Efficient and Versatile Stereoselective Synthesis of Cryptophycins

Christian Alexander Mast,[a] Stefan Eißler,[a] Arvydas Stončius,[a] Hans-Georg Stammler,[b] Beate Neumann,[b] and Norbert Sewald*[a]

Abstract: The cryptophycins are a family of cyclic depsipeptides with four retrosynthetic units **A** to **D** which correspond to the respective amino acids and hydroxy acids. A new synthetic route to unit **A** allows the selective generation of all four stereogenic centres by introducing two of them in a catalytic asymmetric dihydroxylation, followed by substrate-controlled diastereoselective reactions. The diol also serves as the epoxide precursor. This approach provides selective access to stereoisomers of unit **A** (enantiomers, epimers) for structure–activity relationship studies. The unit **A** derivatives were incorporated into cryptophycin-1, cryptophycin-52 and a novel epimer of cryptophycin-52.

Keywords: antitumor agents · asymmetric synthesis · natural products · peptides · total synthesis

Introduction

Cryptophycins form a class of 16-membered macrocyclic depsipeptides which essentially can be subdivided into two structural categories containing either an epoxide ring or an alkene moiety (Figure 1).[1] They are secondary metabolites of bluegreen algae (cyanobacteria). Cryptophycin-1 (**1**) was isolated from *Nostoc* sp. ATCC 53789 by Schwartz et al. in 1990 as the first representative[2] while the same compound along with 24 additional cryptophycins has been isolated form *Nostoc* sp. GSV 224.[3] As a number of cryptophycins display considerable tumour-selective cytotoxicity both against multidrug-resistant tumour cell lines and solid tumours implanted in mice,[3,4] they are considered a promising lead structure. The synthetic cryptophycin-52 has already been subject to clinical phase 1 and 2 trials.[5] In contrast to their epoxy analogues, desepoxy cryptophycins do not display significant cytotoxicity as structure–activity relationship (SAR) studies have shown.[3]

[a] Dr. C. A. Mast, Dipl.-Biochem. S. Eißler, Dr. A. Stončius, Prof. Dr. N. Sewald
Department of Chemistry, Organic and Bioorganic Chemistry
Bielefeld University
Universitätsstrasse 25, 33615 Bielefeld (Germany)
Fax: (+49) 521-106-8094
E-mail: norbert.sewald@uni-bielefeld.de

[b] Dr. H.-G. Stammler, B. Neumann
Department of Chemistry, Inorganic Chemistry
Bielefeld University
Universitätsstrasse 25, 33615 Bielefeld (Germany)

Results and Discussion

Retrosynthetic analysis of cryptophycin-1 (**1**) gives the four units **A**–**D** (Figure 1). The synthesis of unit **A** with four stereogenic centres and the oxirane ring is the most challenging part. Due to their pharmacological importance several cryptophycin syntheses have been published since 1994, which differ mainly in the synthesis of unit **A** and the state at which the oxirane functionality is introduced.[1,6] Our approach is distinct from these as it relies on a catalytic asymmetric dihydroxylation[7] in the first step. The stereogenic diol formed both allows the introduction of the additional stereogenic centres under substrate control of diastereoselectivity and serves as the epoxide precursor.[6f,h] Here we describe the stereoselective syntheses of the unit **A** derivatives **A**″, *epi*-**A**″ and *ent*-**A**″ in form of the protected precursors **5**, *epi*-**5**, and *ent*-**5** and their conversion to cryptophycin-1 (**1**), cryptophycin-52 (**2**) and a novel epimer of cryptophycin-52, respectively.

Scheme 1 summarizes the first part of the syntheses of **5** and *ent*-**5** including the introduction of all four stereogenic centres. Dienoate **6** is transformed into a 5:1 mixture of the regioisomeric diols[8] **7a**,**b** with high enantioselectivity (*ee* 98%) by an asymmetric dihydroxylation (AD) requiring the chiral ligand 1,4-bis-(9-*O*-dihydroquinidinyl)phthalazine [$(DHQD)_2PHAL$] only in catalytic amounts. After synthesis of the corresponding acetonides pure **8a** can be isolated chromatographically. 1,4-Addition of MeLi to enoate **8a** provides ester **9** as almost the sole diastereomer (*dr* 98:2). We have already reported on the complementary diastereo-

 DOI: 10.1002/chem.200500282

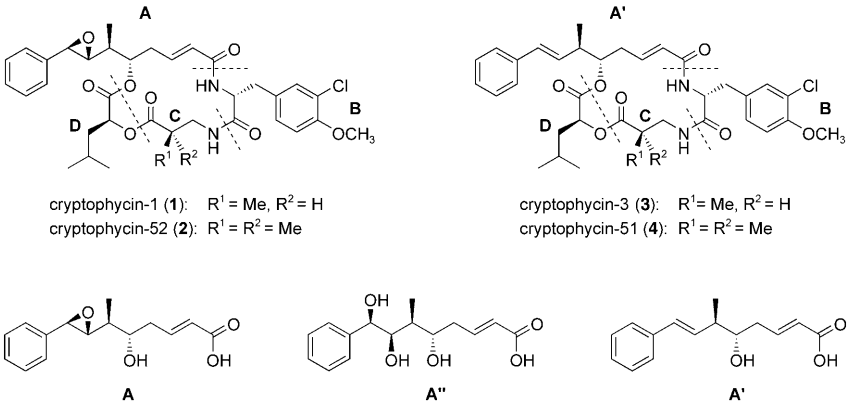
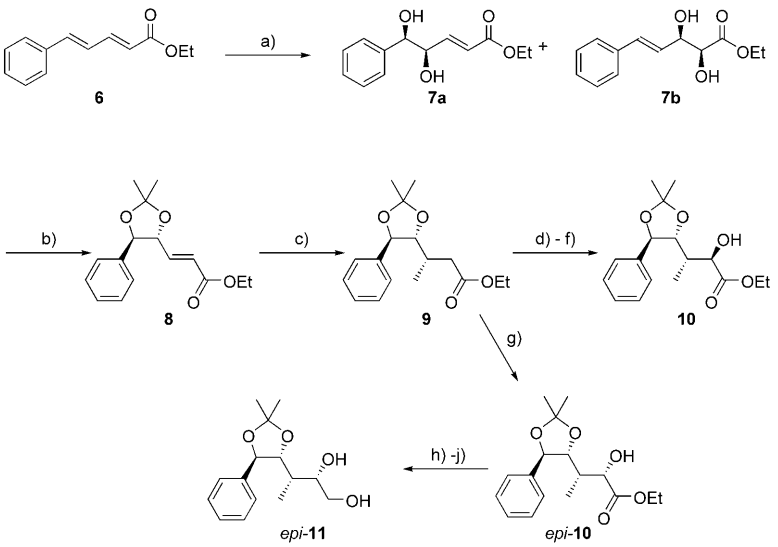


Figure 1. Selected cryptophycins with their retrosynthetic interfaces presented as dotted line, along with the structures of the cryptophycin units **A**, **A**′ and compound **A**″.



Scheme 1. a) See ref. [8], 86%; b) $(MeO)_2CMe_2/Me_2CO$, *p*-TosOH, RT, separation of the regioisomers, 79%; c) hexane/Et_2O, Me_3SiCl, MeLi, 72%; d) LDA, Me_3SiCl, THF, −78°C; e) $Pb(OAc)_4$, CH_2Cl_2, −78°C (*dr* 92:8); f) EtOH, NaOEt, RT, separation of epimers, 59% (steps d–f); g) LDA, MoOPH, −78°C (*dr* 82:18), separation of epimers, 59%; h) TBSCl, imidazole, DMF, 60°C, 94%; i) $LiBH_4$, THF, reflux, 86%; j) $(n\text{Bu})_4\text{NF}\cdot 3\,H_2O$), THF, RT, 89%.

selectivities of 1,4-additions of MeLi (*syn*-selectivity) and miscellaneous cuprate reagents (*anti*-selectivity) to **8a**.[9,10] Hence, application of organocuprates will provide access to additional diastereomers of unit **A** for structure–activity relationship studies.

The α-hydroxyester **10** is accessible by diastereoselective acetoxylation of the silyl ketene acetal derived from **9**. Base-catalysed transesterification gives **10** and eventually leads to **5** while the diastereoselective electrophilic hydroxylation of the Li enolate derived from **9** with oxodiperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide) (MoOPH) gives *epi*-**10** and eventually provides *epi*-**5**. Thus, a catalytic amount of chiral ligand employed in the AD reaction is the sole source of chirality in both the syntheses of **5** and *epi*-**5**. The X-ray structure of diol *epi*-**11**[11] being derived in an epimerization-free reaction from *epi*-**10** gives unambiguous evidence for the diastereoselectivity of the 1,4-addition, the electrophilic hydroxylation and the acetoxylation (Figure 2).

After protection of the α-hydroxy group of esters **10** and *epi*-**10** as allyl ethers (Scheme 2), reduction with $LiAlH_4$ yields the primary alcohols **12** and *epi*-**12**, respectively. Reduction of the corresponding silyl ethers proved to be accompanied by a partial silyl group migration to the newly formed primary alcohol, as it was also observed in the conversion of silylated *epi*-**10** to *epi*-**11** (Scheme 1). Tosylation and subsequent substitution with cyanide provides the corresponding nitriles from which the aldehydes **13** and *epi*-**13**, respectively, are accessible by reduction with DIBAH. The α,β-unsaturated ester unit is introduced in a highly (*E*)-selective manner by a Horner–Wadsworth–Emmons reaction. Pd^0-catalysed cleavage of the allyl ethers provides **5** and *epi*-**5**, respectively.

The syntheses of **5** and *epi*-**5** proceed by using analogous reactions with similar yields even though different reaction conditions are required in some steps. For example, the conversion of *epi*-**10** requires NaH as the base whereas transformation of **10** under identical reaction conditions results in considerable epimerization and the formation of by-products. The overall yield of both the syntheses of **5** (13 steps) and *epi*-**5** (11 steps) is 17.4%. By complete analogy to the synthesis of **5** its enantiomer *ent*-**5** is accessible using the quinine ligand 1,4-bis(9-*O*-dihydroquininyl)phthalazine $(DHQ)_2PHAL$ instead of its quinidine analogue $(DHQD)_2PHAL$ in the AD reaction, which gives the enantiomer of **5** since all further stereogenic centres are introduced under substrate control of diastereoselectivity. Hence, an analogous synthesis of *ent*,*epi*-**5** should be possible as well (Figure 3).

The syntheses of unit **D** (**14**) and unit **B** (**17**) succeed as described in the literature.[12,13] Unit **C** of cryptophycin-1 **15a** is synthesised from succinic anhydride with a chiral oxazolidinone as the source of chirality. The unit **C** of cryptophycin-52 (**15b**) is synthesised from ethyl cyanoacetate,

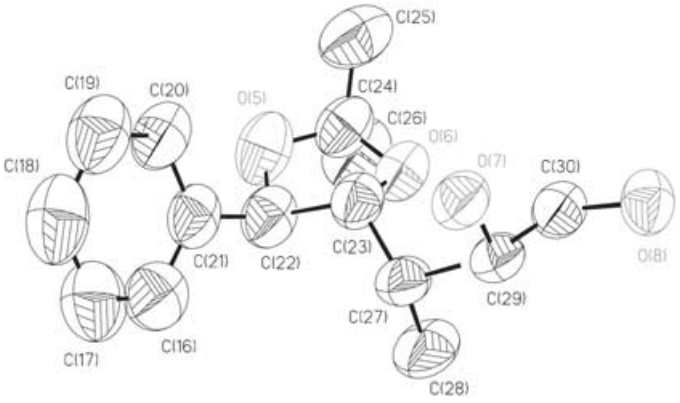
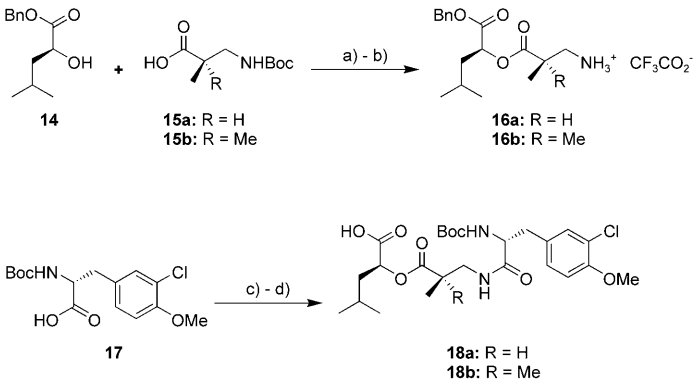
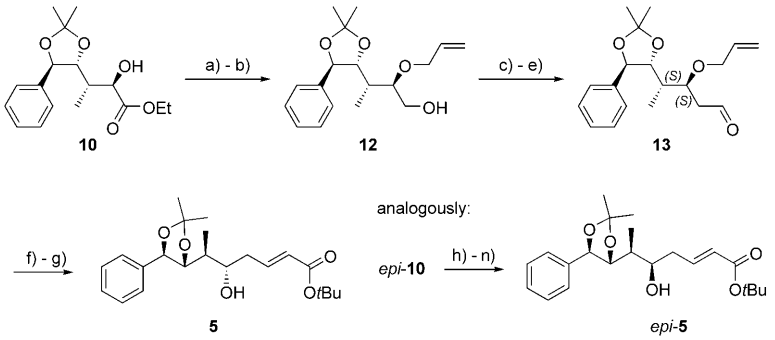


Figure 2. X-ray crystal structure of *epi*-**11**.



Scheme 3. a) CH_2Cl_2, NEt_3, DMAP, EDC, 0 °C→RT, 95–98 %; b) CH_2Cl_2, TFA, 0 °C; c) **16a**,**b**, CH_2Cl_2, NEt_3, HOAt, EDC, 87–95 % (steps b–c); d) H_2, Pd/C, EtOAc, quantitative.



Scheme 2. a) 1) LDA, THF, −78 °C, 2) AllBr, DMF, −78 °C→RT, 85 %; b) $LiAlH_4$, THF, 5 °C→RT, 99 %; c) TosCl, DABCO, CH_2Cl_2, 94 %; d) NaCN, $NaHCO_3$, DMSO, 60 °C, 99 %; e) DIBAH, toluene, −78 °C, 92 %; f) $(EtO)_2P(O)CH(Na)C(O)OtBu$, THF, −78 °C→RT, 85 %; g) *p*-$TolSO_2Cl$, $[Pd(PPh_3)_4]$, CH_2Cl_2, RT, 97 %; h) NaH, DME, AllBr, RT–60 °C, 89 %; i) analogous to b), 98 %; j) analogous to c), 91 %; k) NaCN, $NaHCO_3$, DMSO, 60–80 °C, 98 %; l) analogous to e), 93 %; m) analogous to f), 83 %; n) analogous to g), 100 %.

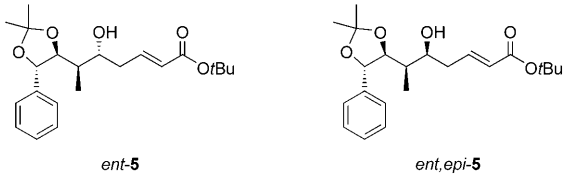


Figure 3.

which is transformed to 3-amino-2,2-dimethylpropan-1-ol according to the literature,[14] then the amino group is protected with Boc followed by oxidation of the primary hydroxy group by $RuO_4/NaIO_4$.[15]

After condensation of **14** with **15a** or **15b** to give the units **C**–**D** (**16a** and **16b**, respectively) and cleavage of the Boc protecting group, condensation with unit **B** and hydrogenolytic cleavage of the benzyl ester moiety yields the assembled units **D**–**C**–**B** (**18a** and **18b**, respectively, Scheme 3).

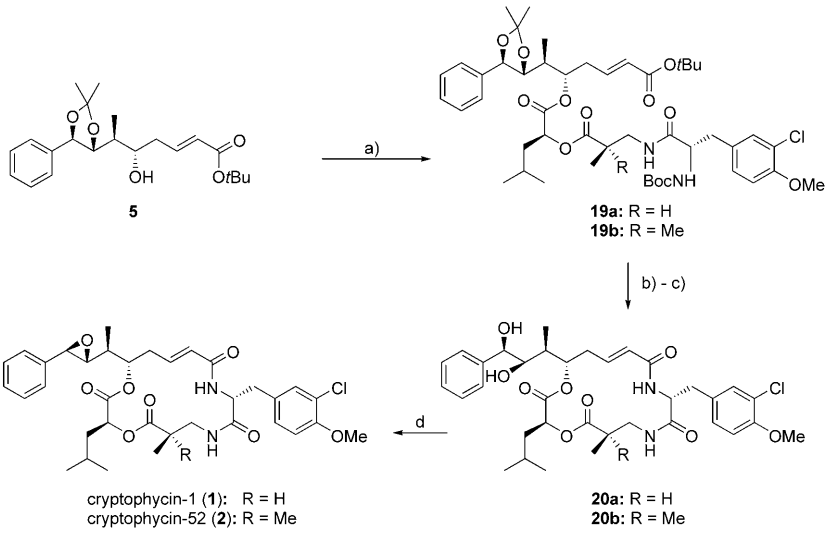
The condensation of these fragments with the unit **A** precursor proceeds as shown in Scheme 4. After cleavage of all protecting groups, macrolactamization is carried out with HATU under pseudo-high-dilution conditions. Premature cleavage of the dioxolane ring occurs upon treatment with TFA (Scheme 4, step b), but the secondary hydroxyl groups do not interfere with macrolactamization. The stereospecific transformation of the *syn*-diol to the epoxide follows a procedure described in the literature.[7] The enantiomer of cryptophycin-52 (*ent*-**2**) is accessible according to the same coupling strategy from *ent*-**5** and the enantiomers of the amino acid derivatives **14** and **17**, correspondingly.

Conclusion

In summary we established an efficient synthesis of unit **A** which relies on one step involving asymmetric catalysis, and subsequent substrate-controlled reactions. It provides selective access to many stereoisomers of both cryptophycin-52 and cryptophycin-1 as well as other cryptophycins which have the unit **A** in common with these. Cryptophycin-1 (**1**), cryptophycin-52 (**2**), and an epimer of cryptophycin-52 were synthesized following this route.

Experimental Section

General methods: ^1H and ^{13}C NMR: Bruker DRX-500 and DRX-600, spectra were recorded at 295 K in $CDCl_3$, chemical shifts were calibrated to the resonance of tetramethylsilane. Chemical shifts were assigned with respect to the individual cryptophycin units present in the molecule. IR: Jasco FT/IR 410. Optical Rotation: Jasco polarimeter DIP-360, reported $[\alpha]_D\{c[g\,100\,mL^{-1}]$, solvent} at the given temperature. MS: Autospec X magnet sector field mass spectrometer with EBE geometry (Vacuum



Scheme 4. a) CH_2Cl_2, NEt_3, DMAP, **18a**,**b**, EDC, 0 °C→RT, 93–97 %; b) CH_2Cl_2, TFA, H_2O, 0 °C→RT; c) DMF, DIPEA, HATU, 0 °C (**20a**: 77 %, **20b**: 70 % steps b–c); d) 1) CH_2Cl_2, $(CH_3O)_3CH$, PPTS, RT, 2 h, 2) CH_2Cl_2, AcBr, RT, 6 h, 3) DME/EtOH 3:2, $KHCO_3$, $(n\text{Bu})_4\text{NBr}$, 40 °C, 24 h (**1**: 71 %, **2**: 89 %).

Generators) (CI), Esquire 3000 ion trap mass spectrometer (Bruker Daltonik) (ESI), HRMS: APEX III (Bruker Daltonik) 7 T (ESI-FT-ICR-MS). Flash Chromatography: silica gel 0.04–0.063 mm (Merck). Thin-layer chromatography (TLC): silica gel 60 F_{254} on aluminium support. All solvents used in the reactions were distilled before use or purchased in the quality *pro analysi*. Tetrahydrofuran, toluene and ethylene glycol dimethyl ether were distilled from sodium/benzophenone, ethanol was distilled from sodium and diethyl phthalate; dichloromethane, dimethylformamide and triethylamine were distilled from CaH_2. Petroleum ether with a boiling range of 40–60 °C was used. Reactions were generally run under argon in flame-dried glassware. All commercially available compounds were used as received unless stated otherwise.

Ethyl (4*R*,5*R*,*E*)-4,5-dihydroxy-5-phenylpent-2-enoate (7a): *t*BuOH (200 mL) and $(DHQD)_2PHAL$ (0.390 g, 5×10^{-4} mol) were added to a solution of $K_3[Fe(CN)_6]$ (49.388 g, 0.150 mol), K_2CO_3 (20.732 g, 0.150 mol) and $K_2OsO_4{\cdot}2H_2O$ (0.184 g, 5×10^{-4} mol) in H_2O (250 mL). $CH_3SO_2NH_2$ (4.756 g, 0.050 mol) and ethyl (2*E*,4*E*)-5-phenyl-2,4-pentadienoate (10.113 g, 0.050 mol) in *t*BuOH (50 mL) were added. The mixture was cooled to 0 °C and stirred until the reaction was complete. After quenching with solid Na_2SO_3 (75.000 g) the stirred mixture was warmed to RT. After adding H_2O (300 mL) and Et_2O (360 mL) and phase separation the aqueous phase was extracted with Et_2O. The organic phases were dried over Na_2SO_4 and purified by flash chromatography on silica gel (hexane/EtOAc 1:1). An inseparable mixture of the regioisomers **7a**,**b** was obtained. R_f = 0.23, 0.26 (hexane/EtOAc 1:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.40–7.24 ppm (m, 5H, Ph), 6.71 (dd, J = 15.7, 4.4 Hz, 1H, CH_3CH), 6.04 (dd, J = 15.7, 1.8 Hz, 1H, $CHCO_2Et$), 4.49 (d, J = 6.8 Hz, 1H, PhCH), 4.34 (ddd, J = 6.7, 4.5, 1.8 Hz, 1H, CHO), 4.13 (q, J = 7.1 Hz, 2H, CH_2), 3.20 (br m, 2H, OH), 1.24 ppm (t, J = 7.1 Hz, 3H, CH_3); (only the signals for the main product **7a** are given; **7a**/**7b** 5:1); ^{13}C NMR (62.9 MHz, $CDCl_3$): **7a**: δ = 166.4, 145.7, 139.7, 128.6, 128.4, 126.8, 122.3, 77.0, 75.3, 60.5, 14.2 ppm; **7b**: δ = 172.8, 136.3, 132.6, 128.6, 128.0, 127.5, 126.7, 74.0, 73.7, 62.2, 14.2 ppm; IR (film, NaCl): $\tilde{\nu}$ = 3428, 3031, 2981, 2900, 2360, 2341, 1716, 1658, 1454, 1369, 1307, 1176, 1110, 1049, 983, 763, 701 cm^{-1}.

Ethyl 3-[(4*R*,5*R*,*E*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]propenoate (8): *p*-Toluenesulfonic acid monohydrate (0.540 g, 2.84 mmol) was added to the solution of the regioisomers **7a**,**b** (9.450 g, 40.00 mmol) in acetone (120 mL) and 2,2-dimethoxypropane (120 mL). The mixture was stirred at RT until the reaction was complete. Then NEt_3 (1.149 g, 11.36 mmol, 1.57 mL) was added dropwise. The solvent was evaporated in vacuo and the residue was dissolved in EtOAc (40 mL) and hexane was added (160 mL). The mixture was dried over Na_2SO_4 and filtered. After evaporation of the solvent in vacuo a separable mixture of the ketals of the regioisomeric diols **7a**,**b** was obtained. Purification by flash chromatography on silica gel (hexane/EtOAc 8:1) gave ketal **8** (8.732 g, 31.60 mmol, 79 %). R_f = 0.30 (hexane/EtOAc 8:1); $[\alpha]_D^{22}$ (1.44 g/100 mL, $CHCl_3$): +72.5; $[\alpha]_D^{24}$ (1.23 g/100 mL, MeOH): +90.5; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.32 (m, 5H, Ph), 6.90 (dd, J = 15.6, 5.4 Hz, 1H, CH_3CH), 6.07 (dd, J = 15.6, 1.4 Hz, 1H, $CHCO_2Et$), 4.69 (d, J = 8.6 Hz, 1H,PhCH), 4.35 (ddd, J = 8.5, 5.5, 1.4 Hz, 1H,CHO), 4.20 (q, J = 7.1 Hz, 2H, CH_3CH_2), 1.60 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.29 ppm (t, 7.1 Hz, 3H, CH_3CH_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.9, 142.5, 136.4, 128.7, 128.6, 126.5, 123.2, 110.1, 60.6, 27.1, 26.9, 14.2 ppm; IR (film, NaCl): $\tilde{\nu}$ = 3066, 3033, 2985, 1722, 1662, 1494, 1456, 1371, 1301, 1276, 1238, 1164, 1054, 1118, 1083, 979, 890, 858, 809, 757, 700 cm^{-1}; MS (CI, NH_3): m/z (%): 294 (10.3) $[M+NH_4]^+$, 277 (2.3) $[M+H]^+$, 236 (100.0) $[M+NH_4-Me_2CO]^+$, 219 (8.5) $[M+H-Me_2CO]^+$; elemental analysis calcd (%) for $C_{16}H_{20}O_4$ (276.3): C 69.55, H 7.30; found: C 69.36, H 7.41.

Ethyl (3*S*)-3-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-butanoate (9): MeLi (45.00 mmol in Et_2O/*n*-hexane 2:1, 127 mL) was added to a solution of **8** (8.290 g, 30.00 mmol) and Me_3SiCl (6.518 g, 60.00 mmol, 7.58 mL) in *n*-hexane (285 mL) at −93 °C during 2.5 h. The mixture was stirred for additional 6 h at −78 °C and then allowed to warm up to RT. Then sat. NH_4Cl solution (150 mL) was added at 0 °C and some H_2O was added if necessary in order to achieve a homogeneous aqueous layer. The phases were separated and the aqueous phase was extracted with hexane. The organic extracts were dried over Na_2SO_4 and pure **9** was obtained as a colourless liquid (6.315 g, 21.60 mmol, 72 %) after evaporation to dryness and purification of the residue by flash chromatography on silica gel (hexane/EtOAc 8:1). R_f = 0.33 (hexane/EtOAc 8:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.33 (m, 4H, Ar-H), 7.30 (m, 1H, Ar-H), 4.72 (d, J = 8.6 Hz, 1H, PhCH), 4.10–4.04 (m, J = 7.1 Hz, 2H, CH_2CH_3), 3.81 (dd, J = 8.7, 3.5 Hz, 1H, CHO), 2.38 (dd, J = 14.6 Hz, 4.4 Hz, 1H, CH_2), 2.25 (m, 1H, CH_3CH), 2.20 (dd, J = 14.6, 9.2 Hz, 1H, CH_2), 1.54 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.18 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.04 ppm (d, J = 6.6 Hz, 3H, CH_3CH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.5, 138.0, 128.6, 128.4, 127.0, 108.6, 85.6, 80.3, 60.3, 39.0, 30.4, 27.2, 27.1, 14.3, 14.2 ppm; IR (film, NaCl):$\tilde{\nu}$ = 3089, 3066, 3031, 2983, 2935, 1735, 1494, 1456, 1371, 1284, 1240, 1166, 1087, 1056, 1029, 1002, 889, 813, 757, 700 cm^{-1}; MS (CI, NH_3): m/z (%): 310 (1.9) $[M+NH_4]^+$, 293 (2.3) $[M+H]^+$, 252 (19.3) $[M+NH_4-Me_2CO]^+$, 235 (100.0) $[M+H-Me_2CO]^+$; elemental analysis calcd (%) for $C_{17}H_{24}O_4$ (292.4): C 69.84, H 8.27; found: C 69.73, H 8.08.

Ethyl (2*R*,3*R*)-3-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-2-hydroxybutanoate (10): Compound **9** (5.847 g, 20.00 mmol) in THF (80 mL) was added to a 0.57 M solution of LDA (22.00 mmol) in THF (38.6 mL) at −78 °C. After 15 min of stirring, Me_3SiCl (2.607 g, 24.00 mmol, 3.03 mL) was added. After being stirred for 1 h at −78 °C the reaction mixture was allowed to warm to RT. The solvent was evaporated in vacuo and the residue was extracted with *n*-hexane and filtered. Evaporation of the filtrate gave (3*S*)-3-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-1-ethoxy-1-trimethylsilyloxybut-1-ene as an orange oil (7.444 g). ^{1}H NMR (500 MHz, C_6D_6): δ = 7.49 (m, 2H, Ar-H), 7.18 (m, 2H, Ar-H), 7.10 (m, 1H, Ar-H), 4.98 (d, J = 7.9 Hz, 1H, PhCH), 3.92 (dd, J = 7.8 Hz, 1H, J = 7.0 Hz, CHO), 3.70–3.65 (m, J = 7.1 Hz, 2H, CH_3CH_2), 3.53 (d, J = 9.5 Hz, 1H, $CHCO_2Et$), 3.05 (m, 1H, CH_3CH), 1.56 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.30 (d, J = 6.8 Hz, 3H, CH_3CH), 0.98 (t, J = 7.1 Hz,

3H, CH_3CH$_2$), 0.03 ppm (s, 9H, SiMe$_3$); ^{13}C NMR (126 MHz, C_6D_6): δ = 152.8, 140.7, 128.4, 127.9, 127.8, 108.7, 88.3, 88.0, 82.4, 62.5, 33.6, 27.6, 18.6, 15.0, −0.4 ppm.

The silyl ketene acetal (7.291 g, 20.00 mmol) was dissolved in CH_2Cl_2 (80 mL) without further purification and $Pb(OAc)_4$ (10.641 g, 24.00 mmol) in CH_2Cl_2 (80 mL) was added at −78 °C. The reaction mixture was allowed to reach RT overnight. Then the solvent was evaporated and the residue was extracted with hexane. The organic extracts were concentrated to one third of the initial volume. A mixture of both epimeric α-acetoxy ethylesters ethyl (2*R*,3*R*)-2-acetoxy-3-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]butanoate and ethyl (2*S*,3*R*)-2-acetoxy-3-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-butanoate (5.677 g, 16.20 mmol, 81 %, *dr* 92:8) was isolated as a pale yellow oil upon flash chromatography on silica gel (hexane/EtOAc 5:1). R_f = 0.27 (hexane/EtOAc 5:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.29 (m, 5H, Ar), 4.84 (d, 1H, *J* = 6.8 Hz, C*H*CO$_2$Et), 4.78 (d, 1H, *J* = 8.8 Hz, PhCH), 4.21–4.01 (m, 2H, CH$_3$C*H*$_2$), 3.98 (dd, *J* = 8.8, 2.5 Hz, 1H, CHO), 2.25 (m, 1H, CH$_3$C*H*), 2.09 (s, 3H, CH$_3$CO), 1.53 (s, 3H, CH$_3$), 1.47 (s, 3H, CH$_3$), 1.17 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$), 1.09 ppm (d, *J* = 7.1 Hz, 3H, C*H*$_3$CH); (only the signals for the main product are given); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.3, 169.5, 137.6, 128.6, 128.4, 126.9, 108.9, 81.8, 80.2, 74.6, 61.2, 34.6, 27.2, 27.0, 20.6, 14.0, 10.2; MS (CI, NH_3): *m*/*z* (%): 368 (7.4) $[M+NH_4]^+$, 351 (0.7) $[M+H]^+$, 310 (38.1) $[M+NH_4-Me_2CO]^+$, 293 (100.0) $[M+H-Me_2CO]^+$; elemental analysis calcd (%) for $C_{19}H_{26}O_6$ (350.4): C 65.13, H 7.48; found: C 65.16, H 7.48.

A solution of a mixture of the epimeric α-acetoxy ethylesters (6.307 g, 18.00 mmol) and NaOEt (0.122 g, 1.80 mmol) in EtOH (90 mL) was stirred until saponification was complete. Then sat. NH_4Cl solution (108 mL) was added at 0 °C. The mixture was extracted with hexane/EtOAc 4:1 and the organic extracts were dried over Na_2SO_4. Pure **10** was obtained as a white solid (3.983 g, 72 %) after evaporation of solvent and purification by flash chromatography on silica gel (hexane/EtOAc 4:1). R_f = 0.24 (hexane/EtOAc 4:1); m.p. 44–45 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 5H, Ar), 4.75 (d, *J* = 8.9 Hz, 1H, PhCH), 4.09 (d, *J* = 4.3 Hz, 1H, CHO), 4.07–3.97 (m, 2H, CH$_3$C*H*$_2$), 3.84 (dd, *J* = 8.9, 2.1 Hz, 1H, CHO), 2.89 (s, 1H, OH), 2.15 (m, 1H, CH$_3$C*H*), 1.55 (s, 3H, CH$_3$), 1.48 (s, 3H, CH$_3$), 1.19 (d, 3H, *J* = 7.1 Hz, C*H*$_3$CH), 1.02 ppm (t, 3H, *J* = 7.1 Hz, C*H*$_3$CH$_2$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.8, 137.4, 128.6, 128.4, 126.7, 109.3, 82.6, 80.3, 74.6, 61.2, 35.7, 27.2, 27.0, 13.9, 10.7 ppm; IR (film, NaCl): $\tilde{\nu}$ = 3487, 3064, 3033, 2984, 2936, 2906, 1737, 1605, 1495, 1455, 1371, 1235, 1169, 1101, 1044, 1026, 889, 813, 758, 701 cm^{-1}; MS (CI, NH_3): *m*/*z* (%): 326 (2.3) $[M+NH_4]^+$, 309 (5.2) $[M+H]^+$, 291 (5.4) $[M-OH]^+$, 251 (68.4) $[M+H-Me_2CO]^+$, 233 (18.1) $[M+H-H_2O-Me_2CO]^+$; elemental analysis calcd (%) for $C_{17}H_{24}O_5$ (308.4): C 66.21, H 7.84; found: C 66.20, H 7.77.

Ethyl (2*S*,3*R*)-3-[(4*S*,5*S*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-2-hydroxybutanoate (*epi*-10): A solution of **9** (5.656 g, 19.345 mmol) in THF (77 mL) was added dropwise to a solution of LDA (3.108 g, 29.017 mmol) in THF (50.9 mL) at −78 °C. The mixture was stirred for 30 min, then MoOPH (12.600 g, 29.02 mmol) was added during a period of 30 min. The mixture was stirred for 3 h at −78 °C, then it was allowed to warm to RT. At 0 °C sat. Na_2SO_3 solution (58 mL) and sat. NH_4Cl solution (58 mL) were added and the mixture was warmed to RT and extracted with *t*BuOMe. The combined organic extracts were concentrated and washed with 2 M HCl and sat. $NaHCO_3$ solution. Drying over Na_2SO_4, evaporation of the solvent in vacuo and purification by flash chromatography on silica gel (hexane/EtOAc 4:1) gave pure *epi*-**10** as a white solid (3.532 g, 59 %). R_f = 0.30 (hexane/EtOAc 4:1); m.p. 81–83 °C; $[\alpha]_D^{24}$ (1.000 g/100 mL, MeOH): +13.2; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (m, 2H, Ar-H), 7.36 (m, 2H, Ar-H), 7.31 (m, 1H, Ar-H), 4.90 (d, *J* = 8.7 Hz, 1H, PhCH), 4.28 (d, *J* = 2.4 Hz, 1H, CHO), 4.26–4.18 (m, 2H, C*H*$_2$CH$_3$), 4.01 (dd, *J* = 8.6, 4.2 Hz, 1H, CHO), 2.87 (s, 1H, OH), 2.27 (m, 1H, CH$_3$C*H*), 1.56 (s, 3H, CH$_3$), 1.50 (s, 3H, CH$_3$), 1.28 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$), 0.92 ppm (d, 3H, *J* = 7.1 Hz, C*H*$_3$CH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.1, 137.8, 128.6, 128.4, 127.3, 108.7, 84.1, 80.7, 71.8, 61.8, 37.4, 27.3, 27.1, 14.2, 8.9 ppm; IR (KBr): $\tilde{\nu}$ = 3517, 3033, 2989, 2931, 2894, 1718, 1456, 1375, 1243, 1170, 1124, 1103, 1064, 1049, 1016, 889, 757, 700 cm^{-1}; MS (CI, NH_3): *m*/*z* (%): 326 (3.1) $[M+NH_4]^+$, 309 (< 1.0) $[M+H]^+$, 268 (100.0) $[M+NH_4-Me_2CO]^+$, 251 (34.5) $[M+H-Me_2CO]^+$, 233 (6.2) $[M+H-H_2O-Me_2CO]^+$; elemental analysis calcd (%) for $C_{17}H_{24}O_5$ (308.4): C 66.21, H 7.84; found: C 66.22, H 8.11.

(2*S*,3*S*)-3-[(4*R*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]-butan-1,2-diol (*epi*-11): A solution of *epi*-**10** (0.340 g, 1.10 mmol), *tert*-butyl dimethylsilyl chloride (0.249, 1.65 mmol), and imidazole (0.112 g, 1.65 mmol) in DMF (3.3 mL) was stirred at 60 °C until the reaction was complete as monitored by TLC. Then the solvent was evaporated in vacuo and the residue was dissolved in H_2O (25 mL). The mixture was extracted with petrol ether and the organic extracts were washed with brine and dried over Na_2SO_4. After evaporation of the solvent in vacuo the silyl ether was obtained as a colourless oil (0.436 g, 94 %). R_f = 0.58 (hexane/EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5H, Ar-H), 4.71 (d, *J* = 8.6 Hz, 1H, PhCH), 4.15–4.03 (m, 3H, CH$_3$C*H*$_2$, CHOSi), 3.87 (dd, 1H, *J* = 8.6 Hz, 2.9 Hz, CHO), 2.07 (m, 1H, CH$_3$C*H*), 1.53 (s, 3H, CH$_3$), 1.47 (s, 3H, CH$_3$), 1.18 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$), 1.11 (d, *J* = 7.0 Hz, 3H, C*H*$_3$CH), 0.82 (s, 9H, Me$_3$CSi), −0.12 ppm (s, 3H, SiMe), −0.03 ppm (s, 3H, SiMe); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.7, 138.0, 128.6, 128.3, 126.9, 108.9, 82.6, 81.0, 74.6, 60.6, 38.3, 27.13, 27.08, 25.6, 18.1, 14.1, 9.3, −5.0, −5.5 ppm; ^{29}Si NMR (99.4 MHz, $CDCl_3$): δ = 20.9 ppm; IR (film): $\tilde{\nu}$ = 3065, 3032, 2984, 2932, 2887, 2857, 1753, 1733, 1471, 1462, 1370, 1253, 1155, 1043, 884, 838, 779, 756, 735, 700, 678, 647 cm^{-1}; MS (CI, NH_3): *m*/*z* (%): 440 (0.3) $[M+NH_4]^+$, 423 (1.6) $[M+H]^+$, 382 (9.3) $[M+NH_4-Me_2C]^+$, 365 (100.0) $[M+H-Me_2CO]^+$; elemental analysis calcd (%) for $C_{23}H_{38}O_5Si$ (422.6): C 65.36, H 9.06; found: C 65.37, H 9.17.

$LiBH_4$ (57 mg, 2.62 mmol) was added at RT to a solution of the silyl ether (0.341 g, 0.81 mmol) in THF (2.0 mL), then the mixture was heated under reflux until the reaction was complete. Sat. NH_4Cl solution (10 mL) and an amount of a 2 M HCl solution sufficient to dissolve all solid components were added dropwise at 0 °C. The mixture was extracted with hexane and the organic extracts were washed with sat. $NaHCO_3$ solution and dried over Na_2SO_4. After evaporation of the solvent in vacuo a mixture of the primary and the secondary silyl ether was obtained (0.264 g, 86 %). Primary silyl ether: R_f = 0.28 (hexane/EtOH 60:3); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (m, 4H, Ar-H), 7.29 (m, 1H, Ar-H), 4.82 (d, *J* = 8.9 Hz, 1H, PhCH), 3.89 (dd, *J* = 8.8, 2.5 Hz, 1H,CHO), 3.70 (m, 1H, CHO), 3.56 (d, *J* = 6.3 Hz, 2H, C*H*$_2$OSi), 2.46 (s, 1H, OH), 1.90 (m, 1H, CH$_3$C*H*), 1.55 (s, 3H, CH$_3$), 1.49 (s, 3H, CH$_3$), 1.05 (d, 3H, *J* = 7.1 Hz, C*H*$_3$CH), 0.82 (s, 9H, (CH$_3$)$_3$C), 0.02 (s, 3H, CH$_3$Si), −0.01 ppm (s, 3H, CH$_3$Si); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 137.8, 128.5, 128.2, 126.6, 108.6, 85.0, 80.0, 74.2, 64.4, 33.8, 27.2, 27.1, 25.8, 18.1, 7.9, −5.45, −5.46 ppm; ^{29}Si NMR (99.4 MHz, $CDCl_3$): δ = 20.7; secondary silyl ether: R_f = 0.17 (hexane/EtOH 60:3); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (m, 5H, Ar), 4.68 (d, *J* = 9.1 Hz, 1H, PhCH), 4.12 (dd, *J* = 9.1, 1.2 Hz, 1H,CHO), 3.63 (m, 2H), 3.54 (m, 1H), 2.28 (s, 1H, OH), 1.81 (m, 1H, CH$_3$C*H*), 1.56 (s, 3H, CH$_3$), 1.47 (s, 3H, CH$_3$), 1.07 (d, 3H, *J* = 7.2 Hz, C*H*$_3$CH), 0.69 (s, 9H, (CH$_3$)$_3$C), −0.05 (s, 3H, CH$_3$Si), −0.27 ppm (s, 3H, CH$_3$Si); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 137.5, 128.6, 128.3, 126.8, 108.8, 80.6, 80.4, 75.3, 63.7, 36.1, 27.2, 27.1, 25.6, 17.8, 10.0, −4.8, −5.1 ppm; ^{29}Si NMR (99.4 MHz, $CDCl_3$): δ = 18.7 (s).

(*n*-Bu)$_4$NF·3H$_2$O (0.329 g, 1.04 mmol) was added to the solution of the silyl ether mixture in THF (3.1 mL) and stirred until the reaction was complete. Then 2 M HCl (347 μL, 0.69 mmol) was added and pure *epi*-**11** was obtained as a white solid (0.164 g, 89 %) after evaporation of the solvent in vacuo and flash chromatography on silica gel (hexane/EtOAc 3:2). R_f = 0.22 (hexane/EtOAc 3:2); $[\alpha]_D^{28}$ (1.016 g/100 mL, MeOH): +13.0; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (m, 5H, Ar), 4.79 (d, *J* = 8.9 Hz, 1H, PhCH), 3.97 (dd, *J* = 8.9, 2.0 Hz, 1H,CHO), 3.71 (m, 1H,CHO), 3.65 (dd, *J* = 11.3, 6.2 Hz, 1H, CH$_2$), 3.50 (dd, *J* = 11.4, 4.1 Hz, 1H, CH$_2$), 2.72 (s, 2H, OH), 1.82 (m, 1H, CH$_3$CH), 1.57 (s, 3H, CH$_3$), 1.49 (s, 3H, CH$_3$), 1.06 ppm (d, *J* = 7.1 Hz, 3H, C*H*$_3$CH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 137.2, 128.7, 128.5, 126.7, 108.9, 84.1, 79.9, 74.5, 63.5, 34.4, 27.2, 27.0, 8.2 ppm; IR (KBr): $\tilde{\nu}$ = 3326, 3241, 3034, 2978, 2938, 2890, 1494, 1454, 1370, 1337, 1233, 1166, 1100, 1047, 999, 971, 892, 851, 810, 755, 698, 637 cm^{-1}; MS (CI, NH_3): *m*/*z* (%): 267 (4.4) $[M+H]^+$, 249 (4.3) $[M+H-H_2O]^+$, 226 (55.6) $[M+NH_4-Me_2CO]^+$, 209 (33.5) $[M+H-Me_2CO]^+$, 191 (100.0) $[M+H-Me_2CO-H_2O]^+$; elemental analy-

sis calcd (%) for $C_{15}H_{22}O_4$ (266.3): C 67.65, H 8.33; found: C 67.48, H 8.34.

(2*R*,3*S*)-2-(Allyloxy)-3-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-butan-1-ol (12): A 0.57 M solution of LDA (10.00 mmol) in THF (17.5 mL) was added to a solution of **10** (3.084 g, 10.00 mmol) in THF (20 mL) at −78 °C. After 20 min of stirring allyl bromide (1.815 g, 15.00 mmol, 1.30 mL) in DMF (20 mL) was added. Stirring was continued for 15 min, then the reaction was allowed to warm up to RT and stirred overnight. The solvent was evaporated in vacuo and the residue was extracted with hexane. The extracts were filtered and the solvent was evaporated in vacuo. Purification by flash chromatography on silica gel (hexane/EtOAc 8:1) gave the allyl ether (2.967 g, 85%) of **12**. R_f = 0.29 (hexane/EtOAc 8:1); $[\alpha]_D^{23}$ (1.102 g/100 mL, MeOH): +40.5; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.31 (m, 4H, Ar-H), 7.28 (m, 1H, Ar-H), 5.81 (ddm, J = 17.3, 10.3 Hz, 1H, CH_2CH=CH_2), 5.22 (dm, J = 17.2 Hz, 1H, CH_2CH=CH_2), 5.15 (dm, J = 10.4 Hz, 1H, CH_2CH=CH_2), 4.78 (d, J = 8.9 Hz, 1H, PhCH), 4.11–4.21 (m, 3H, CH_3CH_2, CHO), 4.05 (ddm, J = 12.8, 5.5 Hz, 1H, CH_2CH=CH_2), 3.86 (ddm, J = 12.8, 6.0 Hz, 1H, CH_2CH=CH_2), 3.79 (d, J = 8.6 Hz, 1H, CHO), 2.08 (m, 1H, CH_3CH), 1.53 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.24 (t, J = 7.1 Hz, 3H, CH_3CH_2), 1.03 ppm (d, J = 7.0 Hz, 3H, CH_3CH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.1, 137.7, 133.9, 128.5, 128.2, 126.9, 117.6, 108.5, 81.4, 80.5, 79.8, 71.5, 60.7, 35.4, 27.12, 27.06, 14.2, 9.6 ppm; IR (film): $\tilde{\nu}$ = 3066, 3032, 2983, 2935, 2910, 1747, 1647, 1604, 1495, 1456, 1425, 1379, 1371, 1342, 1304, 1234, 1188, 1167, 1097, 1026, 1001, 926, 887, 758, 700 cm^{-1}; MS (CI, NH_3): m/z (%): 366 (5.7) $[M+NH_4]^+$, 349 (0.4) $[M+H]^+$, 308 (24.5) $[M+NH_4-Me_2CO]^+$, 291 (100.0) $[vH-Me_2CO]^+$; elemental analysis calcd (%) for $C_{20}H_{28}O_5$ (348.4): C 68.94, H 8.10; found: C 68.82, H 8.29.

A solution of the allyl ether (3.484 g, 10.00 mmol) in THF (20 mL) was added dropwise at 5–10 °C to a solution of $LiAlH_4$ (0.285 g, 7.50 mmol) in THF (15 mL). The reaction mixture was allowed to warm up to RT and stirred overnight. The reaction mixture was cooled to 0 °C and hexane/EtOAc 8:1 (105 mL) was added. Then 1 M HOAc (53 mL) was added dropwise. The mixture was allowed to warm up to RT and after phase separation the aqueous phase was extracted with hexane/EtOAc 8:1. The organic extracts were dried over Na_2SO_4. Evaporation of the solvent gave **12** as a slightly turbid colourless oil (3.022 g, 99%). R_f = 0.12 (hexane/EtOAc 9:1); $[\alpha]_D^{25}$ (1.102 g/100 mL, MeOH): +7.7; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 5H, Ar-H), 5.84 (m, 1H, CH_2CH=CH_2), 5.17 (dm, J = 17.2 Hz, 1H, CH_2CH=CH_2), 5.10 (dm, 1H, J = 10.4 Hz, CH_2CH=CH_2), 4.75 (d, J = 9.0 Hz, 1H, PhCH), 4.02 (dd, J = 9.0, 1.6 Hz, 1H, CHO), 3.99–3.97 (m, 2H, CH_2CH=CH_2), 3.73 (dd, J = 12.0, 4.1 Hz, 1H, CH_2OH), 3.50 (dd, 1H, J = 12.0, 4.9 Hz, CH_2OH), 3.30 (m, 1H, CHO), 2.37 (s, 1H, OH), 1.95 (m, 1H, CH_3CH), 1.55 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.05 (d, 3H, ^3J = 7.0 Hz, CH_3CH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 137.7, 134.7, 128.6, 128.3, 126.7, 116.9, 108.5, 82.5, 81.8, 79.9, 71.1, 61.3, 32.9, 27.10, 27.08, 8.5; IR (film): $\tilde{\nu}$ = 3465, 3066, 3032, 2983, 2931, 2914, 2887, 1645, 1604, 1495, 1454, 1423, 1379, 1371, 1342, 1236, 1169, 1128, 1099, 1045, 1028, 995, 960, 922, 889, 814, 756, 700 cm^{-1}; MS (CI, NH_3): m/z (%): 324 (11.8) $[M+NH_4]^+$, 307 (0.8) $[M+H]^+$, 266 (11.4) $[M+NH_4-Me_2CO]^+$, 249 (100.0) $[M+H-Me_2CO]^+$; elemental analysis calcd (%) for $C_{18}H_{26}O_4$ (306.4): (348.4): C 70.56, H 8.55; found: C 70.66, H 8.84.

(3*S*,4*S*)-3-(Allyloxy)-4-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-pentanal (13): Tosyl chloride (3.432 g, 18.00 mmol) was added at 0 °C to a solution of **12** (3.677 g, 12.00 mmol) and DABCO (2.019 g, 18.00 mmol) in CH_2Cl_2 (36 mL). The mixture was stirred at RT until **12** could not be detected any more by TLC. EtOAc (180 mL) was added to the reaction mixture and after filtration the residue was extracted with EtOAc. The filtrate and the organic extracts were washed with H_2O and sat. $NaHCO_3$ solution and dried over Na_2SO_4. After solvent evaporation in vacuo and purification by flash chromatography on silica gel (hexane/EtOAc 8:1) the tosylate was obtained as a white solid (5.171 g, 94%). R_f = 0.16 (hexane/EtOAc 8:1); m.p. 73 °C; $[\alpha]_D^{26}$ (1.000 g/100 mL, $CHCl_3$): −5.3; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (d, J = 8.2 Hz, 2H, Ar-H), 7.36–7.27 (m, 7H, Ar-H), 5.73 (m, 1H, CH_2CH=CH_2), 5.10 (dm, J = 17.2 Hz, 1H, CH_2CH=CH_2), 0.98 ppm (d, J = 7.0 Hz, 3H, CH_3CH), 5.06 (dm, J = 10.4 Hz, 1H, CH_2CH=CH_2), 4.69 (d, J = 8.9 Hz, 1H, PhCH), 4.27 (dd, J = 10.8, 2.2 Hz, 1H, CH_2OTos), 4.00–3.92 (m, 3H, CHO and CH_2CH=CH_2, CH_2OTos), 3.87 (ddm, J = 12.6, 5.7 Hz, 1H, CH_2CH=CH_2), 3.42 (m, 1H, CHO), 2.43 (s, 3H, $ArCH_3$), 1.84 (m, 1H, CH_3CH), 1.50 (s, 3H, CH_3), 1.44 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 144.7, 137.6, 134.5, 133.0, 129.8, 128.6, 128.3, 128.0, 126.6, 116.9, 108.5, 81.9, 79.7, 79.3, 71.7, 70.7, 33.7, 27.1, 21.6, 8.8 ppm; IR (KBr): $\tilde{\nu}$ = 3089, 3033, 2981, 2920, 2891, 1647, 1597, 1496, 1466, 1425, 1387, 1358, 1309, 1294, 1230, 1211, 1178, 1132, 1097, 1068, 1026, 989, 945, 831, 818, 795, 760, 710, 700, 664 cm^{-1}; MS (CI, NH_3): m/z (%): 478 (17.5) $[M+NH_4]^+$, 461 (0.6) $[M+H]^+$, 420 (29.0) $[M+NH_4-Me_2CO]^+$, 403 (30.6) $[M+H-Me_2CO]^+$; elemental analysis calcd (%) for $C_{25}H_{32}O_6S$ (460.6): C 65.19, H 7.00; found: C 65.02, H 7.02.

The tosylate (2.303 g, 5.00 mmol), NaCN (0.368 g, 7.50 mmol) and $NaHCO_3$ (0.630 g, 7.50 mmol) were dissolved in DMSO (50 mL) and the mixture was stirred at 60 °C until the reaction was complete (approx. 5 h). After adding *t*BuOMe (500 mL) the solution was washed with H_2O and brine. Drying over Na_2SO_4 and solvent evaporation in vacuo gave the nitrile as a white solid (1.557 g, 99%). R_f = 0.55 (toluene/CH_3CN 75:10); m.p. 89–90 °C; $[\alpha]_D^{26}$ (1.000 g/100 mL, MeOH): +22.9; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.31 (m, 5H, Ar-H), 5.85 (m, 1H, CH_2CH=CH_2), 5.21 (dm, J = 17.2 Hz, 1H, CH_2CH=CH_2), 5.14 (dm, J = 10.4 Hz, 1H, CH_2CH=CH_2), 4.72 (d, J = 8.9 Hz, 1H, PhCH), 4.05 (ddm, J = 12.6, 5.8 Hz, 1H, CH_2CH=CH_2), 4.00 (ddm, J = 12.6, 5.7 Hz, 1H, CH_2CH=CH_2), 3.92 (dd, J = 8.9, 1.8 Hz, 1H, CHO), 3.54 (m, 1H, $CHCH_2$), 2.70 (dd, J = 17.0, 3.2 Hz, 1H, CH_2CN), 2.44 (dd, J = 17.0, 7.6 Hz, 1H, CH_2CN), 1.96 (m, 1H, CH_3CH), 1.54 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.06 ppm (d, 3H, ^3J = 7.0 Hz, CH_3CH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 137.3, 134.1, 128.7, 128.5, 126.6, 118.2, 117.6, 108.9, 82.2, 80.0, 77.5, 71.4, 35.3, 27.1, 27.0, 20.9, 7.9 ppm; IR (KBr): $\tilde{\nu}$ = 3097, 3066, 3035, 2983, 2931, 2910, 2868, 2858, 2249, 1647, 1495, 1456, 1431, 1410, 1389, 1367, 1344, 1311, 1294, 1269, 1242, 1223, 1165, 1124, 1103, 1084, 1061, 1041, 1024, 1012, 989, 957, 924, 891, 854, 812, 760, 706, 656, 640 cm^{-1}; MS (CI, NH_3): m/z (%): 333 (16.5) $[M+NH_4]^+$, 316 (8.8) $[M+H]^+$, 275 (38.4) $[M+NH_4-Me_2CO]^+$, 258 (100.0) $[M+H-Me_2CO]^+$; elemental analysis calcd (%) for $C_{19}H_{25}NO_3$ (315.4): C 72.35, H 7.99, N 4.44; found: C 72.22, H 7.94, N 4.42.

A 1.0 M solution of DIBAH (3.90 mmol, 3.90 mL) in toluene was added to a solution of the nitrile in toluene (30 mL) at −78 °C. The reaction mixture was stirred for 2 h at −78 °C, then AcOH (1.874 g, 31.20 mmol, 1.78 mL) was added in toluene (3.6 mL). While warming to 10 °C, 1 M AcOH (30 mL) was added. The reaction mixture was extracted with hexane and the organic extracts were washed with 1 M AcOH and sat. $NaHCO_3$ solution. Drying over Na_2SO_4 and evaporation of the solvent in vacuo gave pure **13** as a colourless oil (0.878 g, 92%).

***tert*-Butyl (5*S*,6*S*,*E*)-6-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-5-hydroxyhept-2-enoate (5)**: A solution of *tert*-butyl diethyl phosphonoacetate (1.466, 5.81 mmol) in THF (5.8 mL) was added dropwise at 0 °C to a suspension of NaH (0.139 g, 5.81 mmol) in THF (12 mL). The mixture was allowed to warm up to RT and stirred until the reaction was complete. Then the mixture was cooled to −78 °C and a solution of **13** (1.850 g, 5.81 mmol) in THF (5.8 mL) was added dropwise. Stirring was continued for 3 h at −78 °C, then the mixture was allowed to warm up to RT. After treatment with a sat. NH_4Cl solution the mixture was extracted with Et_2O. The organic extracts were washed with H_2O and sat. $NaHCO_3$ solution and dried over Na_2SO_4. After solvent evaporation in vacuo and purification by flash chromatography on silica gel (hexane/EtOAc 12:1) pure *tert*-butyl (5*S*,6*S*,*E*)-5-(allyloxy)-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-hept-2-enoate was obtained as a colourless oil (2.065 g, 85%). R_f = 0.24 (hexane/EtOAc 12:1); $[\alpha]_D^{28}$ (0.84 g/100 mL, MeOH): +18.1; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.34 (m, 4H, Ar-H), 7.30 (m, 1H, Ar-H), 6.76 (dm, J = 15.5 Hz, 1H, CH=CH-CO), 5.82 (m, 1H, CH_2CH=CH_2), 5.65 (dm, J = 15.6 Hz, 1H, CH=CH-CO), 5.16 (dm, J = 17.2 Hz, 1H, CH_2CH=CH_2), 5.09 (dm, J = 10.4 Hz, 1H, CH_2CH=CH_2), 4.69 (d, J = 8.9 Hz, 1H, PhCH), 4.00 (dd, J = 8.9, 2.7 Hz, 1H, CHO), 3.88–3.97 (m, 2H, CH_2CH=CH_2), 3.32 (m, 1H, $CHCH_2$), 2.36 (dddd, J = 15.0, 7.0, 3.3 Hz, 1.5 Hz, CH_2), 2.23 (m, 1H, CH_2), 1.85 (m, 1H, CH_3CH), 1.54 (s, 3H, CH_3C), 1.48 (s, 3H, CH_3C), 1.46 (s, 9H, $(CH_3)_3C$), 1.04 ppm (d, J = 6.9 Hz, 3H, CH_3CH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.7,

144.5, 137.8, 134.8, 128.6, 128.3, 126.9, 124.9, 116.8, 108.5, 82.5, 80.5, 80.1, 80.0, 71.0, 35.9, 34.2, 28.2, 27.2, 27.1, 9.1 ppm; IR (film): $\tilde{\nu}$ = 3066, 3031, 2981, 2933, 2908, 1714, 1653, 1605, 1495, 1456, 1426, 1368, 1328, 1288, 1238, 1156, 1094, 1078, 1045, 1027, 990, 923, 889, 854, 814, 757, 700 cm^{-1}; MS (CI, NH_3): *m/z* (%): 434 (41.3) $[M+NH_4]^+$, 376 (6.5) $[M+NH_4-Me_2CO]^+$, 359 (54.1) $[M+H-Me_2CO]^+$, 320 (100.0) $[M+NH_4-Me_2CO-C_4H_8]^+$; elemental analysis calcd (%) for $C_{25}H_{36}O_5$ (416.6): C 72.08, H 8.71; found: C 72.24, H 8.63.

p-Toluenesulfinic acid (0.911 g, 5.83 mmol) was added at RT to a solution of $[Pd(PPh_3)_4]$ (0.911 g, 0.49 mmol) and *tert*-butyl (5*S*,6*S*,*E*)-5-(allyloxy)-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-hept-2-enoate (2.026 g, 4.86 mmol) in CH_2Cl_2 (49 mL). After 2 h no more starting material could be detected by TLC. NEt_3 (0.590 g, 0.81, 5.83 mmol) was added to the reaction mixture, then the solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 and filtered through silica gel by first eluting impurities with CH_2Cl_2 and then the product with hexane/EtOAc 4:1. After solvent evaporation in vacuo and purification by flash chromatography on silica gel (hexane/EtOAc 4:1) pure *tert*-butyl-(5*S*,6*S*,*E*)-6-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-5-hydroxyhept-2-enoate (**5**) could be obtained as a white solid (1.772 g, 97%). R_f = 0.21 (hexane/EtOAc 4:1); $[\alpha]_D^{25}$ (1.00 g/100 mL, $CHCl_3$): −10.7; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.28 (m, 5H, Ar-H), 6.77 (dm, *J* = 15.6 Hz, 1H, C*H*=CH-CO), 5.67 (dm, *J* = 15.6 Hz, 1H, CH=C*H*-CO), 4.79 (d, *J* = 8.9 Hz, 1H, PhCH), 4.05 (dd, *J* = 8.9, 2.3 Hz, 1H, CHO), 3.70 (ddd, *J* = 8.1, 5.1, 5.1 Hz, 1H, C*H*CH_2), 2.44 (s, 1H, OH), 2.36–2.23 (m, 2H, CH_2), 1.78 (m, 1H, CH_3C*H*), 1.56 (s, 3H, MeC), 1.49 (s, 3H, MeC), 1.45 (s, 9H, Me_3C), 1.07 ppm (d, *J* = 7.0 Hz, 3H, CH_3CH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.5, 143.9, 137.3, 128.7, 128.5, 126.7, 125.4, 108.9, 82.7, 80.1, 79.9, 73.6, 37.7, 36.4, 28.1, 27.2, 27.0, 10.9 ppm; IR (film): $\tilde{\nu}$ = 3486, 3063, 3032, 2981, 2934, 2903, 1712, 1653, 1495, 1456, 1368, 1329, 1236, 1154, 1089, 1043, 1026, 983, 888, 853, 815, 757, 700 cm^{-1}; MS (CI, NH_3): *m/z* (%): 394 (18.0) $[M+NH_4]^+$, 377 (1.3) $[M+H]^+$, 336 (11.3) $[M+NH_4-Me_2CO]^+$; elemental analysis calcd (%) for $C_{22}H_{32}O_5$ (376.5): C 70.19, H 8.57; found: C 69.99, H 8.31.

***tert*-Butyl (5*R*,6*S*,*E*)-6-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-5-hydroxyhept-2-enoate (*epi*-5)**: Allyl bromide (2.193 mmol, 1.57 mL) was added to a solution of NaH (0.580 g, 24.17 mmol) in DME (14 mL). Then a solution of α-hydroxy ester *epi*-**10** in DME (30 mL) was added dropwise. The mixture was stirred for 2 h at RT and at 60 °C until the reaction was complete as monitored by TLC. Then sat. NH_4Cl solution was added dropwise at 0 °C. After warming to RT H_2O (134 mL) was added and the mixture was extracted with hexane. The combined organic extracts were dried over Na_2SO_4 and the solvent was evaporated in vacuo. After purification by flash chromatography on silica gel (hexane/EtOAc 8:1) pure ethyl (2*S*,3*R*)-2-(allyloxy)-3-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-butanoate was obtained as a colourless oil (3.747 g, 89%). R_f = 0.27 (hexane/EtOAc 8:1); $[\alpha]_D^{21}$ (1.69 g/100 mL, MeOH): +14.7; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (m, 2H, Ar-H), 7.35 (m, 2H, Ar-H), 7.30 (m, 1H, Ar-H), 5.68 (m, 1H, CH_2C*H*=CH_2), 5.11 (dm, *J* = 17.3 Hz, 1H, CH_2CH=CH_2), 5.07 (dm, *J* = 10.4 Hz, 1H, CH_2CH=CH_2), 4.79 (d, *J* = 8.6 Hz, 1H, PhCH), 4.10–4.22 (m, 2H, CH_3CH_2), 3.97 (dd, *J* = 8.6, 6.0 Hz, 1H, CHO), 3.78–3.82 (m, 2H, CHO, CH_2CH=CH_2), 3.18 (ddm, *J* = 12.0, 5.9 Hz, 1H, CH_2CH=CH_2), 2.23 (m, 1H, CH_3C*H*), 1.55 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.22 (t, 3H, *J* = 7.1 Hz, C$H_3$$CH_2$), 1.03 ppm (d, 3H, *J* = 7.0 Hz, CH_3CH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.8, 138.1, 134.0, 128.6, 128.5, 127.8, 117.4, 108.4, 83.0, 81.7, 78.5, 71.2, 60.8, 38.5, 27.2, 27.2, 14.2, 10.8 ppm; IR (film): $\tilde{\nu}$ = 3066, 3033, 2984, 2935, 2882, 1749, 1731, 1648, 1605, 1496, 1456, 1427, 1371, 1337, 1238, 1205, 1168, 1056, 1027, 924, 890, 860, 815, 758, 701 cm^{-1}; MS (CI, NH_3): *m/z* (%): 366 (15.6) $[M+NH_4]^+$, 349 (10.9) $[M+H]^+$, 308 (35.0) $[M+NH_4-Me_2CO]^+$, 291 (100.0) $[M+H-Me_2CO]^+$; elemental analysis calcd (%) for $C_{20}H_{28}O_5$ (348.4): C 68.94, H 8.10; found: C 68.68, H 8.14.

A solution of ethyl (2*S*,3*R*)-2-(allyloxy)-3-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-butanoate (3.736 g, 10.72 mmol) in THF (21 mL) was added to a suspension of $LiAlH_4$ (0.306 g, 8.04 mmol, 1.5 equiv) in THF (16 mL) at 5 to 10 °C. The mixture was allowed to reach RT and stirred until the reaction was complete as monitored by TLC. Then the mixture was cooled to 0 °C and hexane/EtOAc 8:1 (113 mL) was added. After dropwise addition of 1 M AcOH (57 mL) and warming to RT the phases were separated and the aqueous phase was extracted with hexane/EtOAc 8:1. The combined organic layers were dried over K_2CO_3 and evaporation of the solvent in vacuo gave pure (2*S*,3*S*)-2-(allyloxy)-3-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-butan-1-ol as a colourless oil (3.207 g, 98%). R_f = 0.16 (hexane/EtOAc 4:1); $[\alpha]_D^{25}$ (1.59 g/100 mL, MeOH): +16.4; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 5H, Ar-H), 5.66 (m, 1H, CH_2C*H*=CH_2), 5.08–4.98 (m, 2H, CH_2CH=CH_2), 4.70 (d, 1H, *J* = 8.9 Hz, PhCH), 4.06 (dd, *J* = 8.9 Hz, 2.0 Hz, 1H, CHO), 3.80 (ddm, *J* = 12.5, 5.7 Hz, 1H, CH_2CH=CH_2), 3.60–3.68 (m, 3H, CH_2OH, CH_2CH=CH_2), 3.31 (m, 1H, CHO), 2.32 (s, 1H, OH), 2.00 (m, 1H, CH_3C*H*), 1.54 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.08 ppm (s, *J* = 7.1 Hz, 3H, CH_3CH); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 137.7, 134.8, 128.6, 128.4, 127.0, 116.8, 108.8, 81.9, 81.2, 80.5, 70.4, 61.6, 33.0, 27.2, 27.1, 9.9 ppm; IR (film): $\tilde{\nu}$ = 3458, 3066, 3032, 2983, 2933, 2885, 1647, 1604, 1495, 1456, 1425, 1379, 1371, 1342, 1236, 1169, 1132, 1105, 1047, 997, 924, 889, 812, 758, 700 cm^{-1}; MS (CI, NH_3): *m/z* (%): 324 (1.7) $[M+NH_4]^+$, 307 (1.0) $[M+H]^+$, 266 (12.9) $[M+NH_4-Me_2CO]^+$, 249 (58.4) $[M+H-Me_2CO]^+$; elemental analysis calcd (%) for $C_{18}H_{26}O_4$ (306.4): C 70.56, H 8.55; found: C 70.56, H 8.48.

TosCl (2.734 g, 14.34 mmol) was added to a solution of (2*S*,3*S*)-2-(allyloxy)-3-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-butan-1-ol (2.928 g, 9.56 mmol) and DABCO (3.007 g, 15.77 mmol) in CH_2Cl_2 (29 mL) at 0 °C. The mixture was stirred for 5 min at 0 °C and then at RT until the reaction was complete as monitored by TLC. EtOAc (143 mL) was added, then the mixture was filtered and the residue was extracted with EtOAc. The combined organic extracts and the filtrate were washed with H_2O and sat. $NaHCO_3$ solution and the solvent was evaporated in vacuo. After purification by flash chromatography on silica gel (hexane/EtOAc 8:1) pure (2*S*,3*S*)-2-(allyloxy)-3-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-butyl 4-methylbenzenesulfonate was obtained as a highly viscous colourless oil (4.022 g, 91%). R_f = 0.18 (hexane/EtOAc 8:1); $[\alpha]_D^{21}$ (1.19 g/100 mL, $CHCl_3$): +6.1; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.72 (dm, *J* = 8.3 Hz, 2H, arom. CH), 7.36–7.26 (m, 7H, arom. CH), 5.59 (m, 1H, CH_2C*H*=CH_2), 5.04–4.96 (m, 2H, CH_2CH=CH_2), 4.65 (d, 1H, *J* = 8.7 Hz,PhCH), 4.13 (dd, 1H, *J* = 10.9, 3.7 Hz, CH_2OTos), 3.99 (dd, *J* = 10.9, 6.6 Hz, 1H, CH_2OTos), 3.89 (dd, *J* = 8.8 Hz, 3.4 Hz, 1H, CHO), 3.76 (ddm, *J* = 12.6, 5.5 Hz, 1H, CH_2CH=CH_2), 3.43–3.53 (m, 2H, CHO, CH_2CH=CH_2), 2.43 (s, 3H, Ar-CH_3), 1.93 (m, 1H, CH_3C*H*), 1.47 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 0.99 ppm (d, *J* = 7.0, 3H, CH_3CH); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 144.7, 137.8, 134.5, 133.1, 129.8, 128.6, 128.4, 127.9, 127.1, 116.7, 108.7, 81.6, 80.6, 78.7, 71.0, 70.0, 34.5, 27.1, 21.6, 9.7 ppm; IR (film): $\tilde{\nu}$ = 3066, 3032, 2983, 2933, 2898, 1647, 1599, 1495, 1456, 1365, 1308, 1292, 1236, 1190, 1176, 1097, 1045, 1028, 987, 964, 889, 816, 791, 758, 702, 667 cm^{-1}; MS (CI, NH_3): *m/z* (%): 478 (51.1) $[M+NH_4]^+$, 461 (14.7) $[M+H]^+$, 420 (45.2) $[M+NH_4-Me_2CO]^+$, 403 (39.8) $[M+H-Me_2CO]^+$; elemental analysis calcd (%) for $C_{25}H_{32}O_6S$ (460.6): C 65.19, H 7.00; found: C 65.18, H 7.00.

The solution of (2*S*,3*S*)-2-(allyloxy)-3-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-butyl 4-methylbenzenesulfonate (2.763 g, 6.00 mmol), NaCN (0.441 g, 9.00 mmol) and $NaHCO_3$ (0.756 g, 9.00 mmol) in DMSO (60 mL, p.a.) was stirred for 18 h at 60 °C and for 25 h at 80 °C. After that period of time all starting material had disappeared according to TLC. After addition of *t*BuOMe (600 mL) the mixture was washed with H_2O and brine and dried over Na_2SO_4. After evaporation of the solvent in vacuo (3*R*,4*S*)-3-(allyloxy)-4-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]pentanenitrile was obtained as a pale yellow oil (1.855 g, 98%). R_f = 0.33 (hexane/EtOAc 4:1); $[\alpha]_D^{21}$ (1.40 g/100 mL, MeOH): +29.9; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.30 (m, 5H, Ar-H), 5.62 (m, 1H, CH_2C*H*=CH_2), 5.07–5.03 (m, 2H, CH_2CH=CH_2), 4.67 (d, *J* = 8.9 Hz, 1H, PhCH), 3.99 (dd, *J* = 8.9 Hz, 2.6 Hz, 1H, CHO), 3.80 (ddm, *J* = 12.4, 5.7 Hz, 1H, CH_2CH=CH_2), 3.52–3.56 (m, 2H, CH_2CH=CH_2, C*H*CH_2), 2.53 (m, 2H, CH_2CN), 2.02 (m, 1H, CH_3C*H*), 1.54 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.07 ppm (d, *J* = 7.1 Hz, 3H, CH_3CH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 137.4, 133.9, 128.7, 128.5, 127.0, 118.3, 117.5, 109.0, 80.9, 80.7, 77.2, 70.7, 35.0, 27.3, 27.1, 20.5, 9.7 ppm; IR (film): $\tilde{\nu}$ = 3066, 3032, 2985, 2935, 2898, 2251, 1647, 1604, 1495, 1456, 1425, 1379, 1371, 1346, 1236, 1169, 1099, 1045, 993, 928, 889, 812, 758, 702, 642 cm^{-1}; MS (CI, NH_3): *m/z* (%): 333 (27.1) $[M+NH_4]^+$, 316 (100.0) $[M+H]^+$, 275 (50.8)

$[M+NH_4-Me_2CO]^+$, 258 (89.1) $[M+H-Me_2CO]^+$; elemental analysis calcd (%) for $C_{19}H_{25}NO_3$ (315.4): C 72.35, H 7.99, N 4.44; found: C 72.26, H 7.97, 4.41.

A 1.0 M solution of DIBAH in toluene (3.25 mL, 3.25 mmol DIBAH) was added dropwise at −78 °C to a solution of (3*R*,4*S*)-3-(allyloxy)-4-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]pentanenitrile (0.789 g, 2.50 mmol) in toluene (25 mL). After stirring for 2 h at −78 °C a solution of AcOH (1.561 g, 26 mmol, 1.48 mL) in toluene (3 mL) was added. The mixture was stirred for 5 min in the cold, then 1 M AcOH (25 mL) was added while the mixture was allowed to warm up to about 10 °C. Then the mixture was extracted with hexane, the combined organic extracts were washed with 1 M AcOH and sat. $NaHCO_3$ solution and dried over Na_2SO_4. After evaporation of the solvent in vacuo (3*R*,4*S*)-3-(allyloxy)-4-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]pentanal was obtained as a white solid (0.727 g, 91 %). $R_f=0.50$ (toluene/CH_3CN 75:10); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=9.75$ (m, 1H, CHO), 7.41–7.27 (m, 5H, Ar-H), 5.54 (m, 1H, CH_2CH=CH_2), 5.00–4.91 (m, 2H, CH_2CH=CH_2), 4.67 (d, $J=8.9$ Hz, 1H, PhCH), 4.03 (dd, $J=8.9$, 2.3 Hz, 1H, CHO), 3.79 (dt, $J=8.4$, 4.2, 4.2 Hz, 1H, $CHCH_2$), 3.64 (ddm, $J=12.2$, 5.7 Hz, 1H, CH_2CH=CH_2), 3.45 (ddm, $J=12.3$, 5.7 Hz, 1H, CH_2CH=CH_2), 2.65 (ddd, $J=17.0$, 8.4, 2.4 Hz, 1H, CH_2CHO), 2.52 (ddd, $J=17.0$, 4.1 Hz, 1.6 Hz, 1H, CH_2CHO), 2.01 (m, 1H, CH_3CH), 1.55 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.04 ppm (d, $J=7.0$ Hz, 3H, CH_3CH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=201.8$, 137.8, 134.4, 128.6, 128.4, 127.1, 116.9, 109.0, 81.1, 80.9, 76.6, 70.1, 45.4, 34.4, 27.3, 27.2, 9.9 ppm; MS (CI, NH_3): *m*/*z* (%): 336 (1.1) $[M+NH_4]^+$, 319 (0.6) $[M+H]^+$, 278 (51.2) $[M+NH_4-Me_2CO]^+$, 261 (45.3) $[M+H-Me_2CO]^+$; elemental analysis calcd (%) for $C_{19}H_{26}O_4$ (318.4): C 71.67, H 8.23; found: C 71.53, H 8.27.

A solution of *tert*-butyl diethyl phosphonoacetate (1.272 g, 5.04 mmol) in THF (5.0 mL) was added dropwise at 0 °C to a suspension of NaH (0.121 g, 5.04 mmol) in THF (10 mL). The mixture was allowed to warm up to RT and stirred until the reaction was complete. Then the mixture was cooled to −78 °C and a solution of (3*R*,4*S*)-3-(allyloxy)-4-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]pentanal (1.606 g, 5.04 mmol) in THF (5.0 mL) was added dropwise. Stirring was continued for 3 h at −78 °C and then the mixture was allowed to warm up to RT. After treatment with a sat. NH_4Cl solution the mixture was extracted with Et_2O. The organic extracts were washed with H_2O and sat. $NaHCO_3$ solution and dried over Na_2SO_4. After solvent evaporation in vacuo and purification by flash chromatography on silica gel (hexane/EtOAc 12:1) pure *tert*-butyl (5*R*,6*S*,*E*)-5-(allyloxy)-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-hept-2-enoate was obtained as a white solid (1.743 g, 83 %). $R_f=0.25$ (hexane/EtOAc 12:1); $[\alpha]_D^{24}$ (1.11 g/100 mL, $CHCl_3$): +18.6; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.39$–7.32 (m, 4H, Ar-H), 7.29 (m, 1H, Ar-H), 6.78 (dm, $J=15.6$ Hz, 1H, CH=CH-CO), 5.72 (dm, $J=15.6$ Hz, 1H, CH=CH-CO), 5.62 (m, 1H, CH_2CH=CH_2), 4.99–5.06 (m, 2H, CH_2CH=CH_2), 4.66 (d, $J=8.9$ Hz, 1H, PhCH), 3.99 (dd, $J=8.8$, 3.1 Hz, 1H, CHO), 3.69 (ddm, $J=12.3$, 5.7 Hz, 1H, CH_2CH=CH_2), 3.40 (ddm, $J=12.3$, 5.7 Hz, 1H, CH_2CH=CH_2), 3.30 (m, 1H, $CHCH_2$), 2.40–2.29 (m, 2H, CH_2), 1.89 (m, 1H, CH_3CH), 1.54 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.46 (s, 9H, $(CH_3)_3C$), 1.05 ppm (d, $^3J=7.0$ Hz, 3H, CH_3CH); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=165.7$, 144.5, 137.9, 134.7, 128.5, 128.4, 127.2, 124.9, 116.7, 108.7, 81.9, 81.1, 80.0, 79.9, 70.2, 35.5, 33.8, 28.1, 27.2, 27.2, 9.8 ppm; IR (film): $\tilde{\nu}=3065$, 3031, 2981, 2934, 2902, 1714, 1653, 1605, 1495, 1476, 1456, 1426, 1390, 1379, 1368, 1328, 1288, 1237, 1154, 1098, 1086, 1045, 1028, 990, 922, 889, 854, 813, 757, 701 cm^{-1}; MS (CI, NH_3): *m*/*z* (%): 434 (6.3) $[M+NH_4]^+$, 417 (0.8) $[M+H]^+$, 378 (1.8) $[M+NH_4-C_4H_8]^+$, 376 (3.3) $[M+NH_4-Me_2CO]^+$, 359 (78.2) $[M+H-Me_2CO]^+$; elemental analysis calcd (%) for $C_{25}H_{36}O_5$ (416.6): C 72.08, H 8.71; found: C 71.85, H 8.80.

p-Toluenesulfinic acid (0.740 g, 4.735 mmol) was added at RT to a solution of $[Pd(PPh_3)_4]$ (0.456 g, 0.395 mmol) and *tert*-butyl (5*R*,6*S*,*E*)-5-(allyloxy)-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-hept-2-enoate (1.644 g, 3.95 mmol) in CH_2Cl_2 (39 mL). After 1.5 h no more starting material could be detected by TLC. NEt_3 (0.479 g, 0.66 mL) was added to the reaction mixture, then the solvent was evaporated in vacuo. The residue was resolved in CH_2Cl_2 and filtered through silica gel by first eluting impurities with CH_2Cl_2 and then the product with hexane/EtOAc 4:1. After solvent evaporation in vacuo and purification by flash chromatography on silica gel (hexane/EtOAc 4:1) pure *tert*-butyl (5*R*,6*S*,*E*)-6-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-5-hydroxyhept-2-enoate (*epi*-**5**) could be obtained as a virtually colourless, highly viscous oil (1.488 g, 100 %). $R_f=0.26$ (hexane/EtOAc 4:1); $[\alpha]_D^{22}$ (1.08 g/100 mL, $CHCl_3$): +9.3; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.39$–7.27 (m, 5H, Ar-H), 6.78 (dm, 1H, $J=15.6$ Hz, CH=CH-CO), 5.77 (dm, 1H, $J=15.6$ Hz, CH=CH-CO), 4.78 (d, 1H, $J=8.9$ Hz, PhCH), 3.91 (dd, 1H, $J=8.9$, 2.2 Hz, CHO), 3.83 (ddd, $J=8.2$, 5.1, 2.3 Hz, 1H, CHO), 2.59 (s, 1H, OH), 2.41 (m, 1H, CH_2), 2.22 (m, 1H, CH_2), 1.68 (m, 1H, CH_3CH), 1.56 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.45 (s, 9H, $(CH_3)_3C$), 1.09 ppm (d, $J=7.0$ Hz, 3H, CH_3CH); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=165.7$, 144.1, 137.3, 128.7, 128.5, 126.6, 125.2, 109.0, 86.5, 80.1, 80.0, 74.0, 37.2, 36.1, 28.1, 27.2, 27.0, 6.4; IR (film): $\tilde{\nu}=3500$, 3062, 3033, 2981, 2934, 2898, 1712, 1653, 1605, 1455, 1368, 1330, 1236, 1154, 1095, 1044, 1026, 983, 889, 853, 817, 757, 738, 701, 644 cm^{-1}; MS (CI, NH_3): *m*/*z* (%): 394 (75.8) $[M+NH_4]^+$, 377 (1.5) $[M+H]^+$, 336 (26.4) $[M+NH_4-Me_2CO]^+$, 319 (1.4) $[M+H-Me_2CO]^+$; HRMS (ESI): *m*/*z*: calcd for $C_{22}H_{32}O_5Na$: 399.21420; found: 399.21374 $[M+Na]^+$, 775.43 $[2M+Na]^+$.

Preparation of the partially protected CD units 16a,b: NEt_3 (1.5 equiv) was added at 0 °C to a solution of **14** (1.5 equiv) and **15a**,**b** (1.0 equiv) in dry CH_2Cl_2 (4.02 mL mmol^{-1}), followed by DMAP (0.5 equiv) and EDC (1.6 equiv). The mixture was stirred for 1 h at 0 °C and then for 23 h at RT. After the reaction was complete according to TLC analysis, the solvent was evaporated in vacuo and the residue was dissolved in EtOAc (50.51 mL mmol^{-1}). The solution was washed with cold 5 % $KHSO_4$ solution, sat. $NaHCO_3$ solution and brine. The organic extracts were dried over Na_2SO_4 and the solvent was evaporated in vacuo. After flash chromatography on silica gel (hexane/EtOAc 4:1) the pure condensation products of **14** with **15a** and **15b**, respectively, were obtained as colourless oils.

Fully protected **CD** unit from **15a**: Yield: 0.396 g, 98 %. $R_f=0.39$ (hexane/EtOAc 4:1); $[\alpha]_D^{20}$ (1.63 g/100 mL $CHCl_3$): −53.8; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=7.42$–7.28 (m, 5H, Ar-H), 5.20 (d, $J=12.2$ Hz, 1H, uD-CH_2Ph), 5.15 (d, $J=12.2$ Hz, 1H, uD-CH_2Ph), 5.14 (br m, 1H, NH), 5.13 (dd, $J=9.4$, 4.3 Hz, 1H, uD-H$^{\alpha}$), 3.37 (m, 1H, uC-H$^{\beta}$), 3.20 (ddd, $J=13.8$, 8.4, 5.4 Hz, 1H, uC-H$^{\beta}$), 2.77 (m, 1H, uC-H$^{\alpha}$), 1.92–1.56 (m, 3H, uD-H$^{\beta}$, uD-H$^{\gamma}$), 1.43 (s, 9H, $OC(CH_3)_3$), 1.17 (d, $J=7.2$ Hz, 3H, uC-C$^{\alpha}CH_3$), 0.94 (d, $J=5.1$ Hz, 3H, uD-H$^{\delta}$), 0.91 ppm (d, $J=5.2$ Hz, 3H, uD-H$^{\delta}$); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=174.8$, 170.6, 156.0, 135.3, 128.62, 128.59, 128.3, 79.2, 71.0, 67.1, 43.2, 40.4, 39.5, 28.4, 24.7, 23.0, 21.6, 14.5 ppm; IR (film): $\tilde{\nu}=3393$, 1740, 1717, 1510, 1457, 1174 cm^{-1}.

Fully protected **CD** unit from **15b**: Yield: 1.010 g, 95 %. $R_f=0.40$ (hexane/EtOAc 4:1); $[\alpha]_D^{20}$ (0.64 g/100 mL $CHCl_3$): −40.5; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=7.42$–7.28 (m, 5H, Ar-H), 5.38 (m, 1H, NH), 5.21 (d, $J=12.1$ Hz, 1H, uD-CH_2Ph), 5.15 (d, $J=12.1$ Hz, 1H, uD-CH_2Ph), 5.10 (dd, $J=9.7$, 3.3 Hz, 1H, uD-H$^{\alpha}$), 3.39–3.18 (m, 2H, uC-H$^{\beta}$), 1.94–1.57 (m, 3H, uD-Hβ, uD-H$^{\gamma}$), 1.44 (s, 9H, $OC(CH_3)_3$), 1.20 (s, 6H, uC-CH_3), 0.94 (d, $J=5.9$ Hz, 3H, uD-H$^{\delta}$), 0.91 ppm (d, $J=5.7$ Hz, 3H, uD-H$^{\delta}$); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=176.5$, 170.8, 156.4, 135.2, 128.61, 128.59, 128.4, 79.0, 71.0, 67.2, 48.7, 44.0, 39.5, 28.4, 24.8, 23.0, 23.0, 22.3, 21.5 ppm; IR (film): $\tilde{\nu}=3390$, 1738, 1719, 1510, 1143 cm^{-1}.

A solution of the condensation products of **14** with **15a**,**b** (1 equiv) in dry CH_2Cl_2 (8.2 mL mmol^{-1}) containing anisole (2.1 equiv) was cooled to 0 °C and TFA (48 equiv) was added dropwise. The mixture was stirred at 0 °C until all starting material had disappeared according to TLC analysis. Then dry toluene (97 equiv) was added and the solvent was evaporated. Remaining trace amounts of solvent were co-evaporated with dry toluene twice, then the residual oil **16a**,**b** was stored over KOH and used in the next step without further purification.

Unit **B** precursor **17** (1.3 equiv) was dissolved in dry CH_2Cl_2 (32 equiv) and NEt_3 (3.2 equiv) was added. The solution was cooled to 0 °C then a solution of **16a** or **16b** (1.0 equiv) in CH_2Cl_2 (125 equiv) was added dropwise, followed by HOAt (1.3 equiv) and EDC (1.5 equiv). After stirring for 1 h at 0 °C and 20 h at RT the solvent was evaporated in vacuo and the residue was dissolved in EtOAc (101 mL mmol^{-1}) and Et_2O (101 mL mmol^{-1}). The suspension was cooled to 0 °C and washed with water, cold 5 % $KHSO_4$ solution, sat. $NaHCO_3$ solution and brine, dried

over Na_2SO_4 and the solvent was evaporated in vacuo. After flash chromatography on silica gel (hexane/EtOAc 3:2) the pure condensation products of **16a,b** were obtained as a viscous oil.

Condensation product of **16a**: Yield: 0.569 g, 95%. R_f=0.41 (PE/EtOAc 1:1); $[\alpha]_D^{20}$ (1.25 g/100 mL $CHCl_3$): −35.6; ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.42–7.30 (m, 5H, Ar-H), 7.21 (m, 1H, Ar-H), 7.04 (m, 1H, Ar-H), 6.95–6.85 (m, 2H, Ar-H, NH), 5.22 (d, J=12.2 Hz, 1H, uD-H$^\beta$), 5.15 (d, J=12.2 Hz, 1H, uD-H$^\beta$), 5.13 (dd, J=9.5, 3.7 Hz, 1H, uD-H$^\alpha$), 5.12 (br m, 1H, NH), 4.32 (dd, J=14.0, 6.5 Hz, 1H, uB-H$^\alpha$), 3.85 (s, 3H, OCH_3), 3.67 (m, 1H, uC-H$^\beta$), 3.16 (ddd, J=13.7, 9.2, 4.7 Hz, 1H, uC-H$^\beta$), 3.01 (dd, J=13.8, 6.5 Hz, 1H, uB-H$^\beta$), 2.93 (m, 1H, uB-H$^\beta$), 2.75 (m, 1H, uC-H$^\alpha$), 1.89–1.57 (m, 3H, uD-H$^\beta$, uD-H$^\gamma$), 1.39 (s, 9H, $OC(CH_3)_3$), 1.16 (d, J=7.2 Hz, 3H, uC-CH_3), 0.93 (d, J=6.0 Hz, 3H, uD-H$^\delta$), 0.90 ppm; (d, J=6.2 Hz, uD-H$^\delta$); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=173.9, 171.3, 171.2, 155.2, 153.8, 134.9, 131.1, 130.0, 128.7, 128.6, 128.3, 122.1, 112.1, 79.8, 70.8, 67.5, 56.1, 55.9, 55.7, 41.7, 40.3, 39.4, 37.9, 28.3, 24.8, 23.0, 21.5, 14.7 ppm; IR (film): $\tilde{\nu}$=3309, 1740, 1659, 1504, 1258, 1173 cm^{-1}; MS (ESI): m/z: calcd for $C_{32}H_{44}ClN_2O_8$: 619.3; found: 619.2 $[M+H]^+$.

Condensation product of **16b**: Yield: 0.530 g, 87%. R_f=0.40 (PE/EtOAc 3:2); $[\alpha]_D^{20}$ (1.35 g/100 mL $CHCl_3$): −29.6; ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.43–7.30 (m, 5H, Ar-H), 7.22 (m, 1H, Ar-H), 7.04 (m, 1H, Ar-H), 7.01 (br m, 1H, NH), 6.79 (m, 1H, Ar-H), 5.25 (d, J=12.2 Hz, 1H, uD-H$^\beta$), 5.18 (d, J=12.2 Hz, 1H, uD-H$^\beta$), 5.19–5.15 (m, 2H, uD-H$^\alpha$, NH), 4.34 (m, 1H, uB-H$^\alpha$), 3.83 (s, 3H, OCH_3), 3.55 (dd, J=13.5, 7.9 Hz, uC-H$^\beta$), 3.25 (dd, J=13.4, 4.8 Hz, 1H, uC-H$^\beta$), 3.02 (dd, J=13.8, 6.5 Hz, 1H, uB-CH_2Ph), 2.92 (m, 1H, uB-CH_2Ph), 1.91–1.57 (m, 3H, uD-H$^\beta$, uD-H$^\gamma$), 1.39 (s, 9H, $OC(CH_3)_3$), 1.18 (s, 3H, uC-CH_3), 1.17 (s, 3H, uC-CH_3), 0.93 (d, J=6.4 Hz, 3H, uD-H$^\delta$), 0.90 ppm (d, J=6.4 Hz, 3H, uD-H$^\delta$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=175.9, 171.6, 171.4, 155.1, 153.9, 134.9, 131.3, 131.1, 130.2, 128.7, 128.3, 122.2, 112.1, 79.8, 70.9, 67.7, 56.1, 47.3, 43.8, 39.4, 38.2, 28.3, 24.9, 23.3, 23.0, 22.3, 21.5 ppm; IR (film): $\tilde{\nu}$ = 3331, 1734, 1669, 1504, 1142 cm^{-1}; MS (ESI): m/z: calcd for $C_{33}H_{46}ClN_2O_8$: 633.3; found: 633.3 $[M+H]^+$.

The condensation product of **16a,b** (0.73 mmol) was dissolved in EtOAc (41.2 mL mmol^{-1}) and Pd/C (10%) (0.103 g mmol^{-1}) was added. Gaseous nitrogen was conducted for 0.5 h, then the mixture was stirred under a hydrogen atmosphere (1 atm) for 3 h. The mixture was filtered through a Celite pad and the solvent was evaporated in vacuo. The crude products **18a,b** were used in the next step without further purification.

Preparation of deprotected 19a,b: A solution of **18a** or **18b** (1.3 equiv) in CH_2Cl_2 (8.9 mL mmol^{-1}) was added to **5** (1.0 equiv) at RT, followed by NEt_3 (1.0 equiv). After cooling the mixture to 0°C, DMAP (0.8 equiv) and EDC (1.63 equiv) were added consecutively. The mixture was stirred for 1 h at 0°C and for 30 h at RT, then the solvent was evaporated in vacuo and the residue was partitioned between EtOAc (178 mL mmol^{-1}) and H_2O (90 mL mmol^{-1}). The phases were separated and the organic phase was washed with cold 5% $KHSO_4$ solution, H_2O, sat. $NaHCO_3$ solution and brine and dried over Na_2SO_4. The solvent was evaporated in vacuo. After flash chromatography on silica gel (hexane/EtOAc 3:2) pure **19a** and **19b** were obtained as solid foams. **19a**: Yield: 0.180 g, 93%. R_f=0.40 (hexane/EtOAc 3:2); $[\alpha]_D^{20}$ (0.775 g/100 mL $CHCl_3$): −43.5; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.39–7.28 (m, 5H, Ar-H), 7.25 (m, 1H, Ar-H), 7.11 (m, 2H, Ar-H, NH), 6.83 (m, 1H, Ar-H), 6.73 (ddd, J=14.6, 8.6, 6.1 Hz, 1H, uA-CH_2-CH=), 5.89 (d, J=8.2 Hz, 1H, NH), 5.66 (d, J=15.7, 1H, uA-CH-CO), 5.05 (m, 1H, uA-CHCH$_2$), 4.90 (dd, J=10.0, 1.3 Hz, 1H, uD-H$^\alpha$), 4.70 (d, J=8.8 Hz, 1H, uA-PhCH), 4.39 (ddd, J=7.2, 7.2, 4.4 Hz, 1H, uB-H$^\alpha$), 3.84 (s, 3H, OCH_3), 3.81 (br d, J=8.2 Hz, 1H, uA-CHO), 3.72 (m, 1H, uC-H$^\beta$), 3.27 (dd, J=13.8, 4.4 Hz, 1H, uB-H$^\beta$), 3.11 (ddd, J=12.1, 10.2, 2.7 Hz, 1H, uC-H$^\beta$), 2.87 (dd, J=13.5, 9.7 Hz, 1H, uB-H$^\beta$), 2.57 (m, 1H, uC-H$^\alpha$), 2.50 (m, 1H, uA-CH_2), 2.26 (ddd, J=14.8, 9.1, 9.1 Hz, 1H, uA-CH_2), 1.86 (m, 1H, uA-CH_3CH), 1.74–1.62 (m, 2H, uD-H$^\beta$, uD-H$^\gamma$), 1.49 (m, 1H, uD-H$^\beta$), 1.48 (s, 3H, uA-CH_3), 1.46 (s, 9H, $OC(CH_3)_3$), 1.43 (s, 3H, uA-CH_3), 1.34 (s, 9H, $OC(CH_3)_3$), 1.12 (d, 3H, J=8.2 Hz, uC-CH_3CH), 1.10 (d, J=7.5 Hz, 3H, uA-CH_3CH), 0.90 (d, J=6.3 Hz, 3H, uD-H$^\delta$), 0.83 ppm (d, J=6.3 Hz, 3H, uD-H$^\delta$); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=173.4, 171.6, 170.4, 165.9, 155.9, 153.6, 142.0, 137.5, 131.2, 131.0, 128.7, 128.5, 128.5, 126.5, 125.7, 121.9, 112.0, 108.9, 81.8, 80.4, 79.9, 79.5, 75.3, 70.2, 56.1, 42.2, 40.9, 39.3, 37.1, 35.5, 34.8, 28.2, 28.1, 27.1, 27.0, 24.7, 23.1, 21.2, 14.6, 9.5 ppm; IR (film): $\tilde{\nu}$=3345, 1742, 1716, 1505, 1257, 1169 cm^{-1}; MS (ESI): m/z: calcd for $C_{47}H_{68}ClN_2O_{12}$: 887.4; found: 887.3 $[M+H]^+$.

Compound **19b**: Yield: 0.843 g, 97%. R_f=0.40 (hexane/EtOAc 3:2); $[\alpha]_D^{25}$ (0.152 g/100 mL $CHCl_3$): −33.6; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.42–7.29 (m, 5H, Ar-H), 7.29 (m, 1H, Ar-H), 7.17 (m, 1H, Ar-H), 7.14 (m, 1H, NH), 6.84 (m, 1H, Ar-H), 6.76 (ddd, J=15.1, 9.1, 6.0 Hz, 1H,uA-CH_2-CH=), 5.86 (d, J=8.8 Hz, 1H, NH), 5.69 (d, J=15.7 Hz, 1H, uA-CH-CO), 5.09 (m, 1H, uA-CHCH$_2$), 4.89 (dd, J=9.4, 1.9 Hz, 1H, uD-H$^\alpha$), 4.71 (d, J=8.8 Hz, 1H, uA-PhCH), 4.43 (ddd, J=8.0, 8.0, 5.8 Hz, 1H, uB-H$^\alpha$), 3.85 (s, 3H, OCH_3), 3.83 (dd, J=9.7, 2.2 Hz, 1H, uA-CHO), 3.63 (dd, J=13.2, 8.8 Hz, 1H, uC-H$^\beta$), 3.29 (dd, J=13.8, 5.0 Hz, 1H, uC-H$^\beta$), 3.25 (dd, J=14.1, 4.7 Hz, 1H, uB-H$^\beta$), 2.85 (dd, J=13.5, 9.7 Hz, 1H, uB-H$^\beta$), 2.53 (br d, J=15.1 Hz, 1H, uA-CH_2), 2.30 (ddd, J=15.9, 7.7, 7.7 Hz, 1H, uA-CH_2), 1.88 (m, 1H, uA-CH_3CH), 1.76–1.63 (m, 2H, uD-H$^\beta$, uD-H$^\gamma$), 1.49 (s, 3H, uA-CH_3), 1.48 (s, 9H, $OC(CH_3)_3$), 1.47 (m, 1H, uD-H$^\beta$), 1.44 (s, 3H, uA-CH_3), 1.35 (s, 9H, $OC(CH_3)_3$), 1.18 (s, 3H, uC-CH_3), 1.12 (d, J=6.9 Hz, 3H, uA-CH_3CH), 1.09 (s, 3H, uC-CH_3), 0.92 (d, J=6.3 Hz, 3H, uD-H$^\delta$), 0.85 ppm (d, J=6.3 Hz, 3H, uD-H$^\delta$); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=175.4, 171.9, 170.7, 165.9, 155.9, 153.6, 142.1, 137.6, 131.3, 131.1, 128.8, 128.6, 128.5, 126.5, 125.8, 121.9, 112.0, 109.0, 81.9, 80.4, 80.0, 79.5, 75.4, 70.3, 56.3, 56.1, 47.5, 43.8, 39.3, 37.6, 35.5, 34.8, 28.2, 28.1, 27.2, 27.0, 24.8, 23.2, 21.8, 21.2, 9.6 ppm; IR (film): $\tilde{\nu}$=3352, 1740, 1711, 1699, 1662, 1505, 1256, 1151 cm^{-1}; MS (ESI): m/z: calcd for $C_{48}H_{69}ClNaN_2O_{12}$: 923.4; found: 923.6 $[M+Na]^+$.

A solution of the protected acyclic depsipeptide **19a,b** in CH_2Cl_2 (11.0 mL mmol^{-1}) and H_2O (1.1 mL mmol^{-1}) was cooled to 0°C, then TFA (10.9 mL mmol^{-1}) was added dropwise and the mixture was stirred until all starting material and intermediates had disappeared (HPLC monitoring). Then the solvent was evaporated and the obtained solid was dried over KOH in vacuo. The obtained deprotected derivative was used in the next step without further purification.

A solution of the deprotected acyclic depsipeptide (1.0 equiv) in DMF (52.4 mL mmol^{-1}) and a solution of HATU (1.5 equiv) in DMF (52.4 mL mmol^{-1}) were added simultaneously using a dual syringe pump at a rate of 0.01 mL min^{-1} to a solution of DIPEA (3.0 equiv) in DMF (47.1 mL mmol^{-1}) at 0°C. The mixture was stirred for 0.5 h at 0°C and for 1 h at RT. The solvent was evaporated in vacuo and the residue was dissolved in EtOAc (318 mL mmol^{-1}), washed with sat. $NaHCO_3$ solution and brine and dried over Na_2SO_4. After evaporation of the solvent in vacuo, flash chromatography on silica gel (CH_2Cl_2/EtOH 15:1), and crystallisation from EtOAc/PE pure **20a** or **b** was obtained as a white solid. **20a**: Yield: 0.098 g, 77%; m.p. 125–127°C; $[\alpha]_D^{20}$ (2.020 g/100 mL $CHCl_3$): −5.5; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.39–7.28 (m, 5H, Ar-H), 7.20 (m, 1H, Ar-H), 7.06 (m, 1H, Ar-H), 7.01 (m, 1H, NH), 6.82 (m, 1H, Ar-H), 6.65 (ddd, J=15.5, 10.2, 5.2 Hz, 1H, uA-CH_2CH=), 5.94 (s, br, 1H, NH), 5.73 (d, J=15.7 Hz, 1H, uA-CH-CO), 5.04 (ddd, J=10.0, 7.7, 1.3 Hz, 1H, uA-CHCH$_2$), 4.83 (dd, J=10.0, 3.8 Hz, 1H, uD-H$^\alpha$), 4.78 (dd, J=13.5, 7.9 Hz, 1H, uB-H$^\alpha$), 4.58 (d, J=8.2 Hz, 1H, uA-PhCH), 3.86 (s, 3H, OCH_3), 3.77 (dd, J=8.8, 1.3 Hz, 1H, uA-CHO), 3.49 (ddd, J=12.9, 3.5, 3.5 Hz, 1H, uC-H$^\beta$), 3.27 (m, 1H, uC-H$^\beta$), 3.12 (dd, J=14.4, 5.7 Hz, 1H, uB-H$^\beta$), 2.95 (dd, J=14.4, 7.5 Hz, 1H, uB-H$^\beta$), 2.80 (br s, 2H, OH), 2.72 (ddd, J=13.3, 10.5, 6.8 Hz, 1H, uC-H$^\alpha$), 2.45 (dd, J=13.8, 4.4 Hz, 1H, uA-CH_2), 2.22 (ddd, J=13.7, 11.1, 11.1 Hz, 1H, uA-CH_2), 1.79 (m, 1H, uA-CH_3CH), 1.67 (m, 1H, uD-H$^\beta$), 1.52–1.40 (m, 2H, uD-H$^\beta$, uD-H$^\gamma$), 1.22 (d, J=7.5 Hz, 3H, uC-CH_3CH), 1.01 (d, J=6.9 Hz, 3H, uA-CH_3CH), 0.94 (d, J=6.3 Hz, 3H, uD-H$^\delta$), 0.88 ppm (d, J=6.9 Hz, 3H, uD-H$^\delta$); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=175.4, 171.4, 170.7, 165.9, 153.8, 142.1, 140.7, 130.8, 129.9, 128.6, 128.3, 126.8, 124.7, 122.2, 112.1, 76.6, 75.6, 74.8, 71.3, 56.1, 54.0, 40.9, 39.5, 38.0, 37.9, 35.9, 34.8, 24.6, 23.0, 21.5, 14.3, 9.5 ppm; IR (KBr): $\tilde{\nu}$=3410, 1747, 1726, 1669, 1504, 1258, 1180 cm^{-1}; MS (ESI): m/z: calcd for $C_{35}H_{46}ClN_2O_9$: 673.3; found: 673.3 $[M+H]^+$.

Compound **20b**: Yield: 0.106 g, 70%; m.p. 177–179°C; $[\alpha]_D^{20}$ (1.030 g/100 mL MeOH): −32.5; ^{1}H NMR (500 MHz, CD_3OD): δ=7.41–7.35 (m, 4H, Ar-H), 7.30 (m, 1H, Ar-H), 7.27 (m, 1H, Ar-H), 7.16 (m, 1H, Ar-H), 6.97 (m, 1H, Ar-H), 6.69 (ddd, J=15.1, 11.3, 3.8 Hz, 1H, uA-CH_2CH=), 5.87 (dd, J=15.1, 1.3 Hz, 1H, uA-CH-CO), 5.10 (dd, J=9.7,

9.7 Hz, 1H, uA-C*H*CH_2), 4.93 (dd, J=10.4, 3.5 Hz, 1H, uD-H$^{\alpha}$), 4.56 (d, J=8.2 Hz, 1H, uA-PhC*H*), 4.52 (dd, J=11.6, 3.5 Hz, 1H, uB-H$^{\alpha}$), 3.84 (s, 3H, OCH_3), 3.74 (dd, J=8.3, 1.3 Hz, 1H, uA-CHO), 3.48 (d, J=13.2 Hz, 1H, uC-H$^{\beta}$), 3.18 (dd, J=14.8, 3.5 Hz, 1H, uC-H$^{\beta}$), 3.11 (d, J=13.8 Hz, 1H, uB-H$^{\beta}$), 2.71 (dd, J=14.1, 11.6 Hz, 1H, uB-H$^{\beta}$), 2.61 (d, br, J=13.2 Hz, 1H, uA-CH_2), 2.13 (ddd, J=14.1, 11.9, 11.9 Hz, 1H, uA-CH_2), 1.82 (m, 1H, uA-CH_3C*H*), 1.71 (m, 1H, uD-H$^{\gamma}$), 1.58 (ddd, J=13.8, 8.8, 3.8 Hz, 1H, uD-H$^{\beta}$), 1.45 (m, 1H, uD-H$^{\beta}$), 1.23 (s, 3H, uC-CH_3), 1.19 (s, 3H, uC-CH_3), 1.01 (d, J=6.9 Hz, 3H, uA-CH_3CH), 1.00 (d, J=7.5 Hz, 3H, uD-H$^{\delta}$), 0.97 ppm (d, J=6.3 Hz, 3H, uD-H$^{\delta}$); ^{13}C NMR (125.7 MHz, CD_3OD): δ=179.7, 174.5, 172.6, 169.1, 156.1, 145.1, 144.1, 133.0, 132.3, 130.4, 130.1, 129.9, 129.0, 125.8, 124.0, 114.3, 78.0, 77.9, 76.7, 73.3, 58.3, 57.4, 48.2, 44.9, 41.7, 40.6, 38.4, 37.2, 26.9, 24.29, 24.28, 24.2, 22.8, 10.6 ppm; IR (KBr): $\tilde{\nu}$=3419, 1751, 1719, 1670, 1259, 1151 cm^{-1}; MS (ESI): m/z: calcd for $C_{36}H_{47}ClN_2NaO_9$: 709.3; found: 709.5 [M+H]$^+$.

Preparation of cryptophycin-1 (1) and cryptophycin-52 (2): A solution of 12 equiv trimethylorthoformate (1.30 mL, 7.89 mmol) and PPTS (15 mg) in CH_2Cl_2 (4.10 mL) was added to a solution of diol **20a** or **b** (1.0 equiv). The mixture was stirred for 2 h, then it was passed through a layer of silica gel and washed with a mixture of CH_2Cl_2 (10.0 mL mmol^{-1}) and EtOAc (101 mL mmol^{-1}). After evaporation of the solvent in vacuo the orthoformate was obtained as a white amorphous solid and used in the next step without further purification.

The orthoformate was dissolved in CH_2Cl_2 (1.5 mL mmol^{-1}) and a 0.85 M solution of acetyl bromide in CH_2Cl_2 (0.2 equiv) was added. The mixture was stirred for 4 h, then it was cooled to 0 °C, diluted with CH_2Cl_2 (10.0 mL mmol^{-1}) and washed with sat. $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue was dissolved in PE/EtOAc 1:4, filtered through silica gel, and washed. The solvent was evaporated in vacuo. The bromoformate was obtained as a solid and used in the next step without further purification.

The bromoformate was dissolved in DME (0.62 mL mmol^{-1}) and a 12.5 mM solution of NBu_4Br in EtOH (0.005 equiv) was added, followed by freshly powdered $KHCO_3$ (0.50 equiv). The suspension was stirred at 40 °C for 27 h, then the reaction mixture was diluted with CH_2Cl_2 (15.8 equiv), passed through a layer of silica gel and washed with CH_2Cl_2/EtOAc 1:1. After flash chromatography on silica gel (CH_2Cl_2/EtOAc 1:1) the solvent was evaporated in vacuo and the residue was dissolved in CH_3CN/H_2O and lyophilised. The pure cryptophycin was obtained as a white solid. Cryptophycin-1 (**1**): 0.047 g, 72 %; $[\alpha]_D^{23}$ (1.420 g/100 mL $CHCl_3$): −24.9; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.42–7.30 (m, 3H, Ar-H), 7.27–7.22 (m, 2H, Ar-H), 7.20 (m, 1H, Ar-H), 7.06 (m, 1H, Ar-H), 7.03 (m, 1H, NH), 6.83 (m, 1H, Ar-H), 6.68 (ddd, J=15.4, 10.0, 5.3 Hz, 1H, uA-CH_2C*H*=), 5.85 (m, 1H, NH), 5.74 (d, J=15.1 Hz, 1H, uA-C*H*-CO), 5.16 (ddd, J=10.7, 4.4, 1.3 Hz, 1H, uA-C*H*CH_2), 4.83 (dd, J=10.1, 3.1 Hz, 1H, uD-H$^{\alpha}$), 4.79 (ddd, J=8.3, 8.3, 5.8 Hz, 1H, uB-H$^{\alpha}$), 3.86 (s, 1H, OCH_3), 3.69 (d, J=1.9 Hz, 1H, uA-PhC*H*), 3.44 (ddd, J=13.5, 4.1, 4.1 Hz, 1H, uC-H$^{\beta}$), 3.34 (m, 1H, uC-H$^{\beta}$), 3.14 (dd, J=14.4, 5.0 Hz, 1H, uB-H$^{\beta}$), 2.99 (dd, J=14.4, 8.2 Hz, 1H, uB-H$^{\beta}$), 2.92 (dd, J=7.5, 1.9 Hz, 1H, uA-C*H*O), 2.70 (m, 1H, uC-H$^{\alpha}$), 2.55 (dd, J=14.4, 5.0 Hz, 1H, uA-CH_2), 2.45 (ddd, J=14.4, 10.7, 10.7 Hz, 1H, uA-CH_2), 1.80 (m, 1H, uA-CH_3C*H*), 1.75–1.62 (m, 2H, uD-H$^{\beta}$, uD-H$^{\gamma}$), 1.34 (m, 1H, uD-H$^{\beta}$), 1.22 (d, J=6.9 Hz, 3H, uC-CH_3CH), 1.14 (d, J=6.9 Hz, 3H, uA-CH_3CH), 0.86 (d, J=6.9 Hz, 3H, uD-H$^{\delta}$), 0.84 ppm (d, J=6.9 Hz, 3H, uD-H$^{\delta}$); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=175.7, 171.0, 170.7, 165.4, 153.9, 141.1, 136.7, 130.9, 129.8, 128.7, 128.6, 128.3, 125.6, 125.2, 122.3, 112.2, 76.2, 71.3, 63.0, 59.0, 56.1, 53.8, 40.9, 40.6, 39.4, 38.2, 36.7, 35.1, 24.5, 22.9, 21.3, 14.2, 13.6 ppm; IR (film): $\tilde{\nu}$=1750, 1721, 1679, 1504 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{35}H_{44}ClN_2O_8$: 655.2781; found: 655.2786 [M+H]$^+$, 677.2604; [M+Na]$^+$.

Cryptophycin-52 (2): (purified by chromatography, PE/EtOAc 1:3); 0.051 g, 94 %; R_f=0.37 (PE/EtOAc 1:1); $[\alpha]_D^{23}$ (0.510 g/100 mL $CHCl_3$): +24; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.40–7.31 (m, 3H, Ar-H), 7.29–7.22 (m, 3H, Ar-H, NH), 7.19 (m, 1H, Ar-H), 7.04 (m, 1H, Ar-H), 6.83 (m, 1H, Ar-H), 6.76 (ddd, J=15.1, 10.7, 4.4, 1H, uA-CH_2-C*H*=), 5.81 (m, 1H, NH), 5.73 (dd, J=15.1, 1.3 Hz, 1H, uA-CH-CO), 5.19 (ddd, J=10.4, 5.0, 0.9 Hz, 1H, uA-C*H*CH_2), 4.83 (dd, J=10.0, 3.8 Hz, 1H, uD-H$^{\alpha}$), 4.73 (ddd, J=7.4, 7.4, 5.5 Hz, 1H, uB-H$^{\alpha}$), 3.86 (s, 3H, OCH_3), 3.69 (d, J=1.9 Hz, 1H, uA-PhC*H*), 3.44 (dd, J=13.5, 9.1 Hz, 1H, uC-H$^{\beta}$), 3.11 (dd, J=14.4, 4.4 Hz, 1H, uB-H$^{\beta}$), 3.08 (dd, J=13.5, 3.5 Hz, 1H, uC-H$^{\beta}$), 3.00 (dd, J=14.4, 8.2 Hz, 1H, uB-H$^{\beta}$), 2.92 (dd, J=7.5, 1.9 Hz, 1H, uA-CHO), 2.57 (m, 1H, uA-CH_2), 2.45 (ddd, J=14.8, 11.0, 11.0 Hz, 1H, uA-CH_2), 1.79 (m, 1H, uA-CH_3C*H*), 1.75–1.60 (m, 2H, uD-H$^{\beta}$, uD-H$^{\gamma}$), 1.29 (m, 1H, uD-H$^{\beta}$), 1.22 (s, 3H, uC-CH_3), 1.16 (s, 3H, uC-CH_3), 1.14 (d, J=6.9 Hz, 3H, uA-CH_3CH), 0.84 (d, J=6.3 Hz, 3H, uD-H$^{\delta}$), 0.82 ppm (d, J=6.3 Hz, 3H, uD-H$^{\delta}$); ^{13}C NMR (125.7 MHz, $CDCl_3$): 178.0, 170.5, 170.4, 165.0, 154.0, 141.8, 136.8, 130.9, 129.6, 128.7, 128.6, 128.2, 125.6, 124.6, 122.4, 112.3, 75.9, 71.1, 63.1, 59.1, 56.1, 54.5, 46.4, 42.7, 40.7, 39.3, 36.9, 35.3, 24.6, 22.9, 22.8, 22.7, 21.2, 13.60 ppm; IR (film): $\tilde{\nu}$=1748, 1719, 1658, 1504, 1148 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{36}H_{45}ClN_2NaO_8$: 691.2757; found 691.2765 [M+Na]$^+$.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft, the EU (Marie Curie Program, Contract No. HMPF-CT-2000-00458) and the Fonds der Chemischen Industrie for financial support of this project.

[1] M. Eggen, G. I. Georg, *Med. Res. Rev.* **2002**, *22*, 85–101.
[2] R. E. Schwartz, C. F. Hirsch, D. F. Sesin, J. E. Flor, M. Chartrain, R. E. Fromtling, G. H. Harris, M. J. Salvatore, J. M. Liesch, K. Yudin, *J. Ind. Microbiol.* **1990**, *5*, 113–124.
[3] a) G. Trimurtulu, I. Ohtani, G. M. L. Patterson, R. E. Moore, T. H. Corbett, F. A. Valeriote, L. Demchik, *J. Am. Chem. Soc.* **1994**, *116*, 4729–4737; b) T. Golakoti, J. Ogino, C. E. Heltzel, T. Le Husebo, C. M. Jensen, L. K. Larsen, G. M. L. Patterson, R. E. Moore, S. L. Mooberry, T. H. Corbett, F. A. Valeriote, *J. Am. Chem. Soc.* **1995**, *117*, 12030–12049; correction: *J. Am. Chem. Soc.* **1996**, *118*, 3323; c) G. V. Subbaraju, T. Golakoti, G. M. L. Patterson, R. E. Moore, *J. Nat. Prod.* **1997**, *60*, 302–305.
[4] a) L. Polin, F. Valeriote, K. White, C. Panchapor, S. Pugh, J. Knight, P. LoRusso, M. Hussain, E. Liversidge, N. Peltier, T. Golakoti, G. Patterson, R. Moore, T. H. Corbett, *Invest. New Drugs* **1997**, *15*, 99–108; b) T. H. Corbett, F. A. Valeriote, L. Demchik, N. Lowichik, L. Polin, C. Panchapor, S. Pugh, K. White, J. Kushner, J. Rake, M. Wentland, T. Golakoti, C. Hetzel, J. Ogino, G. Patterson, R. Moore, *Invest. New Drugs* **1997**, *15*, 207–218; c) R. E. Moore, T. H. Corbett, G. M. L. Patterson, F. A. Valeriote, *Curr. Pharm. Des.* **1996**, *2*, 317–330.
[5] a) J. P. Stevenson, W. Sun, M. Gallagher, R. Johnson, D. Vaughn, L. Schuchter, K. Algazy, S. Hahn, N. Enas, D. Ellis, D. Thornton, P. J. O'Dwyer, *Clin. Cancer Res.* **2002**, *8*, 2524–2529; b) C. D. Smith, X. Zhang, S. L. Mooberry, G. M. L. Patterson, R. E. Moore, *Cancer Res.* **1994**, *54*, 3779–3784.
[6] a) M. A. Tius, *Tetrahedron* **2002**, *58*, 4343–4367; b) G. M. Salamonczyk, K. Han, Z. Guo, C. J. Sih, *J. Org. Chem.* **1996**, *61*, 6893–6900; c) J. D. White, J. Hong, L. A. Robarge, *J. Org. Chem.* **1999**, *64*, 6206–6216; d) D. W. Hoard, E. D. Moher, M. J. Martinelli, B. H. Norman, *Org. Lett.* **2002**, *4*, 1813–1815; e) D. L. Varie, C. Shih, D. A. Hay, S. L. Andis, T. H. Corbett, L. S. Gossett, S. K. Janisse, M. J. Martinelli, E. D. Moher, R. M. Schultz, J. E. Toth, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 369–374; f) K. M. Gardinier, J. W. Leahy, *J. Org. Chem.* **1997**, *62*, 7098–7099; g) C. Pousset, M. Haddad, M. Larchevêque, *Tetrahedron* **2001**, *57*, 7163–7167; h) L.-H. Li, M. A. Tius, *Org. Lett.* **2002**, *4*, 1637–1640.
[7] H. C. Kolb, K. B. Sharpless, *Tetrahedron* **1992**, *48*, 10515–10530.
[8] H. Becker, M. A. Soler, K. B. Sharpless, *Tetrahedron* **1995**, *51*, 1345–1376.
[9] C. A. Mast, PhD Thesis, Bielefeld University (Germany), **2003**.
[10] A. Stončius, C. A. Mast, N. Sewald, *Tetrahedron: Asymmetry* **2000**, *11*, 3849–3853.
[11] Crystal structure analysis of *epi*-**11**: $C_{15}H_{22}O_4$, M_r=266.33 g mol^{-1}, monoclinic, space group $C2$, λ=0.71073 Å, a=28.8910(6), b=

8.1160(2), $c=16.1510(4)$ Å, $\beta=123.611(1)°$, $V=3153.93(13)$ Å^3, $Z=8$, $\rho_{ber}=1.122$ g cm^{-3}, $\mu=0.080$ mm^{-1}, $T=293(2)$ K, $\theta=2.52$–$24.94°$, 24109 measured reflections, 5374 unique reflections, 3508 reflections with $[I>2\sigma I]$, R values for observed reflections $[I>2\sigma I]$: $R_1=0.0646$, $wR_2=0.1309$, R values for all data: $R_1=0.1129$, $wR_2=0.1661$; max. electron density: 0.172 e Å^{-3}. CCDC-239385 (*epi*-**11**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

[12] R. A. Barrow, T. Hemscheidt, J. Liang, S. Paik, R. E. Moore, *J. Am. Chem. Soc.* **1995**, *117*, 2479–2490.

[13] F. K. Brown, P. J. Brown, D. M. Bickett, C. L. Chambers, *J. Med. Chem.* **1994**, *37*, 674–688.

[14] H. W. Thompson, J. Swistok, *J. Org. Chem.* **1981**, *46*, 4907–4911.

[15] a) R. E. Moore, M. A. Tius, R. A. Barrow, J. Liang, T. H. Corbett, F. A. Valeriote, T. Golakoti, T. K. Hemscheidt (University of Hawaii, Wayne State University, USA), US Patent 6013626, A, Jan. 11, **2000**; b) P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936–3938.

Received: March 14, 2005
Published online: May 25, 2005

