 (1H, m, OH), 1,06 (9H, s, CH_3 *t*BuPh$_2$Si); ^{13}C NMR δ ppm (100 MHz, $CDCl_3$) 157.5 (C=O), 135.6 (Cq arom.), 135.5 (CH arom.), 134.6 (C5), 132.8 (Cq arom.), 129.9, 128.7, 128.3, 127.8 (CH arom.), 121.8 (C6), 78.1 (C3), 70.8 (C2), 64.1 (C1), 60.0 (C4), 46.0 (N*CH*$_2$Ph), 26.8 (CH_3 *t*BuPh$_2$Si), 19.2 (Cq *t*BuPh$_2$Si); MS (DCI, NH_3): $m/z = 519$ $[M+NH_4]^+$ (100), 502 $[M+H]^+$ (15); HRMS (DCI, NH_3) calcd. for $C_{30}H_{36}NO_4Si$ $[M+H]^+$ 502.2414. Found: 502.2415.

4.3. (2*S*,3*S*,4*R*)-4-Benzylamino-1,2,3-triol-hex-5-en 7

To a solution of oxazolidinone **6** (0.99 g, 1.97 mmol) in a mixture of dioxane/H_2O 3:1 (10 mL/mmol) was added monohydrated lithium hydroxide (0.49 g, 11.80 mmol). The mixture was heated at reflux for 4 h, after which the mixture was concentrated. Water was then added (20 mL), and the aqueous phase extracted three times with CH_2Cl_2. The combined organic layers were successively washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was then purified by medium-pressure column chromatography on silica gel (EtOAc with 0.25% Et_3N) to give 7 (0.30 g, 1.28 mmol, 65% yield): $R_f = 0.11$ (EtOAc with 0.25% Et_3N); $[\alpha]_D^{25} = -20.0$ (*c* 2.75, $CHCl_3$); IR (film) 3453, 2931, 2858, 1638, 1066 cm^{-1}; ^1H NMR δ ppm (400 MHz, $CDCl_3$) 7.36–7.28 (5H, m, phenyl), 5.79 (1H, ddd, $^3J H_5/H_4 = 8.8$ Hz, $^3J H_5/H_{6a} = 10.4$ Hz and $^3J H_5/H_{6b} = 17.2$ Hz, H5), 5.36 (1H, dd, $^3J H_{6a}/H_5 = 10.4$ Hz and $^2J H_{6a}/H_{6b} = 1.6$ Hz, H6a), 5.25 (1H, dd, $^3J H_{6b}/H_5 = 17.2$ Hz and $^2J H_{6a}/H_{6b} = 1.6$ Hz, H6b), 3.91 and 3.64 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 107$ Hz, $^2J_{gem} = 12.8$ Hz, N*CH*$_2$Ph), 3.78–3.73 (2H, m, H1), 3.75–3.72 (1H, m, H2), 3.62 (1H, dd, $^3J H_3/H_2 = 1.8$ Hz and $^3J H_3/H_4 = 4.8$ Hz, H3), 3.24 (1H, dd, $^3J H_4/H_3 = 4.8$ Hz and $^3J H_4/H_5 = 8.8$ Hz, H4); ^{13}C NMR δ ppm (100 MHz, $CDCl_3$) 139.1 (Cq arom.), 136.2 (C5), 128.6, 128.4, 127.4 (CH arom.), 118.6 (C6), 74.0 (C3), 72.3 (C2), 65.4 (C1), 63.7 (C4), 50.5 (N*CH*$_2$Ph); MS (DCI, NH_3): $m/z = 238$ $[M+H]^+$ (100); HRMS (DCI, NH_3) calcd. for $C_{13}H_{20}NO_3$ $[M+H]^+$ 238.1443. Found: 238.1449.

4.4. (2*S*,3*S*,4*R*)-4-Benzylamino-1-*tert*-butyldiphenylsilyloxy-2,3-dioxyisopropylidene-hex-5-en 8

To a solution of aminotriol **7** (0.14 g, 0.60 mmol) in CH_2Cl_2 (10 mL/mmol) were added *tert*-butyldiphenylsilyl chloride (0.17 mL, 0.66 mmol), freshly distilled Et_3N (92 μL, 0.66 mmol) and DMAP (3 mg, 0.02 mmol). The mixture was stirred at rt for 20 h. The mixture was then concentrated and 10 mL of water was added. The aqueous phase was extracted three times with CH_2Cl_2 and twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by medium-pressure column chromatography on silica gel (petroleum ether/EtOAc 9:1) to give the monosilylated compound (0.24 g, 0.51 mmol, 85% yield): $R_f = 0.16$ (petroleum ether/EtOAc 9:1); $[\alpha]_D^{25} = +7.3$ (*c* 0.79, $CHCl_3$); IR (film) 3415, 2929, 2856, 1636, 1111 cm^{-1}; ^1H NMR δ ppm (400 MHz, $CDCl_3$) 7.73–7.67 (4H, m, phenyl), 7.45–7.34 (11H, m, phenyl), 5.80 (1H, ddd, $^3J H_5/H_4 = 8.4$ Hz, $^3J H_5/H_{6a} = 10.4$ Hz and $^3J H_5/H_{6b} = 17.2$ Hz, H5), 5.35 (1H, dd, $^3J H_{6a}/H_5 = 10.4$ Hz and $^2J H_{6a}/H_{6b} = 1.6$ Hz, H6a), 5.24 (1H, dd, $^3J H_{6b}/H_5 = 17.2$ Hz and $^2J H_{6a}/H_{6b} = 1.6$ Hz, H6b), 3.92 and 3.65 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 108$ Hz, $^2J_{gem} = 12.8$ Hz, N*CH*$_2$Ph), 3.82–3.75 (2H, m, H1), 3.78–3.75 (1H, m, H2), 3.73 (1H, dd, $^3J H_3/H_2 = 1.4$ Hz and $^3J H_3/H_4 = 4.8$ Hz, H3), 3.21 (1H, dd, $^3J H_4/H_3 = 4.8$ Hz and $^3J H_4/H_5 = 8.4$ Hz, H4), 1.08 (9H, s, CH_3 *t*BuPh$_2$Si); ^{13}C NMR δ ppm (100 MHz, $CDCl_3$) 139.5 (Cq arom.), 136.6 (C5), 135.6 (CH arom.), 133.1, 132.9 (Cq arom.), 129.8, 128.5, 128.4, 127.8, 127.2 (CH arom.), 118.4 (C6), 72.6 (C2), 72.4 (C3), 66.3 (C1), 64.0 (C4), 50.6 (N*CH*$_2$Ph), 26.9 (CH_3 *t*BuPh$_2$Si), 19.2 (Cq *t*BuPh$_2$Si); MS (DCI, NH_3): $m/z = 476$ $[M+H]^+$ (100); HRMS (DCI, NH_3) calcd. for $C_{29}H_{38}NO_3Si$ $[M+H]^+$ 476.2621. Found: 476.2624. Under an inert atmosphere, to a solution of this monosilylated compound (0.9 g, 0.19 mmol) in freshly distilled 2,2-dimethoxypropane (13 mL/mmol) was added camphor sulfonic acid (0.5 g, 0.21 mmol). The solution was stirred at rt for 24 h and then hydrolysed with a saturated aqueous solution of $NaHCO_3$. The mixture was then concentrated, 10 mL of water added, and the aqueous phase extracted three times with EtOAc. The combined organic layers were successively washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Compound 8 (97 mg, 0.19 mmol, quant.) was obtained as a pure product without purification: $R_f = 0.33$ (petroleum ether/EtOAc 85:15 with 0.25% Et_3N); $[\alpha]_D^{25} = -81.6$ (*c* 1.20, $CHCl_3$); IR (film) 3331, 2930, 2858, 1494, 1111 cm^{-1}; ^1H NMR δ ppm (400 MHz, $CDCl_3$) 7.70–7.67 (4H, m, phenyl), 7.44–7.28 (11H, m, phenyl), 5.61 (1H, dd, $^3J H_5/H_4 = 8.8$ Hz and $^3J H_5/H_{6b} = 6.2$ Hz, H5), 5.22 (1H, s, H6a), 5.19 (1H, d, $^3J H_{6b}/H_5 = 6.2$ Hz, H6b), 4.09 (1H, td, $^3J H_2/H_3 = 5.6$ Hz and $^3J H_2/H_{1a} = {}^3J H_2/H_{1a} = 4.0$ Hz, H2), 4.07 (1H, dd, $^3J H_3/H_2 = 5.6$ Hz and $^3J H_3/H_4 = 6.4$ Hz, H3), 3.90 and 3.63 (2H, AB part of an ABX system,

$\Delta\delta Ha - \delta Hb = 108$ Hz, $^2J_{gem} = 13.6$ Hz, NCH_2Ph), 3.78 and 3.67 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 44$ Hz, $^3JH_{1a}/H_2 = {}^3JH_{1b}/H_2 = 4.0$ Hz and $^3JH_{1a}/H_{1b} = 10.8$ Hz, H1), 3.16 (1H, dd, $^3JH_4/H_3 = 6.4$ Hz and $^3JH_4/H_5 = 8.8$ Hz, H4), 1.41 and 1.37 (6H, 2s, H8 and H9), 1.06 (9H, s, CH_3 *t*BuPh_2Si); ^{13}C NMR δ ppm (100 MHz, $CDCl_3$) 140.4 (Cq arom.), 137.2 (C5), 135.7 (CH arom.), 133.3 (Cq arom.), 129.6, 128.3, 128.1, 127.7, 126.8 (CH arom.), 118.8 (C6), 109.3 (C7), 79.7 (C3), 79.1 (C2), 64.3 (C1), 63.7 (C4), 50.7 (NCH_2Ph), 27.5 (C8 and C9), 26.8 (CH_3 *t*BuPh_2Si), 19.2 (Cq *t*BuPh_2Si); MS (DCI, NH_3): $m/z = 516$ $[M+H]^+$ (100); HRMS (DCI, NH_3) calcd. for $C_{32}H_{42}NO_3Si$ $[M+H]^+$ 516.2934. Found: 516.2938.

4.5. (2*S*,3*S*,4*R*)-4-Benzylamino-1-*tert*-butyldiphenylsilyloxy-4-*tert*-butyloxycarbonylamino-2,3-dioxyisopropylidene-hex-5-en 9

To a solution of compound **8** (0.24 g, 0.47 mmol) and Et_3N (0.13 mL, 0.94 mmol) in CH_2Cl_2 (15 mL/mmol of compound **8**) slowly was added, at 0 °C, Boc_2O (0.11 g, 0.52 mmol). The mixture was then stirred at rt for 48 h and then, hydrolysed with 20 mL of water. The aqueous phase was extracted three times with EtOAc, and the combined organic layers were successively washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by medium-pressure column chromatography on silica gel (petroleum ether/EtOAc 95:5) to give **9** (0.26 g, 0.42 mmol, 89%): $R_f = 0.17$ (petroleum ether/EtOAc 95:5); $[\alpha]_D^{25} = +3.1$ (*c* 1.47, $CHCl_3$); IR (film) 2931, 2858, 1695, 1428, 1058 cm^{-1}; ^{1}H NMR δ ppm (400 MHz, $CDCl_3$) 7.75–7.71 (4H, m, phenyl), 7.46–7.38 (5H, m, phenyl), 7.32–7.24 (6H, m, phenyl), 5.85–5.69 (1H, m, H5), 5.32–5.28 (1H, m, H6a), 5.13–5.06 (1H, m, H6b), 4.71–4.65 (1H, m, H4), 4.66–4.57 (2H, m, NCH_2Ph), 4.47 (1H, t, $^3JH_3/H_2 = {}^3JH_3/H_4 = 7.2$ Hz, H3), 3.97–3.93 (1H, m, H2), 3.94–3.67 (2H, m, H1), 1.51 and 1.34 (6H, 2s, H8 and H9), 1.46 (9H, s, CH_3 Boc), 1.10 (9H, s, CH_3 *t*BuPh_2Si); ^{13}C NMR δ ppm (100 MHz, $CDCl_3$) 156.0 (C=O Boc), 135.9 (CH arom.), 134.2 (C5), 133.6 (Cq arom.), 129.9, 128.3, 127.9 (CH arom.), 119.7 (C6), 109.5 (C7), 79.9 (C2), 77.1 (C3), 63.7 (C1), 60.7 (C4), 49.7 (NCH_2Ph), 28.5 (C8 and C9), 27.6 (CH_3 Boc), 27.0 (CH_3 *t*BuPh_2Si), 19.5 (Cq *t*BuPh_2Si); MS (DCI, NH_3): $m/z = 616$ $[M+H]^+$ (100); HRMS (DCI, NH_3) calcd. for $C_{37}H_{50}NO_5Si$ $[M+H]^+$ 616.3458. Found: 616.3459.

4.6. (2*S*,3*S*,4*R*)-4-Benzylamino-4-*tert*-butyloxycarbonylamino-1-*O*-carbamoyl-2,3-dioxyisopropylidene-hex-5-en 11

To a solution of compound **9** (0.14 g, 0.23 mmol) in anhydrous THF (35 mL/mmol) was added TBAF supported on silica (0.27 g, 0.27 mmol). The mixture was stirred overnight at rt after which it was concentrated. The residue was suspended in EtOAc and filtered. Then, the solvent was evaporated under reduced pressure. The crude product was purified by medium-pressure column chromatography on silica gel (petroleum ether/EtOAc 8:2) to give the deprotected product **10** (72 mg, 0.19 mmol, 85% yield): $R_f = 0.13$ (petroleum ether/EtOAc 8:2); $[\alpha]_D^{25} = +3.6$ (*c* 0.73, $CHCl_3$); IR (film) 3453, 2930, 1690, 1111 cm^{-1}; ^{1}H NMR δ ppm (400 MHz, $CDCl_3$) 7.32–7.24 (5H, m, phenyl), 6.02–5.88 (1H, m, H5), 5.37–5.32 (1H, m, H6a), 5.28–5.14 (1H, m, H6b), 4.77–4.64 (1H, m, H4), 4.57 (2H, s, NCH_2Ph), 4.32–4.21 (1H, m, H3), 3.93–3.82 (1H, m, H2), 3.82–3.76 (2H, m, H1), 1.52 and 1.33 (6H, 2s, H8 and H9), 1.42 (9H, s, CH_3 Boc); ^{13}C NMR δ ppm (100 MHz, $CDCl_3$) 156.1 (C=O Boc), 135.6 (Cq arom.), 133.9 (C5), 128.3, 127.0 (CH arom.), 120.3 (C6), 109.3 (C7), 79.5 (C3), 78.8 (C2), 62.8 (C1), 62.2 (C4), 50.4 (NCH_2Ph), 28.4 (C8 and C9), 27.4 (CH_3 Boc); MS (DCI, NH_3): $m/z = 378$ $[M+H]^+$ (100); HRMS (DCI, NH_3) calcd. for $C_{21}H_{32}NO_5$ $[M+H]^+$ 378.2280. Found: 378.2279. The *para*-nitrophenyl chloroformate was purified by sublimation. Under inert atmosphere, to a solution of deprotected compound (69 mg, 0.18 mmol) in anhydrous pyridine (5 mL/mmol) was added *p*-nitrophenyl chloroformate (55 mg, 0.28 mmol). After 30 min at rt, the mixture was diluted with EtOAc, and washed successively with a saturated aqueous solution of $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a red oil. This intermediate was then solubilised in MeOH (15 mL/mmol), and a 7 M solution of ammonia in MeOH (5 mL/mmol) was added at 0 °C. The mixture was stirred for 1 h at 0 °C and then methanol was evaporated. The crude product was purified by medium-pressure column chromatography on silica gel (petroleum ether/EtOAc 7:3) to give **11** (59 mg, 0.14 mmol, 77% yield): $R_f = 0.24$ (petroleum ether/EtOAc 7:3); $[\alpha]_D^{25} = -3.5$ (*c* 1.26, $CHCl_3$); IR (film) 3359, 2932, 1729, 1692, 1067 cm^{-1}; ^{1}H NMR δ ppm (400 MHz, $CDCl_3$) 7.32–7.25 (5H, m, phenyl), 6.04–5.78 (1H, m, H5), 5.32 (1H, s, H6a), 5.27–5.17 (1H, m, H6b), 5.29 (2H, m, NH_2), 4.88–4.69 (1H, m, H4), 4.69–4.48 (2H, m, NCH_2Ph), 4.36–4.08 (2H, m, H1), 4.21 (1H, t, $^3JH_3/H_2 = {}^3JH_3/H_4 = 7.4$ Hz, H3), 4.08–3.92 (1H, m, H2), 1.53 and 1.34 (6H, 2s, H8 and H9), 1.41 (9H, s, CH_3 Boc); ^{13}C NMR δ ppm (100 MHz, $CDCl_3$) 156.5 (C=O Boc), 155.9 (C=O carbamoyl), 135.4 (Cq arom.), 133.6 (C5), 128.3, 127.1, 126.8 (CH arom.), 120.2 (C6), 109.9 (C7), 79.1 (C3), 76.4 (C2), 65.3 (C1), 61.3 (C4), 50.4 (NCH_2Ph), 28.4 (C8 and C9), 27.2 (CH_3 Boc); MS (DCI, NH_3): $m/z = 421$ $[M+H]^+$ (100); HRMS (DCI, NH_3) calcd. for $C_{22}H_{33}N_2O_6$ $[M+H]^+$ 421.2339. Found: 421.2331.

4.7. (2*S*,3*S*,4*S*)-4-Benzylamino-4-*tert*-butyloxycarbonylamino-1-*O*-carbamoyl-2,3-dioxyisopropyliden-pentanoïc acid 12 and (2*S*,3*S*,4*R*)-4-benzylamino-4-*tert*-butyloxycarbonylamino-1-*O*-carbamoyl-2,3-dioxyisopropyliden-pentanoïc acid 12′

In a solution of alkene **10** (31 mg, 73 μmol) in EtOAc (10 mL/mmol), at −78 °C, O_3 was bubbled until the solution became blue. The ozonide formed was then decomposed by dropping the mixture in 130 μL of a 30% aqueous solution of hydrogen peroxide heated at 50 °C, and stirring it at 50 °C for 5 min. The mixture was then cooled to 0 °C and basified with 2 mL of a saturated aqueous solution of K_2CO_3 and extracted with Et_2O. The aqueous phase was then acidified until pH 4 with a 1 M hydrochloric acid aqueous solution saturated in NaCl, and extracted with Et_2O. The organic layers were succes-

sively washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by medium-pressure column chromatography on silica gel (CH_2Cl_2/EtOAc 7:3) to give a mixture 1:1 of **12** and **12′** (12 mg, 26 μmol, 35% yield): $R_f = 0.08$ (CH_2Cl_2/EtOAc 7:3); IR (film) 3359, 2978, 1729, 1692, 1068 cm^{-1}; Compound **12**: ^1H NMR δ ppm (400 MHz, $CDCl_3$) 9.27 (1H, m, H5), 7.34–7.29 (5H, m, phenyl), 4.70 (2H, d, $J = 12.0$ Hz, NH_2), 4.68–4.56 (1H, d, $^3J_{H4/H3} = 7.2$ Hz, H4), 4.47 and 4.37 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 40$ Hz, $^2J_{gem} = 15.6$ Hz, NCH_2Ph), 4.42–4.34 (1H, m, H3), 4.25–4.17 (2H, m, H1), 4.14–4.08 (1H, m, H2), 1.46 (9H, s, CH_3 Boc), 1.43 and 1.40 (6H, 2s, H8 and H9); Compound **12′**: ^1H NMR δ ppm (400 MHz, $CDCl_3$) 9.39 (1H, m, H5), 7.34–7.29 (5H, m, phenyl), 5.29 (2H, d, $J = 12.0$ Hz, NH_2), 4.55–4.53 (1H, m, H4), 4.47 and 4.37 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 40$ Hz, $^2J_{gem} = 15.6$ Hz, NCH_2Ph), 4.42–4.34 (1H, m, H3), 4.25–4.17 (2H, m, H1), 4.08–4.01 (1H, m, H2), 1.46 (9H, s, CH_3 Boc), 1.43 and 1.40 (6H, 2s, H8 and H9); MS (DCI, NH_3): $m/z = 456$ $[M+NH_4]^+$ (15), 393 $[M-CO_2H]$ (68), 218 (100%).

4.8. (4*R*,5*S*)-3-Benzyl-5-((1*S*)-2-*tert*-butyldiphenylsilyloxy-1-benzyloxyethyl)-4-vinyl-1,3-oxazolan-2-one 13

Under an inert atmosphere, to a solution of oxazolidinone **6** (0.60 g, 1.2 mmol) in anhydrous THF (20 mL/mmol) at 0 °C was added 60% sodium hydride in oil (72 mg, 1.8 mmol). After 5 min, the mixture was warmed up to rt and tetrabutylammonium iodide (22 mg, 0.06 mmol) was added. After 5 min of stirring, benzyl bromide (214 μL, 1.8 mmol) was added. The mixture was stirred at rt for 3.5 h, and was then hydrolysed with a saturated aqueous solution of $NaHCO_3$. THF was evaporated and the residual aqueous phase extracted three times with DCM. The combined organic layers were washed successively with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by medium-pressure column chromatography on silica gel (petroleum ether/EtOAc 9:1) to give **13** (0.50 g, 0.84 mmol, 70% yield): $R_f = 0.25$ (petroleum ether/EtOAc 9:1); $[\alpha]_D^{25} = +84.5$ (*c* 1.90, $CHCl_3$); IR (film) 3405, 3074, 1755, 1589, 1064 cm^{-1}; ^1H NMR δ ppm (400 MHz, $CDCl_3$) 7.65–7.60 (4H, m, phenyl), 7.46–7.39 (6H, m, phenyl), 7.32–7.26 (5H, m, phenyl), 5.63 (1H, td, $^3J_{H5/H4} = {}^3J_{H5/H6a} = 9.0$ Hz and $^3J_{H5/H6b} = 17.0$ Hz, H5), 5.20 (1H, d, $^3J_{H6a/H5} = 9.0$ Hz, H6a), 4.82 and 3.91 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 228$ Hz, $^2J_{gem} = 15.0$ Hz, NCH_2Ph), 4.73 (1H, d, $^3J_{H6b/H5} = 17.0$ Hz, H6b), 4.56 and 4.29 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 68$ Hz, $^2J_{gem} = 12.8$ Hz, OCH_2Ph), 4.35 (1H, dd, $^3J_{H3/H2} = 2.6$ Hz and $^3J_{H3/H4} = 7.2$ Hz, H3), 3.88 and 3.87 (2H, 2d, $^3J_{H1a/H2} = {}^3J_{H1b/H2} = 6.0$ Hz, H1), 3.74 (1H, dd, $^3J_{H4/H3} = 7.2$ Hz and $^3J_{H4/H5} = 9.0$ Hz, H4), 3.34 (1H, td, $^3J_{H2/H1a} = {}^3J_{H2/H1b} = 6.0$ Hz and $^3J_{H2/H3} = 2.6$ Hz, H2), 1.06 (9H, s, CH_3 *t*BuPh$_2$Si); ^{13}C NMR δ ppm (100 MHz, $CDCl_3$) 157.6 (C=O), 137.4, 135.8 (Cq arom.), 135.6 (CH arom.), 134.8 (C5), 133.2, 132.9 (Cq arom.), 129.9, 128.6, 128.4, 127.8 (CH arom.), 121.4 (C6), 77.8 (C3), 76.1 (C2), 72.4 (OCH_2Ph), 62.0 (C1), 59.3 (C4), 45.8 (NCH_2Ph), 26.8 (CH_3 *t*BuPh$_2$Si), 19.1 (Cq *t*BuPh$_2$Si); MS (DCI, NH_3): $m/z = 609$ $[M+NH_4]^+$ (100), 592 $[M+H]^+$ (25); Anal. Calcd for $C_{37}H_{41}NO_4Si$: C, 74.09; H, 6.98; N, 2.37. Found: C, 74.97; H, 7.08; N, 2.45.

4.9. (5*S*,6*S*,1′*S*)-5-Benzylamino-6-(1-benzyloxy-2-*tert*-butyldiphenylsilyloxy)ethyl-1,3-dioxane-2,4-dione 14

In a solution of alkene **13** (53 mg, 90 μmol) in EtOAc (8 mL/mmol), at −78 °C, O_3 was bubbled until the solution became blue. The ozonide formed was then decomposed by dropping it in a solution of 150 μL of a 30% aqueous solution of hydrogen peroxide heated at 80 °C, and stirring the mixture at 80 °C for 5 min. The mixture was then cooled to 0 °C and basified with 2 mL of a saturated aqueous solution of K_2CO_3 and extracted with Et_2O. The aqueous phase was then acidified until pH 4 with a 1 M hydrochloric acid aqueous solution saturated in NaCl, and extracted with Et_2O. The organic layers were successively washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by medium-pressure column chromatography on silica gel (petroleum ether/EtOAc 9:1) to give **14** (19 mg, 32 μmol, 35% yield): $R_f = 0.08$ (petroleum ether/EtOAc 9:1); $[\alpha]_D^{25} = +64.8$ (*c* 1.20, $CHCl_3$); IR (film) 2931, 2858, 1739, 1428, 1114 cm^{-1}; ^1H NMR δ ppm (400 MHz, $CDCl_3$) 7.98 (1H, s, H acid), 7.68–7.63 (5H, m, phenyl), 7.47–7.41 (7H, m, phenyl), 7.29–7.26 (6H, m, phenyl), 6.98–6.96 (2H, m, phenyl), 5.01 (1H, d, $^3J_{H4/H3} = 2.5$ Hz, H4), 4.83 (1H, t, $^3J_{H3/H2} = {}^3J_{H3/H4} = 2.5$ Hz, H3), 4.60 and 4.43 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 69$ Hz, $^2J_{gem} = 16.8$ Hz, NCH_2Ph), 4.51 and 4.29 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 88$ Hz, $^2J_{gem} = 12.1$ Hz, OCH_2Ph), 3.90 and 3.84 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 23$ Hz, $^3J_{H1a/H2} = 7.3$ Hz, $^3J_{H1b/H2} = 5.4$ Hz and $^3J_{H1a/H1b} = 10.5$ Hz, H1), 3.53 (1H, ddd, $^3J_{H2/H1a} = 7.3$ Hz, $^3J_{H2/H1b} = 5.4$ Hz and $^3J_{H2/H3} = 2.5$ Hz, H2), 1.06 (9H, s, CH_3 *t*BuPh$_2$Si); ^{13}C NMR δ ppm (100 MHz, $CDCl_3$) 157.9 (C5 and C6), 137.5 (Cq arom. OBn), 136.2 (Cq arom. NBn), 135.7 (CH arom.), 133.3, 133.0 (Cq arom.), 130.1, 129.1, 128.6, 128.1 (CH arom.), 92.1 (C4), 77.4 (C2), 76.4 (C3), 72.3 (OCH_2Ph), 61.7 (C1), 46.0 (NCH_2Ph), 27.0 (CH_3 *t*BuPh$_2$Si), 19.3 (Cq *t*BuPh$_2$Si); MS (DCI, NH_3): $m/z = 627$ $[M+NH_4]^+$ (100), 564 $[M-CO_2H]$ (27); Anal. Calcd for $C_{36}H_{39}NO_6Si$: C, 70.91; H, 6.45; N, 2.30. Found: C, 71.02; H, 6.54; N, 2.38.

4.10. (2*S*,3*S*,4*S*)-2-Benzyloxy-3-*O*,4-*N*-benzylcarbamate-1-*tert*-butyldiphenylsilyloxy-pentanoïc acid 15

In a solution of alkene **13** (53 mg, 90 μmol) in EtOAc (8 mL/mmol), at −78 °C, O_3 was bubbled until the solution became blue. The ozonide formed was then decomposed by dropping it in 150 μL of a 30% aqueous solution of hydrogen peroxide heated at 50 °C, and then stirring the mixture at 50 °C for 5 min. The mixture was then cooled to 0 °C and basified with 2 mL of a saturated aqueous solution of K_2CO_3 and extracted with Et_2O. The aqueous phase was then acidified until pH 4 with a 1 N hydrochloric acid aqueous solution saturated in NaCl, and extracted with Et_2O. The organic layers were successively washed with brine, dried over $MgSO_4$, filtered and concentrated under

reduced pressure. The crude product was purified by medium-pressure column chromatography on silica gel (petroleum ether/EtOAc 8:2) to give **15** (17.5 mg, 31.5 μmol, 35% yield): $R_f = 0.10$ (petroleum ether/EtOAc 8:2); $[\alpha]_D^{25} = +22.4$ (*c* 0.75, $CHCl_3$); IR (film) 2931, 2858, 1775, 1727, 1428, 1114 cm^{-1}; ^1H NMR δ ppm (400 MHz, $CDCl_3$) 8.02 (1H, s, H acid), 7.66–7.61 (4H, m, phenyl), 7.45–7.38 (6H, m, phenyl), 7.28–7.18 (8H, m, phenyl), 6.93–6.89 (2H, m, phenyl), 5.90 (1H, d, $^3J_{H4/H3} = 1.8$ Hz, H4), 4.75 and 4.16 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 148$ Hz, $^2J_{gem} = 15.2$ Hz, NCH_2Ph), 4.66 (1H, t, $^3J_{H3/H2} = {}^3J_{H3/H4} = 1.8$ Hz, H3), 4.38 and 4.20 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 45$ Hz, $^2J_{gem} = 11.9$ Hz, OCH_2Ph), 3.85 and 3.76 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 23$ Hz, $^3J_{H1a/H2} = 8.2$ Hz, $^3J_{H1b/H2} = 5.1$ Hz and $^3J_{H1a/H1b} = 10.4$ Hz, H1), 3.66 (1H, ddd, $^3J_{H2/H1a} = 8.2$ Hz, $^3J_{H2/H1b} = 5.1$ Hz and $^3J_{H2/H3} = 1.8$ Hz, H2), 1.03 (9H, s, CH_3 *t*BuPh_2Si); ^{13}C NMR δ ppm (100 MHz, $CDCl_3$) 160.1 (C5), 156.9 (C6), 137.2 (Cq arom. OBn), 135.5 (Cq arom.), 135.5 (Cq arom. NBn), 133.0, 132.7 (Cq arom. Phe), 129.9, 128.7, 128.3, 128.0, 127.8 (CH arom.), 83.1 (C4), 78.9 (C3), 76.8 (C2), 72.2 (OCH_2Ph), 60.9 (C1), 45.9 (NCH_2Ph), 26.8 (CH_3 *t*BuPh_2Si), 19.1 (Cq *t*BuPh_2Si); MS (DCI, NH_3): $m/z = 627$ $[M+NH_4]^+$ (100), 564 $[M-CO_2H]$ (35); Anal. Calcd for $C_{36}H_{39}NO_6Si$: C, 70.91; H, 6.45; N, 2.30. Found: C, 71.82; H, 6.37; N, 2.37.

4.11. (2*S*,3*S*,4*S*)-2-Benzoyloxy-3-*O*,4-*N*-benzyl-carbamate-1-*tert*-butyldiphenylsilyloxy-pentanoïc acid 16

In a solution of alkene **13** (53 mg, 90 μmol) in EtOAc (8 mL/mmol), at −78 °C, O_3 was bubbled until the solution became blue. The ozonide formed was then decomposed by dropping it in 150 μL of a 30% aqueous solution of hydrogen peroxide heated at 50 °C, and stirring the mixture at 50 °C for 30 min. The mixture was then cooled to 0 °C and basified with 2 mL of a saturated aqueous solution of K_2CO_3 and extracted with Et_2O. The aqueous phase was then acidified until pH 4 with a 1 M hydrochloric acid aqueous solution saturated in NaCl, and extracted with Et_2O. The organic layers were successively washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was pre-purified by medium-pressure column chromatography on silica gel (petroleum ether/EtOAc 8:2) to give 23 mg of a mixture of compounds **15** and **16** (**15**/**16** 3:2). This mixture was then purified on preparative HPLC column chromatography on silica gel (petroleum ether/CH_2Cl_2/EtOAc 70:24:6) to give **15** (12 mg, 19 μmol, 21% yield) and **16** (8 mg, 12 μmol, 14% yield): $R_f = 0.10$(petroleum ether/EtOAc 8:2). Compound **16**: $[\alpha]_D^{25} = +15.3$ (*c* 0.50, $CHCl_3$); IR (film) 2931, 2858, 1778, 1729, 1427, 1113 cm^{-1}; ^1H NMR δ ppm (400 MHz, $CDCl_3$) 8.07 (1H, s, H acid), 7.90–7.86 (4H, m, phenyl), 7.65–7.57 (5H, m, phenyl), 7.46–7.33 (8H, m, phenyl), 7.05–7.00 (3H, m, phenyl), 6.89–6.82 (2H, m, phenyl), 6.06 (1H, d, $^3J_{H4/H3} = 1.7$ Hz, H4), 5.53 (1H, ddd, $^3J_{H2/H1a} = 7.6$ Hz, $^3J_{H2/H1b} = 6.1$ Hz and $^3J_{H2/H3} = 1.7$ Hz, H2), 4.91 (1H, t, $^3J_{H3/H2} = {}^3J_{H3/H4} = 1.7$ Hz, H3), 4.66 and 4.14 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 130$ Hz, $^2J_{gem} = 15.2$ Hz, NCH_2Ph), 3.91 and 3.83 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 20$ Hz, $^3J_{H1a/H2} = 7.6$ Hz, $^3J_{H1b/H2} = 6.1$ Hz and $^3J_{H1a/H1b} = 10.4$ Hz, H1), 1.03 (9H, s, CH_3 *t*BuPh_2Si); ^{13}C NMR δ ppm (100 MHz, $CDCl_3$) 165.0 (C7), 159.8 (C5), 156.6 (C6), 135.4 (CH arom.), 134.3 (Cq arom.), 133.6 (CH arom.), 132.6, 132.5 (Cq arom.), 130.0, 128.6, 128.3, 128.10, 127.9 (CH arom.), 82.6 (C4), 77.7 (C3), 71.9 (C2), 60.9 (C1), 45.9 (NCH_2Ph), 26.7 (CH_3 *t*BuPh_2Si), 19.1 (Cq *t*BuPh_2Si); MS (DCI, NH_3): $m/z = 641$ $[M+NH_4]^+$ (100), 578 $[M-CO_2H]$ (24); Anal. Calcd for $C_{36}H_{37}NO_7Si$: C, 69.32; H, 5.98; N, 2.25. Found: C, 69.43; H, 6.07; N, 2.36.

4.12. (4*R*,5*S*)-3-Benzyl-5-((1*S*)-2-*O*-carbamoyl-1-benzyl-oxyethyl)-4-vinyl-1,3-oxazolan-2-one 18

To a solution of compound **13** (0.21 g, 0.35 mmol) in anhydrous THF (35 mL/mmol) was added TBAF supported on silica (0.45 g, 0.42 mmol). The mixture was stirred overnight at rt, after which it was concentrated. The residue was suspended in EtOAc and filtered. Then, the solvent was evaporated under reduced pressure. The crude product was purified by medium-pressure column chromatography on silica gel (petroleum ether/EtOAc 5:5) to give the deprotected product **17** (103 mg, 0.29 mmol, 83% yield): $R_f = 0.19$ (petroleum ether/EtOAc 5:5); $[\alpha]_D^{25} = +65.2$ (*c* 1.25, $CHCl_3$); IR (film) 3425, 3074, 1740, 1421, 1058 cm^{-1}; ^1H NMR δ ppm (250 MHz, $CDCl_3$) 7.31–7.22 (8H, m, phenyl), 7.11–7.10 (2H, m, phenyl), 5.61 (1H, td, $^3J_{H5/H4} = {}^3J_{H5/H6a} = 9.9$ Hz and $^3J_{H5/H6b} = 17.0$ Hz, H5), 5.23 (1H, d, $^3J_{H6a/H5} = 9.9$ Hz, H6a), 5.24 and 3.44 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 224$ Hz, $^2J_{gem} = 15.2$ Hz, NCH_2Ph), 4.85 (1H, d, $^3J_{H6b/H5} = 17.0$ Hz, H6b), 4.71 and 4.43 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 35$ Hz, $^2J_{gem} = 11.9$ Hz, OCH_2Ph), 4.30 (1H, dd, $^3J_{H3/H2} = 3.4$ Hz and $^3J_{H3/H4} = 7.0$ Hz, H3), 3.86–3.67 (3H, m, H1 and H4), 3.41 (1H, td, $^3J_{H2/H1a} = {}^3J_{H2/H1b} = 5.8$ Hz and $^3J_{H2/H3} = 3.4$ Hz, H2); ^{13}C NMR δ ppm (63 MHz, $CDCl_3$) 157.8 (C=O), 137.4, 135.6 (Cq arom.), 134.5 (C5), 128.7, 128.6, 128.5, 127.9 (CH arom.), 121.8 (C6), 78.2 (C3), 76.1 (C2), 72.4 (OCH_2Ph), 62.2 (C1), 59.5 (C4), 45.7 (NCH_2Ph); MS (DCI, NH_3): $m/z = 371$ $[M+NH_4]^+$ (100), 354 $[M+H]^+$ (92); Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.42; H, 6.63; N, 4.02. The *para*-nitrophenyl chloroformate was purified by sublimation. Under an inert atmosphere, to a solution of deprotected compound (37 mg, 0.10 mmol) in anhydrous pyridine (5 mL/mmol) was added *p*-nitrophenyl chloroformate (31 mg, 0.16 mmol). After 30 min at rt, the mixture was diluted with EtOAc and washed successively with a saturated aqueous solution of $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a red oil. This intermediate was then solubilised in MeOH (15 mL/mmol), and a 7 M solution of ammonia in MeOH (5 mL/mmol) was added at 0 °C. The mixture was stirred for 1 h at 0 °C and then methanol was evaporated. The crude product was purified by medium-pressure column chromatography on silica gel (petroleum ether/EtOAc 4:6) to give **18** (37 mg, 93 μmol, 90% yield): $R_f = 0.23$ (petroleum ether/EtOAc 4:6); $[\alpha]_D^{25} = +89.2$ (*c* 1.70, $CHCl_3$); IR (film) 3429, 3074, 1742, 1642, 1421,

1058 cm^{-1}; ^1H NMR δ ppm (400 MHz, $CDCl_3$) 7.33–7.29 (8H, m, phenyl), 7.08–7.06 (2H, m, phenyl), 5.61 (1H, td, $^3J_{H5/H4} = {}^3J_{H5/H6a} = 9.0$ Hz and $^3J_{H5/H6b} = 17.0$ Hz, H5), 5.29 (1H, d, $^3J_{H6a/H5} = 9.0$ Hz, H6a), 4.96 and 3.76 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 240$ Hz, $^2J_{gem} = 15.0$ Hz, NCH_2Ph), 4.78 (1H, d, $^3J_{H6b/H5} = 17.0$ Hz, H6b), 4.70 (2H, s, NH_2), 4.69 and 4.40 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 58$ Hz, $^2J_{gem} = 11.9$ Hz, OCH_2Ph), 4.36 and 4.20 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 33$ Hz, $^3J_{H1a/H2} = {}^3J_{H1b/H2} = 5.8$ Hz and $^3J_{H1a/H1b} = 11.6$ Hz, H1), 4.19 (1H, dd, $^3J_{H3/H2} = 3.4$ Hz and $^3J_{H3/H4} = 7.0$Hz, H3), 3.75 (1H, dd, $^3J_{H4/H3} = 7.0$ Hz and $^3J_{H4/H5} = 9.0$ Hz, H4), 3.53 (1H, td, $^3J_{H2/H1a} = {}^3J_{H2/H1b} = 5.8$ Hz and $^3J_{H2/H3} = 3.4$ Hz, H2); ^{13}C NMR δ ppm (100 MHz, $CDCl_3$) 157.3 (C=O oxazo.), 156.0 (C=O carbamoyl), 136.9, 135.6 (Cq arom.), 134.5 (C5), 128.7, 128.6, 128.5, 127.9 (CH arom.), 121.7 (C6), 78.5 (C3), 73.4 (C2), 72.4 (OCH_2Ph), 62.6 (C1), 59.5 (C4), 45.8 (NCH_2Ph); MS (DCI, NH_3): $m/z = 414$ $[M+NH_4]^+$ (100), 397 $[M+H]^+$ (11); HRMS (DCI, NH_3) calcd. for $C_{22}H_{25}N_2O_5$ $[M+H]^+$ 397.1763. Found: 397.1761.

4.13. (2*S*,3*S*,4*S*)-2-Benzyloxy-3-*O*,4-*N*-benzyl-carbamate-1-aminocarbonyloxypentanoic acid 19

In a solution of alkene **18** (19 mg, 48 μmol) in EtOAc (10 mL/mmol), at −78 °C, O_3 was bubbled until the solution became blue. The ozonide formed was then decomposed by dropping it in 80 μL of a 30% aqueous solution of hydrogen peroxide heated at 50 °C, and stirring the mixture at 50 °C for 5 min. The mixture was then cooled to 0 °C and basified with 2 mL of a saturated aqueous solution of K_2CO_3 and extracted with Et_2O. The aqueous phase was then acidified until pH 4 with a 1 M hydrochloric acid aqueous solution saturated in NaCl, and extracted with Et_2O. The organic layers were successively washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by medium-pressure column chromatography on silica gel (petroleum ether/EtOAc 5:5) to give **19** (6 mg, 15 μmol, 30% yield): $R_f = 0.13$ (petroleum ether/EtOAc 5:5); $[\alpha]_D^{25} = +8.6$ (*c* 0.45, $CHCl_3$); IR (film) 3429, 3074, 1742, 1642, 1421, 1058 cm^{-1}; ^1H NMR δ ppm (400 MHz, $CDCl_3$) 8.01 (1H, s, H5), 7.32–7.29 (8H, m, phenyl), 7.08–7.06 (2H, m, phenyl), 5.97 (1H, d, $^3J_{H4/H3} = 1.8$ Hz, H4), 4.80 and 4.15 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 248$ Hz, $^2J_{gem} = 15.2$ Hz, NCH_2Ph), 4.62 and 4.44 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 78$ Hz, $^2J_{gem} = 12.0$ Hz, OCH_2Ph), 4.57 (2H, m, NH_2), 4.47 (1H, t, $^3J_{H3/H2} = {}^3J_{H3/H4} = 1.8$ Hz, H3), 4.36 and 4.19 (2H, AB part of an ABX system, $\Delta\delta Ha - \delta Hb = 68$ Hz, $^3J_{H1a/H2} = 5.2$ Hz, $^3J_{H1b/H2} = 7.2$ Hz and $^3J_{H1a/H1b} = 12.0$ Hz, H1), 4.82 (1H, ddd, $^3J_{H2/H1a} = 5.2$ Hz, $^3J_{H2/H1b} = 7.2$ Hz and $^3J_{H2/H3} = 1.8$ Hz, H2); ^{13}C NMR δ ppm (100 MHz, $CDCl_3$) 157.4 (C5), 157.2 (C=O oxazo.), 155.9 (C=O carbamoyl), 136.9, 135.6 (Cq arom.), 128.7, 128.6, 128.5, 128.2 (CH arom.), 82.3 (C4), 79.1 (C3), 73.8 (C2), 72.3 (OCH_2Ph), 61.8 (C1), 45.8 (NCH_2Ph); MS (DCI, NH_3): $m/z = 432$ $[M+NH_4]^+$ (68), 292 (100); HRMS (DCI, NH_3) calcd. for $C_{21}H_{23}N_2O_7$ $[M+H]^+$ 415.1505. Found: 415.1505.

References

1. Georgopapadakou, N. H.; Walsh, T. J. *Science* **1994**, *264*, 371–373.
2. Ablordeppey, S. Y.; Fan, P.; Ablordeppey, J. H.; Mardenborough, L. *Curr. Med. Chem.* **1999**, *6*, 1151–1195.
3. Georgopapadakou, N. H.; Tkacz, J. S. *Trends Microbiol.* **1995**, *3*, 98–104.
4. Isono, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7490–7505; Isono, K.; Suzuki, S. *Heterocycles* **1979**, *13*, 333–351.
5. Hori, M.; Kakiki, K.; Misato, T. *Agric. Biol. Chem.* **1974**, *38*, 691–698.
6. Ko, K. In *Pesticide Chemistry: Human Welfare and the environment*; Miyamoto, J., Ed.; Pergamon Press: Elmsford, NY, 1983; p 247; For a review on polyoxins and nykkomycins: Zhang, D.; Miller, M. J. *Curr. Pharm. Des.* **1999**, *5*, 73–99.
7. Bowers, B.; Levin, G.; Cabib, E. *J. Bacteriol.* **1974**, *119*, 564–575.
8. Recent work based on carbohydrate chemistry: (a) Harwood, L. M.; Robertson, S. M. *Chem. Commun.* **1998**, 2641–2642; (b) Ghosh, A. K.; Wang, Y. *Tetrahedron* **1999**, *55*, 13369–13376; Savage, I.; Thomas, E. J.; Wilson, P. D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3291–3303; (c) Uchida, K.; Kato, K.; Akita, H. *Synthesis* **1999**, 1678–1686; (d) Bose, A. K.; Banik, B. K.; Mathur, C.; Wagle, D. R.; Manhas, M. S. *Tetrahedron* **2000**, *56*, 5603–5619; (e) Tarrade, A.; Dauban, P.; Dodd, R. H. *J. Org. Chem.* **2003**, *68*, 9521–9524; Recent work based on other chiral compounds: (a) Ghosh, A. K.; Wang, Y. *J. Org. Chem.* **1999**, *64*, 2789–2795; (b) Davis, F. A.; Prasad, K. R.; Carrol, P. J. *J. Org. Chem.* **2002**, *67*, 7802–7806.
9. Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520–6521.
10. Pepper, A. G.; Procter, G.; Voyle, M. *Chem. Commun.* **2002**, 1066–1067.
11. Dehoux, C.; Gorrichon, L.; Baltas, M. *Eur. J. Org. Chem.* **2001**, 1105–1113.
12. Dehoux, C.; Monthieu, C.; Baltas, M.; Gorrichon, L. *Synthesis* **2000**, *10*, 1409–1414.
13. (a) Ayad, T.; Genisson, Y.; Baltas, M.; Gorrichon, L. *Chem. Commun.* **2003**, 582–583; (b) Ayad, T.; Genisson, Y.; Baltas, M. *Org. Biomol. Chem.* **2005**, *3*, 2626–2631.
14. Beresford, K. J. M.; Howe, J. P.; Procter, G. *Tetrahedron Lett.* **1992**, *33*, 3355–3358.
15. Ayad, T.; Genisson, Y.; Broussy, S.; Baltas, M.; Gorrichon, L. *Eur. J. Org. Chem.* **2003**, 2903–2910.
16. Ayad, T.; Faugeroux, V.; Genisson, Y.; André, C.; Baltas, M.; Gorrichon, L. *J. Org. Chem.* **2004**, *69*, 8775–8779.
17. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.
18. Gravier–Pelletier, C.; Milla, M.; Le Merrer, Y.; Depeay, J. C. *Eur. J. Org. Chem.* **2001**, 3089–3096.
19. Heidelberg, T.; Martin, O. R. *J. Org. Chem.* **2004**, *69*, 2290–2301.