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Efficient Synthesis of Cryptophycin-52 and Novel *para*-Alkoxymethyl Unit A Analogues

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Abstract: Cryptophycins are a family of highly cytotoxic, cyclic depsipeptides. They display antitumour activity that is largely maintained for multidrug-resistant tumour cells. Cryptophycins are composed of four building blocks (units A–D) that correspond to the respective amino and hydroxy acids. A new synthetic route to unit A allows the selective generation of all four stereogenic centres in a short, efficient and reliable synthesis and contributes to an easier and faster synthesis of cryptophycins. The first two stereogenic centres are introduced by a catalytic asymmetric dihydroxylation, whereas the remaining two stereogenic centres are introduced with substrate control of diastereoselectivity. The stereogenic diol function also serves as the epoxide precursor. The approach was used to synthesise the native unit A building block as well as three *para*-alkoxymethyl analogues from which cryptophycin-52 and three analogous cryptophycins were prepared. Macrocyclisation of the *seco*-depsipeptides was based on ring-closing metathesis.

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

Introduction

Cryptophycins are sixteen-membered macrocyclic depsipeptides. Virtually all naturally occurring cryptophycins have been isolated from blue-green algae of the genus *Nostoc*,[1] though cryptophycin-24 (arenastatin A) was isolated from the marine sponge *Dysidea arenaria*.[2] Many cryptophycins display significant cytotoxicity that surpasses the activity of known antitumour agents such as vinblastine and paclitaxel by up to three orders of magnitude.[3] The cytotoxicity of the pharmacologically most interesting cryptophycins is hardly influenced by multidrug resistance mechanisms. This is especially true for cryptophycin-1, which also performed well against solid tumours implanted into mice.[1b,c] The structurally closely related cryptophycin-52 (**1**) was the first clinical candidate (Eli Lilly). However, this compound was only moderately successful in clinical studies due to side effects such as a pronounced peripheral neuropathy, which limited the maximum tolerated dose.[4a–c] Cryptophycins have these kinds of side-effects in common with other substances that interact with tubulin, such as paclitaxel.[4d] The identification of second-generation clinical candidates with improved pharmacological profiles is currently underway.[5] A short, efficient and reliable synthesis of the structurally most complex cryptophycin unit A building block, including the enclosed benzylic epoxide, and a less complicated protocol for cryptophycin assembly would therefore be of great interest.

Retrosynthetically, cryptophycins can be divided into the respective hydroxy and amino acid building blocks, that is, units A–D (Scheme 1). These are sequentially coupled to an acyclic depsipeptide precursor that is cyclised either by macrolactamisation,[3a] by a Horner–Wadsworth–Emmons reaction[6] or by ring-closing metathesis.[7] If the epoxide function is not already incorporated into the molecule, it can be obtained by chemical[3a] or chemoenzymatic epoxidation[8] of a precursor with a benzylic double bond. Alternatively, a diol–epoxide transformation of a benzylic diol function[9,10] or the addition of chiral sulfur ylides to unit A building blocks that feature an aldehyde function[11] present viable routes.

We recently reported on a synthesis of cryptophycin-1 and cryptophycin-52 using a macrolactamisation between unit A and unit B for ring closure.[9a] The unit A precursor was prepared with four stereogenic centres including a benzylic *syn*-diol function, which was introduced by an asymmetric dihydroxylation that relied on a catalytic amount of a chiral

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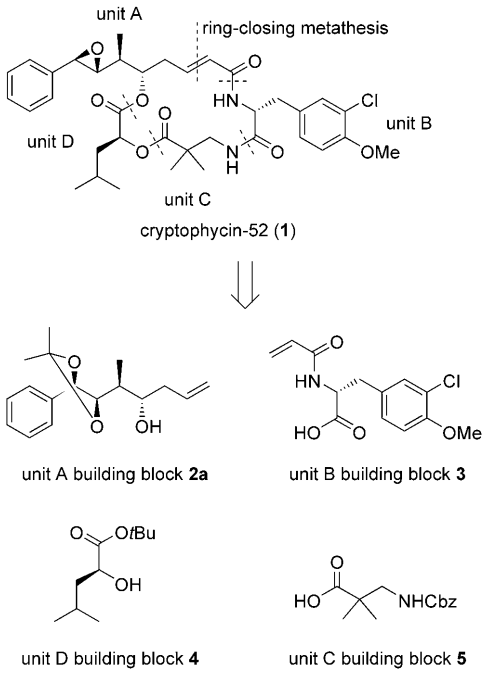


Scheme 1. Retrosynthetic disconnection of cryptophycin-52 (**1**).

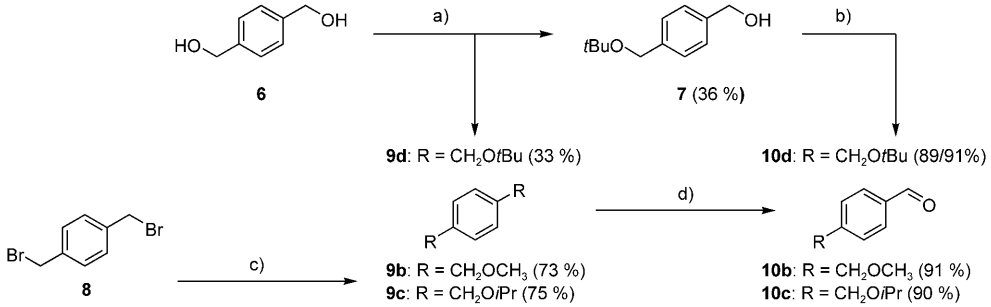
ligand. All remaining stereogenic centres were introduced under substrate control of diastereoselectivity. The diol function was transformed into the epoxide function at the end of the synthesis.[10] This approach to unit A provided selective access not only to a building block with the native configuration, but to diastereomers and enantiomers as well.[9a,12] In this paper, we describe a shorter and far more efficient synthesis of unit A building blocks[13] for the ring-closing metathesis strategy and their application to cryptophycin synthesis.

One of the major drawbacks of cryptophycin-52 is its low water solubility. Polarly functionalised cryptophycin-52 unit A analogues bearing a *para*-hydroxymethyl-, *para*-aminomethyl- and carboxymethyl function are already known, as well as their corresponding ester and amide derivatives.[5b,c] Compared to cryptophycin-52, the unit A *para*-hydroxymethyl-functionalised cryptophycin in particular shows a five- to tenfold higher cytotoxicity against the human leukaemia cell lines CCRF-CEM[5c] and HL-60.[5b] On the other hand, cytotoxicity against the multi-drug-resistant subclone HL-60/Vinc is decreased by a factor of 27, which is a markedly higher value compared to the resistance factor of 5.6 exhibited by the parent compound cryptophycin-52. The corresponding *para*-alkoxymethyl analogues (i.e., ethers of the *para*-hydroxymethyl analogue) have not yet been described. We envisioned that this type of analogues might display an increased bioactivity, a better water solubility and a resistance factor comparable to that of cryptophycin-52. Therefore, a flexible synthetic route to these analogues has been developed. The small series of new cryptophycins designed by us complements the SAR studies undertaken at the *para* position of the unit A arene moiety so far.

Results and Discussion

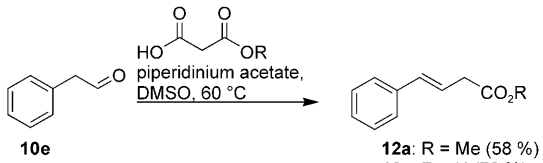
The unit A building blocks **2a–d** were synthesised from benzaldehyde **10a** and the corresponding *para*-substituted analogues **10b–d** (Scheme 3, see below). The methyl ether **9b** and the isopropyl ether **9c** were obtained from *para*-xylene dibromide **8** by a Williamson ether synthesis with methanol and isopropanol, respectively (Scheme 2). That reaction was followed by a de-symmetrising oxidation of the obtained diethers **9b/c** with 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (DDQ) to the *para*-substituted aldehydes **10b/c**.[14] The reactivity of the diethers **9b/c** and **9d** was as expected,[14] that is, the rate of the reaction increased with the electron-releasing properties of the ether alkyl group. We also observed selectivity in the DDQ oxidation of asymmetrically etherified terephthal alcohols. As an example, the oxidation of 1-(*tert*-butoxymethyl)-4-(methoxymethyl)benzene leads with high selectivity to *para*-methoxymethyl benzaldehyde **10b** (results not shown).

The synthesis of terephthal alcohol *tert*-butyl ethers from **6** and *tert*-butanol under acidic conditions led to a mixture of diether **9d** and monoether **7**. Whereas the diether **9d** was oxidised as described above using DDQ, the hydroxyl group of monoether **7** was oxidised with pyridinium chlorochromate (PCC). Both routes gave aldehyde **10d** in excellent yield.



Scheme 2. Syntheses of *para*-alkoxymethyl substituted benzaldehydes: a) *t*BuOH, CH_2Cl_2, H_2SO_4, dry $MgSO_4$, at RT; b) PCC, CH_2Cl_2, NaOAc; c) MeOH, Na, DMSO, reflux (R = CH_2OCH_3) or *i*PrOH, NaH, THF, at RT (R = CH_2O*i*Pr); d) DDQ, CH_2Cl_2, H_2O, at RT.

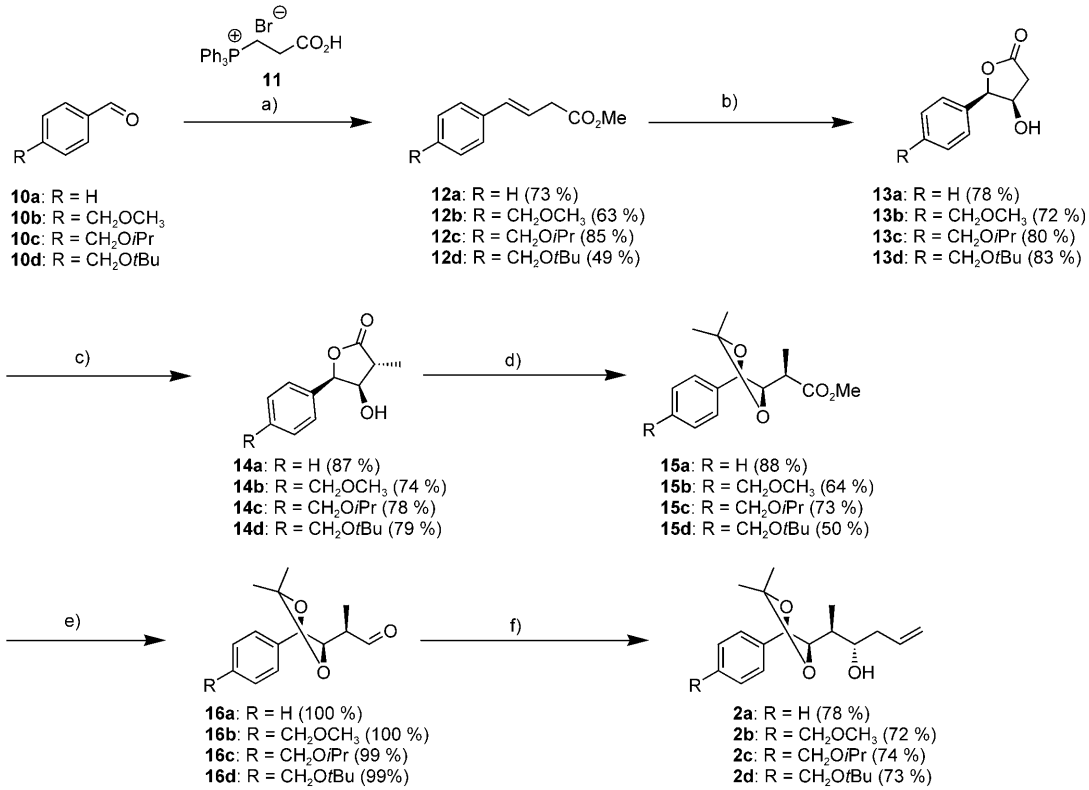
The aldehydes **10a–d** were subjected to a *trans*-selective Wittig reaction[15] using the phosphonium salt **11**[16] that featured a carboxylic acid function (Scheme 3). After deprotonation of **11** with potassium *tert*-butoxide to give the dianion, the ylide reacted cleanly with *E* selectivity to the potassium carboxylates of the corresponding 4-arylbut-3-enoic acids. The β,γ-unsaturated acids were converted into the methyl esters **12a–d** by addition of methyl iodide to the reaction mixture once the Wittig reaction was completed. 4-Phenylbut-3-enoic acid **12e** is commercially available and can be esterified to **12a** with iodomethane and caesium carbonate in 97% yield.[13] The Knoevenagel reaction with phenylacetaldehyde **10e** under piperidinium acetate catalysis presents another viable route that provides either 4-phenylbut-3-enoic acid **12e** using malonic acid (78% yield), or **12a** directly using malonic acid monomethyl ester (58% yield; Scheme 4).[13,17,18]



Scheme 4. Knoevenagel condensation to β,γ-unsaturated acid **12e** and ester **12a** starting from malonic acid and malonic acid monomethyl ester, respectively (NMP = *N*-methylpyrrolidone).

The asymmetric dihydroxylation (AD) of **12a** in the presence of the chiral ligand 1,4-bis-(9-*O*-dihydroquinidinyl)-phthalazine ((DHQD)$_2$-PHAL) has been reported to deliver the β-hydroxy lactone **13a** with 99% *ee*.[19] The sterically demanding analogue **13c** was obtained with 98% *ee* as determined by chiral HPLC. Incorporation of **13b** and **13d** into respective cryptophycin analogues also gave no evidence of minor diastereomers. All synthetic steps following the AD reaction take place under substrate control of diastereoselectivity. Therefore, the enantiomers of **13a–d** and of unit A precursors **2a–d** are accessible by exchanging the chiral ligand within the AD reaction.

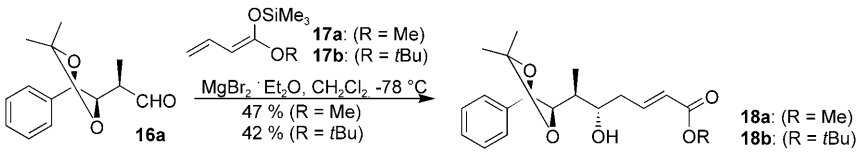
Deprotonation of the lactones **13a–d** with lithium diisopropylamide to the dianions followed by slow addition of a methyl iodide solution at low temperatures provided selective access to the α-methylated lactones **14a–d** with complete diastereo- and chemoselectivity, that is, only one diastereomer and no *O*-methylation was observed in the ^{1}H NMR spectrum and the gas chromatogram of the crude product. A substrate concentration equal or below 0.4 M was shown to be essential to prevent formation of minor amounts of α,α-dimethylation product. Comparison of NMR spectra of cyclic depsipeptides **22b–d**, **23b–d** and **24b–d** with those of known compounds **22a**, **23a** and **1**[9a] reveals close similarities within the C$^{\varepsilon}$HCH$_3$ region of unit A, thus confirming the identical stereochemistry of α-methylat-



Scheme 3. Synthesis of unit A building blocks. a) *t*BuOK, THF, −50 °C to RT, then MeI; b) $K_2OsO_4 \cdot 2H_2O$, (DHQD)$_2$-PHAL, $K_3[Fe(CN)_6]$, K_2CO_3, H_2O/*t*BuOH, 0 °C; c) LDA, MeI, THF, −100 °C to −78 °C; d) $Me_2C(OMe)_2$, MeOH, Amberlyst-15, at RT; e) DIBAL-H, CH_2Cl_2, −78 °C; f) CH_2=$CHCH_2Sn(n-Bu)_3$, $MgBr_2 \cdot Et_2O$, CH_2Cl_2, −78 °C.

ed lactones **14a–d**. Lactone opening to the methyl esters **15a–d** and concomitant protection of the *syn*-diol function as acetonide were effected by treatment of **14a–d** with 2,2-dimethoxypropane and methanol under Amberlyst-15 catalysis.[20] The reaction worked best with **14a** (R = H), whereas in case of the analogues **14b–d**, unconverted starting material and intermediates had to be recycled and reacted a second time to achieve acceptable yields. Thus, there seems to be an unfavourable influence of the electron-donating residue R in **14b–d** on the chemical equilibrium. The methyl esters **15a–d** were selectively reduced to the corresponding aldehydes **16a–d** with diisobutylaluminium hydride.

The vinylogous, magnesium bromide diethyl etherate mediated Mukaiyama aldol addition of crotonate-derived silyl ketene acetals **17a/b** to **16a** proceeds under chelate control of diastereoselectivity (Scheme 5).[13] The desired



Scheme 5. Vinylogous Mukaiyama aldol addition mediated by $MgBr_2 \cdot Et_2O$.

diastereomer was obtained in pure form but only in a yield below 50%. By comparing the physical data in the literature for known compound **18b** with reported data,[9a] the stereochemical outcome of the methylation reaction (**13a→14a**) and those of the final step (**16a→18a/b**) was unequivocally confirmed.

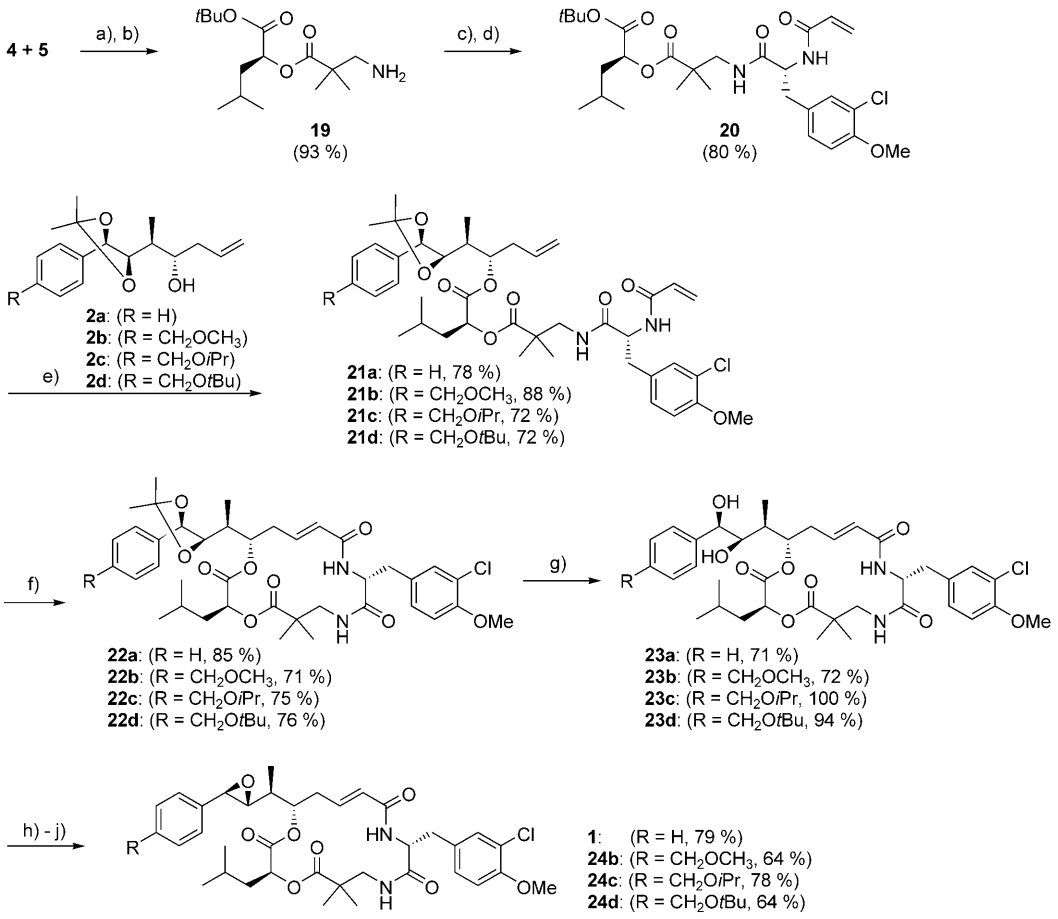
Relative to the Mukaiyama aldol addition, the addition of allyltributylstannane was equally diastereoselective but far more efficient and proceeded under very similar reaction conditions including chelate control of diastereoselectivity (Scheme 3). The reaction provided access to the homoallyl alcohols **2a–d**. These are suitable building blocks for a ring-closing metathesis approach to cryptophycins but can be converted by a cross-metathesis reaction using acrylates to building blocks like **18a/b** as well. The diastereoselectivity of the allylation step depends on the Lewis acid. So far, only $MgBr_2 \cdot Et_2O$ was found to mediate the addition both efficiently and with high diastereoselectivity. Using $MgBr_2 \cdot Et_2O$, only one diastereomer was detected in the gas chromatogram of the crude product.

In summary, the unit A building block **2a** of cryptophycin-52 (**1**) containing all four stereogenic centres was obtained in only six steps and 45% overall yield starting from commercially available 4-phenylbut-3-enoic acid (**12e**). This is by far the shortest and most efficient synthesis of a unit A building block with four stereogenic centres described so far. Comparable syntheses gave unit A building blocks in nine to fourteen steps and 3 to 27% yield.[3] Furthermore, the same approach was successfully applied to the syntheses of the unit A building blocks **2b–d** that were required for the preparation of the *para*-alkoxymethyl cryptophycin-52 analogues **24b–d**.

The assembly of the cryptophycin depsipeptide started with the condensation of unit D building block **4**,[21] and unit C building block **5**,[18,22] providing the respective DC fragment. That strategy was similar to our previous cryptophycin synthesis except for the protecting groups.[9a] The ester condensation was mediated by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) and 4,4-dimethylaminopyridine (DMAP; Scheme 6). The benzyloxycarbonyl protecting group was removed by hydrogenation under Pd/C catalysis, thereby yielding amine **19**, which then was coupled to the unit B building block **3**[7a] (Scheme 6). The activation of acid **3** was effected by EDC·HCl and 1-hydroxy-7-azabenzotriazole (HOAt). The *tert*-butyl ester in the DCB fragment was cleaved with trifluoroacetic acid to give **20**. The different unit A precursors **2a–d** were coupled to **20** under Yamaguchi conditions,[23] which provided reliable access to the *seco*-depsipeptides **21a–d** with hindered ester functions between unit A and unit D. The analogous carbodiimide-mediated reaction resulted in lower yields and in a lower reaction rate.

The ADCB fragments **21a–d** were cyclised by ring-closing metathesis to yield **22a–d** with complete *E* selectivity according to NMR spectroscopic analysis. The reaction was performed in dichloromethane heated at reflux with Grubbs second-generation catalyst.[24] Using the ring-closing metathesis reaction for cyclisation, fewer protecting groups are required in comparison to our previous macrolactamisation strategy.[9a] Georg et al. were the first to use a ring-closing metathesis reaction for cryptophycin cyclisation.[7b] In contrast to our work, the reaction was performed with an epoxide-containing unit A building block. The metathesis reaction also proved to be compatible with a precursor containing a benzylic double bond instead of the epoxide function.[7a]

The acetonide in **22a–d** was cleaved by treatment with trifluoroacetic acid in acetonitrile, tetrahydrofuran and water, thereby yielding the *syn*-diols **23a–d**. The following diol–epoxide transformation to cryptophycin-52 (**1**) and the cryptophycin-52 analogues **24b–d** was effected by a three-step reaction sequence, the first two of which were performed according to the literature.[9a,10a] Cyclic orthoesters of *syn*-diols **23a–d** were obtained by treatment with trimethylorthoformate. Opening the orthoesters with acetyl bromide yielded the corresponding bromohydrin formates. Finally, selective saponification of the bromohydrin formyl esters and a concomitant intramolecular S_N reaction led to the corresponding epoxide functions. A clean reaction was accomplished by treatment of the bromohydrin esters with five equivalents of potassium carbonate as a 0.2 M emulsion in 1,2-dimethoxyethane/ethylene glycol 2:1 v/v. Clean and complete



Scheme 6. Depsipeptide synthesis and diol–epoxide conversion: a) EDC·HCl, DMAP, NEt_3, CH_2Cl_2, 0 °C to RT, 19 h; b) H_2, Pd/C, EtOAc, at RT, 3 h; c) **3**, EDC·HCl, HOAt, NEt_3, CH_2Cl_2, 0 °C to RT, 19 h; d) CH_2Cl_2, TFA, 17 h; e) 2,4,6-trichlorobenzoyl chloride, DMAP, NEt_3, THF, 0 °C, 2.5 h; f) 5 mol % Grubbs second-generation catalyst, CH_2Cl_2, reflux, 6 h; g) H_2O/MeCN/TFA, 36–48 h, 0 °C to RT; h) $(MeO)_3CH$, PPTS, CH_2Cl_2, at RT, 3 h; i) AcBr, CH_2Cl_2, at RT, 5 h; j) K_2CO_3 (5 equiv), DME/ethylene glycol 2:1, at RT, 3 min.

conversion to the epoxides **1** and **24b–d** was observed within a reaction time of only three minutes at room temperature. These reaction conditions represent a marked improvement compared to known syntheses of epoxides from halohydrin esters: The entire amount of potassium carbonate is completely dissolved and therefore cannot be passivated, for example, by the formation of a potassium bromide crust. Additionally, the reaction takes place within minutes instead of hours, thus preventing side reactions. However, while these reaction conditions work well for many cryptophycin-52 analogues, in some unfavourable cases the ester bond between units C and D is cleaved (details will be published in due course). On the other hand, this selective saponification might allow for the deprotection of esterified, hydroxyl-functionalised cryptophycin analogues.

The biological activity of cryptophycin-52 (**1**) and its *para*-alkoxymethyl analogues **24b–d** was determined in cell-based cytotoxicity assays using both the non-multi-drug-resistant human cervix carcinoma cell line KB-3-1 and its multi-drug-resistant P-gp-expressing subclone KB-V1.[25] The cellular reduction of resazurin to resorufin was used as a readout.[26] Cryptophycin-52 (**1**) proved to be highly cytotoxic with an IC_{50} value of 36 pM in the case of KB-3-1 cells (Table 1). Furthermore, its cytotoxicity was only mildly affected by the expression of P-gp in KB-V1 cells (IC_{50} = 95 pM). Hence, a resistance factor of 2.7 (i.e., the cytotoxicity decreased 2.7-fold) was determined. The *para*-methoxymethyl analogue **24b** was both more cytotoxic than cryptophycin-52 (1.5-fold) and more affected by the expression of P-gp in KB-V1 (5.0-fold decrease in cytotoxicity). The *para*-isopropoxymethyl analogue **24c** was about as cytotoxic as cryptophy-

Table 1. Cytotoxicity of cryptophycin-52 (**1**) and its *para*-alkoxymethyl analogues **24b–d**.

Entry	Compound	IC_{50} KB-3-1[a]	IC_{50} KB-V1[a,b]	Ratio[c]
1	**1** (R = H)	36	95	2.7
2	**24b** (R = CH_2OMe)	24	119	5.0
3	**24c** (R = CH_2OiPr)	39	135	3.5
4	**24d** (R = CH_2OtBu)	90	529	5.9

[a] All IC_{50} values were obtained using the resazurin assay and are reported in pM. [b] Multi-drug-resistant cell line expressing P-gp. [c] The ratio of IC_{50} values for the multi-drug-resistant cell line and the non-resistant cell line are referred to as "resistance factors", which is a measure of the extent that cytotoxicity is reduced by resistance mechanisms.

cin-52 but still somewhat more affected by P-gp expression than cryptophycin-52 (3.5-fold decrease in cytotoxicity). The *para-tert*-butoxymethyl analogue **24d** was about 2.5-fold less cytotoxic than cryptophycin-52 for the non-multi-drug-resistant cell line KB-3-1, which is probably due to the fact that the steric bulk of the alkoxy group is beginning to exert a negative influence on cytotoxicity, though the effect is not dramatic.

Conclusion

A very short, highly efficient and versatile synthetic route to a cryptophycin unit A building block has been developed, which was used for the synthesis of cryptophycin-52 as well as of three *para*-alkoxymethyl analogues. The coupling strategy, which relies on ring-closing metathesis for the cyclisation step, reduced the number of required protecting groups relative to a macrolactamisation strategy. The modified procedure for the late introduction of the epoxide function might allow for an easier synthesis of future hydroxyl-functionalised cryptophycins, which would address the low solubility of cryptophycin-52 in water. Additionally, the acid-labile *tert*-butyl ether **24d** represents an interesting starting material for further structural modifications. The obtained unit A analogues showed promising results in the cell-based cytotoxicity assays. In particular, their resistance factors proved to be markedly smaller than that of the hydroxymethyl analogue known from the literature. Additional in vivo experiments are necessary to address the antitumour potential of these novel compounds.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded at 295 K in $CDCl_3$ using Bruker AC-250-P, DRX-500 and DRX-600 instruments. Chemical shifts are calibrated to the resonance of tetramethylsilane and are assigned with respect to the individual cryptophycin units present in the molecule (e.g., unit A = uA). IR spectra were recorded on a Jasco FTIR 410 instrument. Optical rotations were measured using a Jasco polarimeter DIP-360 and are reported as $[\alpha]_D$ (c [g/100 mL]) in the given solvent and at the given temperature. MS spectra were recorded using an Autospec X magnet sector field mass spectrometer with EBE geometry (Vacuum Generators, EI), an Esquire 3000 ion-trap mass spectrometer (Bruker Daltonik, ESI) or an APEX III (Bruker Daltonik, ESI-FT-ICR-MS, HRMS). Flash chromatography was performed using silica gel 60, 0.04–0.063 mm column (Macherey–Nagel); thin-layer chromatography was performed using silica gel 60 F_{254} on an aluminium support. All solvents used in the reactions were distilled before use or purchased in the quality "pro analysi". Toluene was distilled from sodium benzophenone ketyl; methanol was distilled from magnesium; triethylamine, diisopropylamine and dichloromethane were distilled from CaH_2. Ethylene glycol was distilled from flame-dried $MgSO_4$. Reactions were generally run under argon in flame-dried glassware. All commercially available compounds were used as received unless stated otherwise.

Biological tests: The KB-3-1 and KB-V1 cells were cultivated as a monolayer in DMEM (Dulbecco's modified Eagle medium) with glucose (4.5 g L^{-1}), L-glutamine, sodium pyruvate and phenol red (PAA), supplemented with 10% (KB-3-1) and 15% (KB-V1) foetal calf serum (FCS) and 50 μg mL^{-1} gentamycin (Applichem). The cells were maintained at 37°C and 5.3% CO_2/humidified air. KB-V1 cells were selected with 55 nM vinblastine every three weeks. On the day before the test, the cells were detached with trypsin/ethylenediaminetetraacetic acid (EDTA) solution (0.05%/0.02% in phosphate buffered saline solution PBS; PAA) and plated in sterile 96-well plates in a density of 10000 cells in 100 μL medium per well. The dilution series of the compounds were prepared from stock solutions in DMSO of concentrations of 1 mM or 10 mM. The stock solutions were diluted with culture medium (15% FCS). The dilution (100 μL) was added to the wells. Each concentration was tested in six replicates. The control contained the same concentration of DMSO as the first dilution. After incubation for 72 h at 37°C and 5.3% CO_2/humidified air, 30 μL of an aqueous resazurin solution (175 μM) was added to each well. Again, the cells were incubated at the same conditions for 6 h. Then the fluorescence was measured using a TECAN infinite M200. The excitation was effected at a wavelength of 530 nm, whereas the emission was recorded at a wavelength of 588 nm. The IC_{50} values were calculated as a sigmoidal dose response curve using GraphPad Prism (version 4.03).[27] The IC_{50} values equal the drug concentrations, at which vitality is 50%.

Mono-*tert*-butyl ether 7 and di-*tert*-butyl ether 9d: Terephthal aldehyde (1.000 g, 7.46 mmol) was suspended in MeOH (16 mL) and stirred for 30 min at RT. Then the reaction mixture was cooled to 0°C and $NaBH_4$ (903 mg; 23.9 mmol) was added portionwise as a solid. The reaction mixture was stirred for 5 h at RT, then it was neutralised with 1.0 M aqueous HCl solution. The product was extracted with Et_2O (4×100 mL), the organic extracts were washed with brine (20 mL) and dried over Na_2SO_4. The solvent was evaporated in vacuum (50°C) and high vacuum and **6** was obtained as a colourless solid (802 mg, 78%). Compound **6** can be crystallised from H_2O for further purification. R_f = 0.86 (CH_2Cl_2/MeOH 1:1); m.p. 119°C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.35 (s, 4H; Ar-*H*), 4.83 (s, 2H; O*H*), 4.61 ppm (s, 4H; CH_2); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 141.7, 128.0, 65.0 ppm; MS (ESI): m/z: calcd for $[C_8H_{10}O_2+Na]^+$: 161.1; found: 160.9 $[M+Na]^+$.

$MgSO_4$ (5.21 g; 43.3 mmol) was heated to 250°C in high vacuum until the pressure reached 0.01 mbar. The dried solid was suspended in dry CH_2Cl_2 (32 mL). Concentrated H_2SO_4 (0.6 mL) was added and the suspension was stirred for 15 min. Subsequently, alcohol **6** (748 mg; 5.41 mmol) was added as a solution in dry *t*BuOH (10 mL) and dry CH_2Cl_2 (10 mL). The flask was tightly closed and the reaction mixture was stirred 5 d at RT. Then saturated $NaHCO_3$ solution (40 mL) was added carefully and the mixture was diluted with H_2O (100 mL) and CH_2Cl_2 (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3× 50 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. The solvent was removed in vacuum (50°C) and in high vacuum. The residue was purified by flash chromatography on silica gel, after which compounds **7** and **9d** were isolated as pure fractions.

Mono-tert-*butyl ether* ***7***: Yield: 375 mg (36%); R_f = 0.21 (hexane/EtOAc 2:1); m.p. 51°C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.22–7.34 (m, 4H; Ar-*H*), 4.56 (s, 2H; CH_2), 4.42 (s, 2H; CH_2), 2.26 (s, 1H; O*H*), 1.28 ppm (s, 9H; C(CH_3)$_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 139.9, 139.2, 127.6, 126.9, 73.5, 64.9, 63.9, 27.7 ppm; IR (KBr): $\tilde{\nu}$ = 3367 (br vs), 2972 (vs), 2910 (s), 1911 (w), 1806 (vw), 1518 (m), 1569 (m), 1444 (m), 1420 (m), 1390 (s), 1363 (s), 1293 (w), 1193 (vs), 1065 (vs), 1016 (vs), 897 (vs), 826 (s), 768 cm^{-1} (s).

Di-tert-*butyl ether* ***9d***: Yield: 452 mg (33%); R_f = 0.60 (hexane/EtOAc 2:1); m.p. 42°C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.29 (s, 4H; Ar-*H*), 4.42 (s, 4H; CH_2), 1.27 ppm (s, 18H; C(CH_3)$_2$); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 138.9, 127.3, 73.3, 64.0, 27.7 ppm; IR (KBr): $\tilde{\nu}$ = 3433 (br vw), 2975 (vs), 2931 (m), 2911 (m), 2873 (m), 1519 (vw), 1471 (m), 1419 (w), 1390 (s), 1376 (m), 1362 (s), 1194 (vs), 1065 (vs), 1019 (s), 902 (s), 832 (s), 780 (s), 745 cm^{-1} (m).

1,4-Bis(isopropoxymethyl)benzene (9c): A 60% suspension of NaH in paraffin (4.55 g) was dissolved in dry THF (90 mL). Then *p*-xylene dibromide (11.58 g; 43.9 mmol) was added followed by *i*PrOH (90 mL). The mixture was stirred for 4 h at RT. Afterwards H_2O (50 mL) was added to the reaction. The mixture was partitioned between H_2O (200 mL) and EtOAc (1 L). The layers were separated, the organic layer was washed

with brine (150 mL) and dried over Na_2SO_4. The solvent was removed in vacuum (50 °C) and the residue was purified by flash chromatography on silica gel. Compound **9c** was obtained as a slightly yellow liquid (7.27 g, 75 %). R_f = 0.31 (hexane/EtOAc 8:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31 (s, 4H; Ar-*H*), 4.50 (s, 4H; CH_2), 3.66 (hept, J = 6.1 Hz, 2H; C*H*-(CH_3)$_2$), 1.20 ppm (d, J = 6.1 Hz, 12H; CH(CH_3)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 138.2, 127.6, 70.7, 69.8, 22.1 ppm; IR (film): $\tilde{\nu}$ = 2972 (vs), 2931 (s), 2868 (s), 1704 (vw), 1516 (w), 1468 (m), 1421 (w), 1378 (s), 1335 (s), 1211 (m), 1175 (s), 1126 (vs), 1072 (vs), 1021 (m), 923 (m), 806 cm^{-1} (m); MS (EI): *m*/*z* (%): 221 (38) $[M]^+$, 163 (95) $[M-C_3H_7O]^+$, 121 (57) $[M-C_3H_7O-C_3H_7]^+$, 104 (100) $[M-2C_3H_7O]^+$, 43 (95) $[C_3H_7]^+$.

4-(Isopropoxymethyl)benzaldehyde (10c): DDQ (11.98 g; 52.8 mmol) was suspended in CH_2Cl_2 (252 mL) and H_2O (48 mL) was added. Then **7c** (7.822 g; 25.18 mmol) in CH_2Cl_2 (232 mL) was added. The mixture was stirred at RT until all starting material had been consumed (TLC control, about 19 h). Then the mixture was diluted with saturated $NaHCO_3$ solution (127 mL) and CH_2Cl_2 (150 mL). The layers were separated. CH_2Cl_2 (255 mL) was added to the aqueous layer, and the mixture was filtered with suction through a pad of Celite. The layers of the filtrate were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×127 mL). All organic layers were combined, washed with brine (250 mL) and dried over Na_2SO_4. The solvent was removed in vacuum (50 °C) and the residue was purified by flash chromatography on silica gel. Compound **10c** was obtained as colourless oil (5.90 g, 94 %). R_f = 0.33 (hexane/EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.98 (s, 1H; C*H*O), 7.77–7.89 (m, 2H; Ar-*H*), 7.42–7.56 (m, 2H; Ar-*H*), 4.58 (s, 2H; CH_2), 3.70 (sept, J = 6.1 Hz, 1H; C*H*(CH_3)$_2$), 1.24 ppm (d, J = 6.2 Hz, 6H; CH(CH_3)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 192.0, 146.4, 135.6, 129.8, 127.5, 71.6, 69.4, 22.1 ppm; MS (EI): *m*/*z* (%): 135 (45) $[M-C_3H_7]^+$, 119 (100) $[M-C_3H_7O]^+$, 107 (37) $[M-C_3H_7-CHO]^+$, 91 (67) $[M-C_3H_7O-CHO]^+$, 77 (35) $[C_6H_5]^+$.

4-(*tert*-Butoxymethyl)benzaldehyde (10d): The oxidation of **9d** was performed analogously to the preparation of **10c** from **7c**. Yield: 260 mg (91 %). Starting from **7**, pyridinium chlorochromate (2.093 g, 9.71 mmol) and NaOAc (1.061 g, 12.93 mmol) were suspended in dry CH_2Cl_2 (25 mL). Then a solution of **7** (1.257 g, 6.47 mmol) in CH_2Cl_2 (10 mL) was added. The flask that contained the starting material was rinsed with additional CH_2Cl_2 (5 mL). The reaction mixture was stirred for 45 min. Dry Et_2O (100 mL) was added. After sedimentation of the solid components, the supernatant was decanted with a syringe and filtered through cotton and Florisil. The remaining solid was extracted with Et_2O (100 mL) once more, and the supernatant filtered through cotton and Florisil as well. The solid residue was rinsed with Et_2O (50 mL) and the solvent of the combined filtrates was removed in vacuum (50 °C) and high vacuum. The residue was purified by flash chromatography on silica gel and **10d** was obtained as a clear, colourless liquid (1.105 g, 89 %). R_f = 0.23 (hexane/EtOAc 8:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.99 (s, 1H; C*H*O), 7.82–7.88 (m, 2H; Ar-*H*), 7.50–7.55 (m, 2H; Ar-*H*), 4.54 (s, 2H; CH_2), 1.31 ppm (s, 9H; C(CH_3)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 192.1, 147.3, 135.4, 129.8, 127.5, 73.9, 63.6, 27.7 ppm.

(*E*)-Methyl 4-phenylbut-3-enoate (12a): Bromide **11** (6.130 g; 14.76 mmol) was suspended in dry THF (27 mL) and sonicated for 30 min using an ultrasound cleaning bath. Benzaldehyde (**10a**, 1.15 mL, 1.204 g, 11.35 mmol) was added. The mixture was cooled to −20 °C, then a solution of *t*BuOK (3.312 g, 29.52 mmol) in dry THF (40 mL) was added continuously over 2 h. The reaction was stirred for 4 h during which it was allowed to warm to RT. Finally, MeI (3.66 mL, 8.34 g, 58.76 mmol) was added and the mixture was stirred for 40 h at RT. The reaction was quenched by the addition of H_2O (100 mL) and Et_2O (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×100 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (2×50 mL), 5 % $KHSO_4$ solution (50 mL) and brine (50 mL). Then the organic layers were dried over Na_2SO_4 and the solvent was removed in vacuum (50 °C). After flash chromatography on silica gel (hexane/EtOAc 8:1) **12a** was obtained as a colourless liquid (1.468 g, 73 %). R_f = 0.28 (hexane/EtOAc 8:1); b.p. 131 °C (16 mbar); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.02–7.46 (m, 5H; Ar-*H*), 6.48 (d, J = 15.9 Hz, 1H; C$^{\gamma}$*H*), 6.29 (dt, J = 15.9, 7.2 Hz, 1H; C$^{\beta}$*H*), 3.71 (s, 3H; OCH_3), 3.25 ppm (dd, J = 7.1, 1.3 Hz, 2H; C$^{\alpha}$H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.9, 136.7, 133.4, 128.4, 127.5, 126.2, 121.5, 51.8, 38.1 ppm; IR (film): $\tilde{\nu}$ = 3027 (m), 2952 (m), 1740 (vs), 1600 (w), 1497 (m), 1436 (s), 1356 (m), 1295 (m), 1255 (s), 1201 (s), 1163 (vs), 967 (s), 747 cm^{-1} (s); MS (ESI): *m*/*z*: calcd for $C_9H_9^+$: 117.07; found: 117.1 $[M-CO_2Me]^+$; calcd for $C_{11}H_{13}O_2^+$: 177.09; found: 198.9 $[M+H]^+$; calcd for $C_{11}H_{12}O_2Na^+$: 199.07; found: 198.9 $[M+Na]^+$; elemental analysis calcd (%) for $C_{11}H_{12}O_2$ (176.2): C 74.98, H 6.86; found: C 75.26, H 6.71.

(*E*)-Methyl 4-[4-(methoxymethyl)phenyl]but-3-enoate (12b): The procedure is analogous to the one given for **12a**; starting from **10b** and phosphonium salt **11**. Yield: 1.602 g (63 %); R_f = 0.23 (hexane/EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.38 (m, 2H; Ar-*H*), 7.25–7.30 (m, 2H; Ar-*H*), 6.48 (dm, J = 15.9 Hz, 1H; C$^{\gamma}$*H*), 6.29 (dt, J = 15.8, 7.2 Hz, 1H; C$^{\beta}$*H*), 4.43 (s, 2H; CH_2OCH$_3$), 3.71 (s, 3H; CO_2CH_3), 3.37 (s, 3H; CH_2OCH_3), 3.25 ppm (dd, J = 7.1, 1.1 Hz, 2H; C$^{\alpha}$H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.0, 137.5, 136.2, 133.2, 128.0, 126.3, 121.6, 74.4, 58.0, 51.9, 38.2 ppm; IR (film): $\tilde{\nu}$ = 2985 (s), 2951 (s), 2821 (s), 1738 (vs), 1656 (vw), 1611 (vw), 1513 (m), 1435 (s), 1414 (m), 1381 (m), 1361 (m), 1299 (m), 1254 (s), 1197 (s), 1163 (s), 1100 (s), 1016 (w), 969 (s), 942 (w), 917 (vw), 841 (m), 783 cm^{-1} (m); MS (EI): *m*/*z* (%): 220 (57) $[M]^+$, 189 (20) $[M-CH_3O]^+$, 161 (8) $[M-C_2H_3O_2]^+$, 147 (36) $[M-C_3H_5O_2]^+$, 91 (9) $[C_7H_7]^+$, 45 (100) $[C_2H_5O]$.

(*E*)-Methyl 4-[4-(isopropoxymethyl)phenyl]but-3-enoate (12c): The procedure is analogous to the one given for **12a**; starting from **10c** and phosphonium salt **11**. Yield: 2.433 g (85 %); R_f = 0.26 (hexane/EtOAc 6:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25–7.37 (m, 4H; Ar-*H*), 6.48 (dm, J = 15.9 Hz, 1H; C$^{\gamma}$*H*), 6.28 (dt, J = 15.8, 7.2 Hz, 1H; C$^{\beta}$*H*), 4.48 (s, 2H; CH_2O*i*Pr), 3.71 (s, 3H; CO_2CH_3), 3.67 (hept, J = 6.1 Hz, 1H; C*H*(CH_3)$_2$), 3.25 (dd, J = 7.1, 1.0 Hz, 2H; C$^{\alpha}$H$_2$), 1.21 ppm (d, J = 6.1 Hz, 6H; CH-(CH_3)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.0, 138.5, 136.0, 133.2, 127.8, 126.3, 121.4, 70.9, 69.7, 51.9, 38.2, 22.1 ppm; IR (film): $\tilde{\nu}$ = 2971 (m), 1740 (vs), 1512 (vw), 1436 (w), 1379 (w), 1335 (w), 1254 (m), 1201 (m), 1159 (s), 1069 (s), 1017 (w), 968 (m), 799 cm^{-1} (w); MS (EI): *m*/*z* (%): 248 (69) $[M]^+$, 205 (17) $[M-C_3H_7]^+$, 189 (89) $[M-C_2H_3O_2]^+$, 117 (100) $[M-C_4H_9O-C_2H_3O_2]^+$, 91 (20) $[C_7H_7]^+$, 73 (17) $[C_4H_9]^+$, 59 (15) $[C_2H_3O_2]^+$.

(*E*)-Methyl 4-[4-(*tert*-butoxypropoxymethyl)phenyl]but-3-enoate (12d): The procedure is analogous to the one given for **12a**; starting from **10d** and phosphonium salt **11**. Yield: 181 mg (49 %); R_f = 0.21 (hexane/EtOAc 6:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24–7.41 (m, 4H; Ar-*H*), 6.47 (d, J = 15.9 Hz, 1H; C$^{\gamma}$*H*), 6.24 (dt, J = 15.7, 7.2 Hz, 1H; C$^{\beta}$*H*), 4.42 (s, 2H; CH_2O*t*Bu), 3.71 (s, 3H; CO_2CH_3), 3.24 (dd, J = 7.0, 0.6 Hz, 2H; C$^{\alpha}$H$_2$), 1.28 ppm (s, 9H; C(CH_3)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.1, 139.4, 135.7, 133.3, 127.6, 126.2, 121.2, 73.5, 63.9, 51.9, 38.2, 27.7 ppm; IR (film): $\tilde{\nu}$ = 2974 (s), 1740 (vs), 1513 (w), 1436 (m), 1389 (m), 1362 (s), 1253 (s), 1196 (vs), 1161 (s), 1077 (br m), 1017 (m), 968 (m), 895 (w), 840 cm^{-1} (w); MS (EI): *m*/*z* (%): 262 (14) $[M]^+$, 206 (6) $[M-C_4H_9+H]^+$, 189 (44) $[M-C_4H_9O]^+$, 147 (13) $[M-C_4H_9-C_2H_3O_2+H]^+$, 117 (41) $[M-C_4H_9O-C_3H_5O_2]^+$, 58 (31) $[C_4H_9+H]^+$, 43 (100) $[C_3H_7]^+$.

(*E*)-4-Phenylbut-3-enoic acid (12e): A solution of malonic acid (70.97 g, 682 mmol, 2.2 equiv) in DMSO (250 mL) was treated with a solution of AcOH (0.37 mL, 0.39 g, 6.46 mmol, 0.02 equiv) and piperidine (0.64 mL, 0.55 g, 6.47 mmol, 0.02 equiv) in DMSO (15 mL). The reaction solution was warmed to 65 °C and freshly distilled **10a** (36.1 mL, 38.8 g, 309 mmol, 1.0 equiv) was added dropwise within 90 min. After the addition ended, the reaction mixture was stirred for further 1.5 h at 65–70 °C. The solution was cooled to RT, taken up in H_2O (750 mL) and extracted with Et_2O (1×250 mL and 3×200 mL). The combined organic extracts were washed with 5 % aqueous $KHSO_4$ and brine (50 mL each), dried over $MgSO_4$, and evaporated to dryness. The solid residue was recrystallised from toluene/*n*-hexane (10:1 v/v) to give **12e** as colourless crystals (38.95 g, 78 %); m.p. 81–83 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.2 (br s, 1H; CO_2H), 7.36–7.38 (m, 2H; Ar-*H*), 7.29–7.32 (m, 2H; Ar-*H*), 7.23 (m, 1H; Ar-*H*), 6.51 (dm, J = 15.9 Hz, 1H; C$^{\gamma}$*H*), 6.28 (dt, J = 15.9, 7.2 Hz, 1H; C$^{\beta}$*H*), 3.29 ppm (dd, J = 7.1, 1.2 Hz, 2H; C$^{\alpha}H_2$); ^{13}C NMR (126 MHz, $CDCl_3$): 178.2, 136.6, 134.0, 128.6, 127.7, 126.3, 120.8, 38.0 ppm; IR (KBr): $\tilde{\nu}$ = 3059 (w), 2951 (w), 2888 (w), 1703 (s), 1493 (w), 1415 (m),

1403 (m), 1325 (w), 1298 (m), 1279 (w), 1223 (s), 1176 (m), 1066 (w), 975 (m), 912 (w), 745 cm^{-1} (s).

(4*R*,5*R*)-4-Hydroxy-5-phenyldihydrofuran-2(3*H*)-one (13a): $K_2OsO_4{\cdot}2H_2O$ (84 mg; 2.28×10^{-4} mol), $K_3[Fe(CN)_6]$ (22.57 g; 68.55 mmol) and K_2CO_3 (9.475 g; 68.56 mmol) were dissolved in H_2O (114 mL). Then *t*BuOH (90 mL), $(DHQD)_2$-PHAL (178 mg; 2.28×10^{-4} mol) and methanesulfonamide (2.173 g; 22.84 mmol) were added. The reaction mixture was cooled to 0 °C and **12a** (4.026 g; 22.85 mmol) was added. Additional *t*BuOH (24 mL) was used for rinsing. The reaction mixture was stirred at 0 °C until complete conversion was observed (TLC monitoring, about 29 h). Na_2SO_3 (34.27 g; 272 mmol) and H_2O (140 mL) were added and the cooling bath was removed. After dissolution of all solid material, the layers were separated and the aqueous layer was extracted with Et_2O (1×160 mL and 3×110 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL) and dried over Na_2SO_4. The solvent was removed in vacuum (50 °C), the residue was dissolved in EtOAc and filtered through a pad of silica gel. The solvent was removed in vacuum (50 °C) and high vacuum, and the residue was crystallised from EtOAc (1 mL g^{-1}). When the bittern did not yield any more crystals, the solvent was removed in vacuum (50 °C) and the remaining product was isolated by flash chromatography on silica gel. Compound **13a** was obtained as a crystalline or an amorphous solid (3.175 g, 78 %). $R_f=0.16$ (hexane/EtOAc 1:1); m.p. 114–116 °C; $[\alpha]_D^{24}$ (0.92 g/100 mL, MeOH): −37.7; H NMR (500 MHz, $CDCl_3$): $\delta=7.32$–7.47 (m, 5H; Ar-*H*), 5.50 (d, $J=3.5$ Hz, 1H; C$^{\gamma}$*H*), 4.61 (dm, $J=5.1$ Hz, 1H; C$^{\beta}$*H*), 2.88 (ddd, $J=17.6$, 5.1, 1.5 Hz, 1H; C$^{\alpha}H_A$), 2.71 (d, $J=17.6$ Hz, 1H; C$^{\alpha}H_B$), 1.59 ppm (m, 1H; O*H*); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=175.4$, 133.0, 129.0, 128.9, 126.3, 85.0, 70.1, 38.4 ppm; IR (KBr): $\tilde{\nu}=3396$ (vs), 3031 (vw), 2966 (vw), 2917 (w), 1754 (vs), 1498 (w), 1455 (m), 1429 (w), 1397 (m), 1337 (s), 1316 (s), 1273 (m), 1236 (m), 1214 (s), 1197 (m), 1155 (s), 1077 (s), 1022 (s), 990 (s), 928 (m), 900 (w), 869 (vw), 826 (w), 797 (m), 739 (s), 715 (m), 700 cm^{-1} (m); MS (ESI): *m/z*: calcd for $[C_{10}H_{10}O_3+H]^+$: 179.1; found: 178.9 $[M+H]^+$; calcd for $[C_{10}H_{10}O_3+Na]^+$: 201.1; found: 201.0 $[M+Na]^+$; calcd for $[2\,C_{10}H_{10}O_3+Na]^+$: 379.1; found: 379.1 $[2M+Na]^+$.

(4*R*,5*R*)-4-Hydroxy-5-[4-(methoxymethyl)phenyl]dihydrofuran-2(3*H*)-one (13b): The procedure is analogous to the one given for **13a**; starting from **12b**. Yield: 1.117 g (72 %); $R_f=0.16$ (hexane/EtOAc 1:2); m.p. 108–109 °C; $[\alpha]_D^{24}$ (0.92 g/100 mL, MeOH): −35.1; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.36$ (m, 4H; Ar-*H*), 5.46 (d, $J=3.5$ Hz, 1H; C$^{\gamma}$*H*), 4.56 (m, 1H; C$^{\beta}$*H*), 4.43 (s, 2H; CH_2OCH_3), 3.38 (s, 3H; CH_2OCH_3), 2.84 (dd, $J=17.5$, 5.2 Hz, 1H; C$^{\alpha}H_A$), 2.62 (d, $J=17.5$ Hz, 1H; C$^{\alpha}H_B$), 2.13 ppm (s, 1H; O*H*); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=175.8$, 138.9, 132.7, 128.1, 126.5, 85.2, 74.2, 70.0, 58.4, 38.6 ppm; IR (KBr): $\tilde{\nu}=3366$ (br vs) 3004 (vw), 2962 (w), 2909 (w), 2861 (w), 1752 (br vs), 1450 (vw), 1422 (w), 1401 (vw), 1362 (w), 1331 (w), 1304 (m), 1232 (m), 1215 (m), 1161 (s), 1079 (s), 1014 (s), 979 (m), 904 (m), 875 (w), 850 (w), 801 (m), 780 cm^{-1} (m); MS (ESI): *m/z*: calcd for $[C_{12}H_{14}O_4+Na]^+$: 245.1; found: 244.8 $[M+Na]^+$; calcd for $[2\,C_{12}H_{14}O_4+Na]^+$: 467.2; found: 466.9 $[2M+Na]^+$; calcd for $[3\,C_{12}H_{14}O_4+Na]^+$: 689.3; found: 687.8 $[3M+Na]^+$.

(4*R*,5*R*)-4-Hydroxy-5-[4-(isopropoxymethyl)phenyl]dihydrofuran-2(3*H*)-one (13c): The procedure is analogous to the one given for **13a**; starting from **12c**. Yield: 2.990 g (72 %); $R_f=0.22$ (hexane/EtOAc 1:2); $[\alpha]_D^{24}$ (0.92 g/100 mL, MeOH): −35.0; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=7.40$–7.45 (m, 2H; Ar-*H*), 7.33–7.37 (m, 2H; Ar-*H*), 5.49 (d, $J=3.4$ Hz, 1H; C$^{\gamma}$*H*), 4.59 (m, 1H; C$^{\beta}$*H*), 4.51 (s, 2H; CH_2O*i*Pr), 3.71 (hept, $J=6.1$ Hz, 1H; $CH(CH_3)_2$), 2.86 (dd, $J=17.5$, 5.1 Hz, 1H; C$^{\alpha}H_A$), 2.70 (d, $J=17.5$ Hz, 1H; C$^{\alpha}H_B$), 1.62 (s, 1H; O*H*), 1.23 ppm (d, $J=6.1$ Hz, 6H; $CH(CH_3)_2$); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta=175.4$, 140.2, 132.1, 128.1, 126.4, 85.0, 71.5, 70.1, 69.6, 38.5, 22.1 ppm; IR (KBr): $\tilde{\nu}=3493$ (vs), 2968 (s), 2937 (m), 2872 (m), 1751 (vs), 1519 (w), 1469 (w), 1418 (m), 1397 (m), 1377 (m), 1315 (s), 1237 (m), 1217 (s), 1188 (s), 1127 (m), 1075 (vs), 1034 (vs), 990 (m), 922 (m), 903 (vw), 877 (vw), 785 (m), 769 (vs), 698 cm^{-1} (m); MS (ESI): *m/z*: calcd for $[C_{14}H_{18}O_4+Na]^+$: 273.1; found: 273.0 $[M+Na]^+$; calcd for $[2\,C_{14}H_{18}O_4+Na]^+$: 523.2; found: 522.9 $[2M+Na]^+$.

(4*R*,5*R*)-4-Hydroxy-5-[4-(*tert*-butoxymethyl)phenyl]dihydrofuran-2(3*H*)-one (13d): The procedure is analogous to the one given for **13a**; starting from **12d**. Yield: 850 mg (83 %); $R_f=0.20$ (hexane/EtOAc 2:3); $[\alpha]_D^{24}$ (0.95 g/100 mL, MeOH): −28.9; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.40$–7.44 (m, 2H; Ar-*H*), 7.31–7.35 (m, 2H; Ar-*H*), 5.48 (d, $J=3.4$ Hz, 1H; C$^{\gamma}$*H*), 4.57 (m, 1H; C$^{\beta}$*H*), 4.46 (s, 2H; CH_2O*t*Bu), 2.85 (dd, $J=17.4$, 5.2 Hz, 1H; C$^{\alpha}H_A$), 2.68 (d, $J=17.5$ Hz, 1H; C$^{\alpha}H_B$), 1.65 (br s, 1H; O*H*), 1.30 ppm (s, 9H; $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=175.5$, 140.9, 131.8, 128.0, 126.3, 85.1, 73.7, 70.1, 63.7, 38.5, 27.7 ppm; IR (KBr): $\tilde{\nu}=3358$ (br vs), 2966 (s), 1757 (vs), 1517 (vw), 1473 (w), 1425 (w), 1394 (w), 1371 (m), 1306 (m), 1231 (m), 1194 (m), 1161 (vs), 1066 (s), 978 (m), 919 (w), 904 (m), 857 (s), 790 (m), 770 cm^{-1} (w); MS (ESI): *m/z*: calcd for $[C_{15}H_{20}O_4+Na]^+$: 287.1; found: 287.1 $[M+Na]^+$; calcd for $[2\,C_{15}H_{20}O_4+Na]^+$: 551.3; found: 551.0 $[2M+Na]^+$.

(3*R*,4*R*,5*R*)-4-Hydroxy-3-methyl-5-phenyldihydrofuran-2(3*H*)-one (14a): A solution of diisopropylamine (10.2 mL; 72.58 mmol) in dry THF (171 mL) was cooled to −78 °C. Then a 1.6 M solution of *n*-butyl lithium in *n*-hexane (44.9 mL) was added dropwise. The mixture was stirred at −78 °C for 15 min and for further 30 min after removal of the cooling bath. Afterwards, the mixture was cooled to −78 °C again and a solution of **13a** (5.123 g; 28.75 mmol) in dry THF (120 mL) was added over 90 min. The reaction mixture was stirred for further 45 min at −78 °C. Afterwards MeI (12.24 g; 86.26 mmol) in dry THF (89 mL) was added over 150 min at −90 °C. The reaction mixture was stirred for 2 d at −78 °C. The reaction was quenched by addition of dry AcOH (4 mL) in dry THF (6 mL) at −78 °C and the reaction mixture was allowed to reach RT. The solvent was removed in vacuum (50 °C) until a thick, pink suspension was obtained. The residue was dissolved in H_2O (200 mL) and Et_2O (200 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (4×200 mL). The combined organic layers were washed with 5 % aqueous $KHSO_4$ (50 mL) and brine (50 %) and dried over Na_2SO_4. The solvent was removed in vacuum (50 °C) and for several hours in high vacuum. The residue was purified by flash chromatography on silica gel. The product **14a** was obtained as an orange oil, which eventually solidified to give an amorphous solid (4.804 g, 87 %). $R_f=0.24$ (hexane/EtOAc 1:1); $[\alpha]_D^{24}$ (0.92 g/100 mL, MeOH): +24.6; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.30$–7.47 (m, 5H; Ar-*H*), 5.58 (d, $J=4.6$ Hz, 1H; C$^{\gamma}$*H*), 4.26 (m, 1H; C$^{\beta}$*H*), 2.72 (dq, $J=3.0$, 7.0 Hz, 1H; C$^{\alpha}$*H*), 1.72 (d, $J=3.5$ Hz, 1H; O*H*), 1.37 ppm (d, $J=7.7$ Hz, 3H; C$^{\alpha}CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=178.5$, 133.2, 128.94, 128.90, 126.3, 82.5, 75.9, 43.5, 13.0 ppm; IR (KBr): $\tilde{\nu}=3440$ (vs), 3073 (w), 3034 (w), 2984 (s), 2951 (s), 2887 (w), 1742 (vs), 1499 (m), 1489 (s), 1417 (m), 1386 (s), 1325 (s), 1272 (s), 1238 (s), 1217 (m), 1192 (vs), 1115 (s), 1079 (s), 1044 (s), 1022 (m), 985 (vs), 906 (m), 845 (w), 818 (s), 754 (s), 731 (s), 697 cm^{-1} (s); MS (ESI): *m/z*: calcd for $[C_{11}H_{12}O_3+Na]^+$: 215.1; found: 215.0 $[M+Na]^+$; calcd for $[2\,C_{11}H_{12}O_3+Na]^+$: 407.2; found: 407.0 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{11}H_{12}O_3$ (192.2): C 68.74, H 6.29; found: C 68.84, H 6.29.

(3*R*,4*R*,5*R*)-4-Hydroxy-5-[4-(methoxymethyl)phenyl]-3-methyldihydrofuran-2(3*H*)-one (14b): The procedure is analogous to the one given for **14a**; starting from **13b**. Yield: 720 mg (74 %); $R_f=0.21$ (hexane/EtOAc 2:3); m.p. 100–101 °C; $[\alpha]_D^{24}$ (0.92 g/100 mL, MeOH): +23.9; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.38$–7.43 (m, 2H; Ar-*H*), 7.31–7.36 (m, 2H; Ar-*H*), 5.58 (d, $J=4.5$ Hz, 1H; C$^{\gamma}$*H*), 4.45 (s, 2H; CH_2OCH_3), 4.25 (m, 1H; C$^{\beta}$*H*), 3.40 (s, 3H; CH_2OCH_3), 2.70 (dq, $J=3.0$, 7.7 Hz, 1H; C$^{\alpha}$*H*), 1.80 (m, 1H; O*H*), 1.37 ppm (d, $J=7.7$ Hz, 3H; C$^{\alpha}CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=178.4$, 139.0, 132.6, 128.2, 126.4, 82.4, 75.8, 74.2, 58.4, 43.5, 12.7 ppm; IR (KBr): $\tilde{\nu}=3475$ (s), 2991 (m), 2928 (m), 2877 (m), 2827 (w), 2809 (w), 1761 (vs), 1519 (w), 1452 (w), 1426 (w), 1384 (m), 1327 (w), 1300 (m), 1239 (w), 1189 (s), 1094 (s), 1038 (m), 1002 (s), 961 (vw), 950 (w), 905 (w), 861 (m), 839 (vw), 798 (m), 789 (s), 730 (vw), 715 cm^{-1} (w); MS (ESI): *m/z*: calcd for $[C_{13}H_{16}O_4+Na]^+$: 259.1; found: 258.8 $[M+Na]^+$; calcd for $[2\,C_{13}H_{16}O_4+Na]^+$: 495.2; found: 495.0 $[2M+Na]^+$; calcd for $[3\,C_{13}H_{16}O_4+Na]^+$: 731.3; found: 729.7 $[3M+Na]^+$; calcd for $[C_{13}H_{16}O_4+Cl]^-$: 271.1; found: 280.8 $[M+Cl]^-$.

(3*R*,4*R*,5*R*)-4-Hydroxy-5-[4-(isopropoxymethyl)phenyl]-3-methyldihydrofuran-2(3*H*)-one (14c): The procedure is analogous to the one given for **14a**; starting from **13c**. Yield: 1.563 g (78 %); $R_f=0.24$ (hexane/EtOAc 1:1); $[\alpha]_D^{24}$ (0.92 g/100 mL, MeOH): +20.7; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.40$–7.49 (m, 2H; Ar-*H*), 7.31–7.37 (m, 2H; Ar-*H*), 5.60 (d, $J=$

4.4 Hz, 1H; C$^{\gamma}H$), 4.52 (s, 2H; CH_2O*i*Pr), 4.26 (m, 1H; C$^{\beta}H$), 3.71 (hept, J=6.1 Hz, 1H; $CH(CH_3)_2$), 2.73 (dq, J=2.8, 7.7 Hz, 1H; C$^{\alpha}H$), 1.45 (d, J=3.6 Hz, 1H; OH), 1.39 (d, J=7.8 Hz, 3H; C$^{\alpha}CH_3$), 1.23 ppm (d, J=6.1 Hz, 6H; $CH(CH_3)_2$); ^{13}C NMR (126 MHz, $CDCl_3$): δ=178.3, 140.2, 132.0, 128.1, 126.3, 82.3, 75.9, 71.5, 69.6, 43.5, 22.1, 13.0 ppm; IR (KBr): $\tilde{\nu}$=2972 (s), 1740 (vw), 1512 (w), 1436 (m), 1379 (m), 1335 (m), 1299 (w), 1254 (m), 1201 (m), 1160 (s), 1070 (s), 1017 (w), 968 (m), 939 (vw), 839 (w), 799 (w), 711 cm^{-1} (w); MS (ESI): m/z: calcd for $[C_{15}H_{20}O_4+Na]^+$: 287.1; found: 286.9 $[M+Na]^+$; calcd for $[2\,C_{15}H_{20}O_4+Na]^+$: 551.3; found: 550.9 $[2M+Na]^+$; calcd for $[C_{15}H_{20}O_4+Cl]^-$: 299.1; found: 298.9 $[M+Cl]^-$; calcd for $[C_{15}H_{20}O_4-H]^-$: 263.1; found: 262.9 $[M-H]^-$.

(3*R*,4*R*,5*R*)-4-Hydroxy-5-[4-(*tert*-butoxymethyl)phenyl]-3-methyldihydrofuran-2(3*H*)-one (14d): The procedure is analogous to the one given for **14a**; starting from **13d**. Yield: 529 mg (79%); R_f=0.32 (hexane/EtOAc 1:1); $[\alpha]_D^{24}$ (0.94 g/100 mL, MeOH): +20.8; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.38–7.45 (m, 2H; Ar-H), 7.27–7.34 (m, 2H; Ar-H), 5.58 (d, J=4.4 Hz, 1H; C$^{\gamma}H$), 4.46 (s, 2H; CH_2O*t*Bu), 4.23 (m, 1H; C$^{\beta}H$), 2.70 (dq, J=2.9, 7.7 Hz, 1H; C$^{\alpha}H$), 1.60 (br m, 1H; OH), 1.37 (d, J=7.7 Hz, 3H; C$^{\alpha}CH_3$), 1.30 ppm (s, 9H; $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ=178.4, 140.8, 131.8, 128.0, 126.3, 82.4, 75.9, 73.7, 63.7, 43.5, 27.7, 13.0 ppm; IR (KBr): $\tilde{\nu}$=3419 (br s), 2973 (m), 2873 (w), 1766 (vs), 1516 (vw), 1458 (w), 1422 (w), 1390 (w), 1367 (m), 1313 (w), 1231 (w), 1178 (s), 1115 (m), 1065 (m), 1042 (m), 1022 (m), 993 (s), 905 (w), 892 (w), 855 (w), 787 cm^{-1} (w); MS (ESI): m/z: calcd for $[2\,C_{16}H_{22}O_4+Na]^+$: 579.3; found: 579.1 $[2M+Na]^+$; calcd for $[3\,C_{16}H_{22}O_4+Na]^+$: 857.4; found: 856.0 $[3M+Na]^+$.

(*R*)-Methyl 2-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]propanoate (15a): 2,2-Dimethoxypropane (30 mL) and MeOH (7.9 mL) were added to **14a** (4.674 g; 24.32 mmol) and Amberlyst-15 (486 mg). The mixture was stirred for 4 d at RT. Then the mixture was diluted with hexane (500 mL) and filtered. The filtrate was washed with brine (50 mL) and dried over Na_2SO_4. The solvent was removed in vacuum (50 °C) and high vacuum, and the residue was purified by flash chromatography on silica gel. The product **15a** was obtained as an orange oil, which eventually solidified to give an amorphous solid (5.686 g, 88%). R_f=0.25 (hexane/EtOAc 8:1); $[\alpha]_D^{24}$ (0.92 g/100 mL, MeOH): −17.9; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.26–7.40 (m, 5H; Ar-H), 4.74 (d, J=8.4 Hz, 1H; C$^{\gamma}H$), 4.11 (dd, J=8.5, 6.0 Hz, 1H; C$^{\beta}H$), 3.40 (s, 3H; CO_2CH_3), 2.68 (m, 1H; C$^{\alpha}H$), 1.56 (s, 3H; $C(CH_3)_2$), 1.48 (s, 3H; $C(CH_3)_2$), 1.28 ppm (d, J=7.1 Hz, 3H; C$^{\alpha}CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ=173.7, 137.2, 128.55, 128.52, 127.4, 109.0, 83.2, 81.3, 51.5, 41.4, 27.2, 27.1, 12.9 ppm; IR (KBr): $\tilde{\nu}$=3037 (vw), 2984 (m), 2947 (m), 2873 (w), 2360 (vw), 1738 (vs), 1498 (vw), 1454 (m), 1373 (m), 1259 (s), 1225 (s), 1170 (m), 1057 (s), 1007 (m), 931 (vw), 880 (m), 838 (vw), 809 (w), 760 (s), 698 cm^{-1} (s); MS (ESI): m/z: calcd for $[C_{15}H_{20}O_4-C_3H_6O+H]^+$: 207.1; found: 206.9 $[M-C_3H_6O+H]^+$; calcd for $[C_{15}H_{20}O_4+Na]^+$: 287.1; found: 287.0 $[M+Na]^+$; elemental analysis calcd (%) for $C_{15}H_{20}O_4$ (264.3): C 68.16, H 7.63; found: C 68.46, H 7.78.

(*R*)-Methyl 2-{(4*R*,5*R*)-5-[4-(methoxymethyl)phenyl]-2,2-dimethyl-1,3-dioxolan-4-yl}propanoate (15b): The procedure is analogous to the one given for **15a**; starting from **14b**. Yield: 593 mg (64%); R_f=0.23 (hexane/EtOAc 4:1); $[\alpha]_D^{24}$ (1.00 g/100 mL, MeOH): −18.1; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.31–7.38 (m, 4H; Ar-H), 4.75 (d, J=8.5 Hz, 1H; C$^{\gamma}H$), 4.45 (s, 2H; CH_2OCH_3), 4.10 (dd, J=8.4, 5.7 Hz, 1H; C$^{\beta}H$), 3.43 (s, 3H; CO_2CH_3), 3.36 (s, 3H; CH_2OCH_3), 2.67 (m, 1H; C$^{\alpha}H$), 1.56 (s, 3H; $C(CH_3)_2$), 1.47 (s, 3H; $C(CH_3)_2$), 1.27 ppm (d, J=7.1 Hz, 3H; C$^{\alpha}CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ=173.8, 138.6, 136.7, 127.8, 127.4, 109.0, 83.2, 81.0, 74.3, 58.1, 51.6, 41.2, 27.2, 27.1, 12.7 ppm; IR (film): $\tilde{\nu}$=2985 (s), 2936 (s), 2823 (w), 1739 (vs), 1613 (vw), 1516 (vw), 1457 (m), 1436 (m), 1380 (s), 1238 (s), 1169 (m), 1099 (m), 1059 (s), 1020 (w), 970 (vw), 891 (w), 819 cm^{-1} (w); MS (ESI): m/z: calcd for $[C_{17}H_{24}O_5+Na]^+$: 331.2; found: 330.9 $[M+Na]^+$; calcd for $[2\,C_{17}H_{24}O_5+Na]^+$: 639.3; found: 638.1 $[2M+Na]^+$.

(*R*)-Methyl 2-{(4*R*,5*R*)-5-[4-(isopropoxymethyl)phenyl]-2,2-dimethyl-1,3-dioxolan-4-yl}propanoate (15c): The procedure is analogous to the one given for **15a**; starting from **14c**. Yield: 1.411 g (73%); R_f=0.45 (hexane/EtOAc 4:1); $[\alpha]_D^{24}$ (0.92 g/100 mL, MeOH): −17.6; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.33 (m, 4H; Ar-H), 4.75 (d, J=8.5 Hz, 1H; C$^{\gamma}H$), 4.50 (s, 2H; CH_2O*i*Pr), 4.10 (dd, J=8.4, 5.6 Hz, 1H; C$^{\beta}H$), 3.65 (hept, J=6.1 Hz, 1H; $CH(CH_3)_2$), 3.45 (s, 3H; CO_2CH_3), 2.67 (dq, J=5.7, 7.0 Hz, 1H; C$^{\alpha}H$), 1.55 (s, 3H; $C(CH_3)_2$), 1.47 (s, 3H; $C(CH_3)_2$), 1.27 (d, J=7.0 Hz, 3H; C$^{\alpha}CH_3$), 1.20 ppm (d, J=6.1 Hz, 6H; $CH(CH_3)_2$); ^{13}C NMR (126 MHz, $CDCl_3$): δ=173.8, 139.6, 136.4, 127.7, 127.3, 109.0, 83.2, 81.0, 70.9, 69.7, 51.6, 41.1, 27.2, 27.1, 22.12, 22.08, 12.5 ppm; IR (KBr): $\tilde{\nu}$=2981 (s), 2937 (m), 1740 (vs), 1618 (vw), 1517 (vw), 1458 (w), 1436 (w), 1380 (m), 1336 (w), 1238 (m), 1170 (m), 1141 (w), 1060 (vs), 1020 (vw), 983 (vw), 892 (w), 818 cm^{-1} (m); MS (ESI): m/z: calcd for $[C_{19}H_{28}O_5+Na]^+$: 359.2; found: 359.0 $[M+Na]^+$; calcd for $[2\,C_{19}H_{28}O_5+Na]^+$: 695.4; found: 693.9 $[2M+Na]^+$; calcd for $[C_{19}H_{28}O_5-C_2H_3O_2-C_3H_7O+Na]^+$: 219.1; found: 218.8 $[M-C_2H_3O_2-C_3H_7O+Na]^+$.

(*R*)-Methyl 2-{(4*R*,5*R*)-5-[4-(*tert*-butoxymethyl)phenyl]-2,2-dimethyl-1,3-dioxolan-4-yl}propanoate (15d): The procedure is analogous to the one given for **15a**; starting from **14d**. Yield: 325 mg (50%); R_f=0.32 (hexane/EtOAc 5:1); $[\alpha]_D^{24}$ (1.17 g/100 mL, MeOH): −18.4; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.30–7.36 (m, 4H; Ar-H), 4.74 (d, J=8.5 Hz, 1H; C$^{\gamma}H$), 4.44 (s, 2H; CH_2O*t*Bu), 4.10 (dd, J=8.5, 5.3 Hz, 1H; C$^{\beta}H$), 3.46 (s, 3H; CO_2CH_3), 2.66 (dq, J=5.4, 7.0 Hz, 1H; C$^{\alpha}H$), 1.55 (s, 3H; $C(CH_3)_2$), 1.47 (s, 3H; $C(CH_3)_2$), 1.28 (s, 9H; $C(CH_3)_3$), 1.27 ppm (d, J=7.0 Hz, 3H; C$^{\alpha}CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ=173.9, 140.4, 136.1, 127.5, 127.1, 109.0, 83.1, 80.9, 73.5, 63.8, 51.7, 40.9, 27.7, 27.2, 27.1, 12.3 ppm; IR (KBr): $\tilde{\nu}$=2978 (vs), 1739 (vs), 1619 (vw), 1516 (vw), 1457 (m), 1435 (m), 1370 (s), 1237 (vs), 1197 (vs), 1169 (m), 1114 (w), 1061 (vs), 1020 (m), 892 (m), 819 cm^{-1} (m); (ESI): m/z: calcd for $[C_{20}H_{30}O_5+Na]^+$: 373.2; found: 373.2 $[M+Na]^+$; calcd for $[2\,C_{20}H_{30}O_5+Na]^+$: 723.4; found: 721.9 $[2M+Na]^+$.

(*R*)-2-[(4*R*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]propanal (16a): 1.0 M DIBAL-H in toluene (2.0 mL) was added dropwise to a solution of **15a** (230 mg; 0.87 mmol) in dry CH_2Cl_2 (5.4 mL) at −100 °C. The reaction mixture was stirred for 4 h while allowing it to warm to −78 °C. Afterwards, it was cooled to −100 °C again, MeOH (0.6 mL) was added dropwise and the reaction mixture was allowed to warm to RT. Subsequently, aqueous 1.0 M AcOH solution (20 mL) and hexane (20 mL) were added to the reaction mixture, the layers were separated, and the aqueous layer was extracted four times with hexane (20 mL). The combined organic layers were washed with aqueous 1.0 M aqueous AcOH solution (10 mL), saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL) and dried over Na_2SO_4. The crude product was filtered through Celite and the solvent was removed in vacuum (50 °C) and high vacuum. Yield: 203 mg (100%); R_f=0.28 (hexane/EtOAc 8:1); $[\alpha]_D^{24}$ (1.85 g/100 mL, $CHCl_3$): −34.3; ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.59 (s, 1H; CHO) 7.28–7.39 (m, 5H; Ar-H), 4.76 (d, J=8.8 Hz, 1H; C$^{\gamma}H$), 4.23 (dd, J=8.8, 3.1 Hz, 1H; C$^{\beta}H$), 2.52 (dq, J=3.1, 7.0 Hz, 1H; C$^{\alpha}H$), 1.57 (s, 3H; $C(CH_3)_2$), 1.47 (s, 3H; $C(CH_3)_2$), 1.22 ppm (d, J=7.1 Hz, 3H; C$^{\alpha}CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ=202.3, 136.9, 128.74, 128.67, 126.8, 109.3, 81.4, 80.1, 46.0, 27.1, 26.9, 7.8 ppm; IR (film): $\tilde{\nu}$=2985 (s), 2934 (m), 1727 (vs), 1495 (vw), 1455 (m), 1379 (s), 1235 (vs), 1171 (m), 1043 (s), 1027 (m), 995 (m), 958 (vw), 886 (w), 811 (w), 757 (s), 700 cm^{-1} (s); MS (ESI): m/z: calcd for $[C_{14}H_{18}O_3+Na]^+$: 257.1; found: 257.1 $[M+Na]^+$; calcd for $[C_{14}H_{18}O_3+C_6H_{14}Al]^+$: 347.2; found: 347.2 $[M+C_6H_{14}Al]^+$.

(*R*)-2-{(4*R*,5*R*)-5-[4-(Methoxymethyl)phenyl]-2,2-dimethyl-1,3-dioxolan-4-yl}propanal (16b): The procedure is analogous to the one given for **16a**; starting from **15b**. Yield: 349 mg (100%); R_f=0.23 (hexane/EtOAc 4:1); $[\alpha]_D^{24}$ (1.10 g/100 mL, $CHCl_3$): −33.2; ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.61 (d, J=0.7 Hz, 1H; CHO) 7.35 (m, 4H; Ar-H), 4.77 (d, J=8.8 Hz, 1H; C$^{\gamma}H$), 4.46 (s, 2H; CH_2OCH_3), 4.22 (dd, J=8.8, 3.2 Hz, 1H; C$^{\beta}H$), 3.38 (s, 3H; CH_2OCH_3), 2.53 (ddq, J=3.1, 0.6, 7.0 Hz, 1H; C$^{\alpha}H$), 1.57 (s, 3H; $C(CH_3)_2$), 1.48 (s, 3H; $C(CH_3)_2$), 1.23 ppm (d, J=7.1 Hz, 3H; C$^{\alpha}CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ=202.3, 138.9, 136.3, 128.1, 126.9, 109.4, 81.4, 79.9, 74.3, 58.2, 46.0, 27.1, 26.9, 7.8 ppm; IR (film): $\tilde{\nu}$=3438 (vw), 2985 (vs), 2933 (s), 2894 (s), 2823 (m), 1727 (vs), 1516 (w), 1455 (m), 1422 (w), 1380 (s), 1235 (vs), 1171 (s), 1098 (vs), 1045 (s), 1020 (m), 996 (m), 959 (w), 920 (w), 890 (w), 817 cm^{-1} (m); MS (ESI): m/z: calcd for $[C_{16}H_{22}O_4+Na]^+$: 301.1; found: 300.9 $[M+Na]^+$; calcd for $[2\,C_{16}H_{22}O_4+Na]^+$: 579.3; found: 578.0 $[2M+Na]^+$.

(*R*)-2-{(4*R*,5*R*)-5-[4-(Isopropoxymethyl)phenyl]-2,2-dimethyl-1,3-dioxolan-4-yl}propanal (16c): The procedure is analogous to the one given for

16a; starting from **15c**. Yield: 864 mg (99%); R_f=0.31 (hexane/EtOAc 4:1); $[\alpha]_D^{24}$ (1.10 g/100 mL, $CHCl_3$): −30.0; ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.60 (m, 1H; C*H*O), 7.30–7.42 (m, 4H; Ar-*H*), 4.76 (d, J=8.8 Hz, 1H; C$^{\gamma}$*H*), 4.51 (s, 2H; CH_2O*i*Pr), 4.21 (dd, J=8.8, 3.1 Hz, 1H; C$^{\beta}$*H*), 3.67 (m, 1H; C*H*(CH_3)$_2$), 2.51 (dqm, J=3.1, 7.0 Hz, 1H; C$^{\alpha}$*H*), 1.57 (s, 3H; C(CH_3)$_2$), 1.48 (s, 3H; C(CH_3)$_2$), 1.18–1.26 ppm (m, J=7.1 Hz, 9H; C$^{\alpha}CH_3$ and CH(CH_3)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$): δ=202.3, 140.0, 136.0, 127.9, 126.8, 109.3, 81.4, 79.9, 71.1, 69.6, 46.0, 27.1, 26.9, 22.11, 22.09, 7.7 ppm; IR (film): $\tilde{\nu}$=3439 (vw), 2976 (vs), 2934 (s), 2934 (s), 2871 (s), 1728 (vs), 1516 (vw), 1456 (m), 1423 (vw), 1379 (vs), 1335 (m), 1235 (vs), 1172 (m), 1125 (s), 1061 (vs), 1019 (m), 996 (m), 958 (vw), 924 (vw), 890 (w), 817 cm^{-1} (m); MS (ESI): m/z: calcd for $[C_{18}H_{26}O_4+Na]^+$: 329.2; found: 329.2 $[M+Na]^+$; calcd for $[2\,C_{18}H_{26}O_4+Na]^+$: 635.4; found: 634.2 $[2M+Na]^+$.

(*R*)-2-{(4*R*,5*R*)-5-[4-(*tert*-Butoxymethyl)phenyl]-2,2-dimethyl-1,3-dioxolan-4-yl}propanal (16d): The procedure is analogous to the one given for **16a**; starting from **15d**. Yield: 273 mg (99%); R_f=0.33 (hexane/EtOAc 5:1); $[\alpha]_D^{24}$ (1.21 g/100 mL, $CHCl_3$): −30.1; ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.57 (m, 1H; C*H*O), 7.29–7.38 (m, 4H; Ar-*H*), 4.75 (d, J=8.8 Hz, 1H; C$^{\gamma}$*H*), 4.43 (s, 2H; CH_2O*t*Bu), 4.19 (dd, J=8.8, 3.0 Hz, 1H; C$^{\beta}$*H*), 2.52 (dq, J=2.9, 7.0 Hz, 1H; C$^{\alpha}$*H*), 1.55 (s, 3H; C(CH_3)$_2$), 1.46 (s, 3H; C-(CH_3)$_2$), 1.28 (s, 9H; C(CH_3)$_3$), 1.21 ppm (d, J=7.1 Hz, 3H; C$^{\alpha}CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ=202.2, 140.5, 135.7, 127.7, 126.7, 109.2, 81.4, 79.9, 73.5, 63.7, 45.9, 27.7, 27.1, 26.9, 7.6 ppm; IR (film): $\tilde{\nu}$=3444 (br w), 2977 (vs), 2934 (s), 2721 (vw), 1729 (vs), 1516 (w), 1456 (m), 1422 (w), 1370 (s), 1235 (vs), 1196 (vs), 1172 (s), 1062 (vs), 1020 (s), 996 (m), 958 (w), 891 (m), 817 cm^{-1} (m); (ESI): m/z: calcd for $[C_{19}H_{28}O_4+Na]^+$: 343.2; found: 343.2 $[M+Na]^+$; calcd for $[2\,C_{19}H_{28}O_4+Na]^+$: 663.4; found: 665.5 $[2M+Na]^+$.

(2*S*,3*S*)-2-[(4*R*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]hex-5-en-3-ol (2a): A suspension of $MgBr_2$·Et_2O (338 mg; 1.31 mmol) in dry CH_2Cl_2 (1.3 mL) was cooled to −78 °C. Compound **16a** (202 mg; 0.86 mmol) in dry CH_2Cl_2 (0.8 mL) was added and the mixture was stirred for 15 min at −78 °C during which it turned brown. Allyltributylstannane (0.4 mL; 432 mg; 1.31 mmol) in dry CH_2Cl_2 (2.7 mL) was added dropwise. The mixture was stirred at −78 °C for 10 h. Subsequently, saturated $NaHCO_3$ solution (10 mL) was added and the mixture was allowed to warm to RT. The mixture was diluted with Et_2O (40 mL) and H_2O (10 mL), the layers were separated and the aqueous layer was extracted four times with Et_2O (40 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed in vacuum (50 °C) and in high vacuum, the residue was purified by flash chromatography on silica gel. The product **2a** was obtained as a colourless oil (182 mg, 77%). R_f=0.29 (hexane/EtOAc 4:1); $[\alpha]_D^{24}$ (2.21 g/100 mL, $CHCl_3$): −3.3; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.25–7.44 (m, 5H; Ar-*H*), 5.70 (m, 1H; C$^{\beta}$*H*), 4.93–5.04 (m, 2H; C$^{\alpha}H_2$), 4.78 (d, J=9.0 Hz, 1H; C$^{\eta}$*H*), 4.10 (dd, J=9.0, 2.2 Hz, 1H; C$^{\zeta}$*H*), 3.59 (ddd, J=8.2, 5.6, 4.6 Hz, 1H; C$^{\delta}$*H*), 2.39 (s, 1H; O*H*), 2.25 (m, 1H; C$^{\gamma}H_A$), 2.13 (m, 1H; C$^{\gamma}H_B$), 1.77 (m, 1H; C$^{\varepsilon}$*H*), 1.56 (s, 3H; C(CH_3)$_2$), 1.49 (s, 3H; C(CH_3)$_2$), 1.07 ppm (d, J=7.1 Hz, 3H; C$^{\varepsilon}CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ=137.6, 134.9, 128.6, 128.3, 126.8, 117.7, 108.8, 82.7, 80.0, 73.6, 39.4, 36.2, 27.2, 27.1, 10.6 ppm; IR (film): $\tilde{\nu}$=3486 (s), 2983 (vs), 2934 (s), 1640 (w), 1496 (w), 1455 (m), 1380 (s), 1236 (vs), 1169 (s), 1087 (m), 1043 (s), 915 (m), 888 (m), 814 (w), 756 (s), 700 cm^{-1} (s); MS (ESI): m/z: calcd for $[C_{17}H_{24}O_3-C_3H_6O+H]^+$: 219.1; found: 219.1 $[M-C_3H_6O+H]^+$; calcd for $[C_{17}H_{24}O_3+Na]^+$: 299.2; found: 299.2 $[M+Na]^+$; calcd for $[2\,C_{17}H_{24}O_3+Na]^+$: 575.3; found: 575.1 $[2M+Na]^+$.

(2*S*,3*S*)-2-{(4*R*,5*R*)-5-[4-(Methoxymethyl)phenyl]-2,2-dimethyl-1,3-dioxolan-4-yl}hex-5-en-3-ol (2b): The procedure is analogous to the one given for **2a**; starting from **16b**. Yield: 155 mg (72%); R_f=0.17 (hexane/EtOAc 4:1); $[\alpha]_D^{24}$ (1.00 g/100 mL, $CHCl_3$): −5.4; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.29–7.44 (m, 4H; Ar-*H*), 5.71 (dddd, J=14.2, 10.0, 10.0, 7.1 Hz, 1H; C$^{\beta}$*H*), 4.91–5.05 (m, 2H; C$^{\alpha}H_2$), 4.78 (d, J=9.0 Hz, 1H; C$^{\eta}$*H*), 4.44 (s, 2H; CH_2OCH_3), 4.09 (dd, J=8.9, 2.1 Hz, 1H; C$^{\zeta}$*H*), 3.58 (ddd, J=8.2, 5.8, 4.4 Hz, 1H; C$^{\delta}$*H*), 3.36 (s, 3H; CH_2OCH_3), 2.41 (s, 1H; O*H*), 2.25 (m, 1H; C$^{\gamma}H_A$), 2.11 (ddd, J=14.5, 7.8, 7.5 Hz, 1H; C$^{\gamma}H_B$), 1.75 (ddq, J=6.7, 2.0, 6.8 Hz, 1H; C$^{\varepsilon}$*H*), 1.55 (s, 3H; C(CH_3)$_2$), 1.48 (s, 3H; C(CH_3)$_2$), 1.06 ppm (d, J=7.1 Hz, 3H; C$^{\varepsilon}CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ=138.3, 137.1, 134.9, 127.9, 126.8, 117.7, 108.8, 82.6, 79.8, 74.3, 73.5, 58.0, 39.4, 36.3, 27.2, 27.1, 10.6 ppm; IR (film): $\tilde{\nu}$=3485 (s), 3074 (vw), 2983 (vs), 2932 (vs), 1640 (vw), 1516 (vw), 1456 (m), 1420 (w), 1380 (vs), 1236 (vs), 1169 (m), 1097 (vs), 1045 (vs), 1020 (m), 996 (m), 915 (m), 892 (m), 817 cm^{-1} (m); MS (ESI): m/z: calcd for $[C_{19}H_{28}O_4+Na]^+$: 343.2; found: 343.0 $[M+Na]^+$; calcd for $[2\,C_{19}H_{28}O_4+Na]^+$: 663.4; found: 662.2 $[2M+Na]^+$; calcd for $[C_{19}H_{28}O_4+Cl]^-$: 355.2; found: 354.9 $[M+Cl]^-$.

(2*S*,3*S*)-2-{(4*R*,5*R*)-5-[4-(Isopropoxymethyl)phenyl]-2,2-dimethyl-1,3-dioxolan-4-yl}hex-5-en-3-ol (2c): The procedure is analogous to the one given for **2a**; starting from **16c**. Yield: 693 mg (74%); R_f=0.26 (hexane/EtOAc 4:1); $[\alpha]_D^{24}$ (1.13 g/100 mL, $CHCl_3$): −4.7; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.33 (m, 4H; Ar-*H*), 5.73 (dddd, J=14.2, 10.1, 10.1, 7.0 Hz, 1H; C$^{\beta}$*H*), 4.97–5.07 (m, 2H; C$^{\alpha}H_2$), 4.78 (d, J=9.0 Hz, 1H; C$^{\eta}$*H*), 4.51 (s, 2H; CH_2O*i*Pr), 4.09 (dd, J=8.9, 2.2 Hz, 1H; C$^{\zeta}$*H*), 3.67 (qq, J=6.1, 6.1 Hz, 1H; C*H*(CH_3)$_2$), 3.59 (ddd, J=8.3, 5.6, 4.2 Hz, 1H; C$^{\delta}$*H*), 2.31 (s, 1H; O*H*), 2.26 (m, 1H; C$^{\gamma}H_A$), 2.13 (m, 1H; C$^{\gamma}H_B$), 1.76 (ddq, J=6.4, 2.0, 6.9 Hz, 1H; C$^{\varepsilon}$*H*), 1.56 (s, 3H; C(CH_3)$_2$), 1.49 (s, 3H; C(CH_3)$_2$), 1.21 (d, J=6.1 Hz, 6H; CH(CH_3)$_2$), 1.07 ppm (d, J=7.0 Hz, 3H; C$^{\varepsilon}CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ=139.3, 136.7, 134.9, 127.8, 126.8, 117.8, 108.8, 82.6, 79.8, 73.6, 71.0, 69.7, 39.5, 36.2, 27.2, 27.1, 22.12, 22.09, 10.7 ppm; IR (film): $\tilde{\nu}$=3465 (m), 2975 (vs), 2933 (m), 1640 (w), 1515 (vw), 1456 (m), 1379 (vs), 1335 (m), 1236 (vs), 1170 (s), 1126 (s), 1046 (vs), 1020 (s), 995 (m), 915 (m), 816 cm^{-1} (m); MS (ESI): m/z: calcd for $[C_{21}H_{32}O_4+Na]^+$: 371.2; found: 371.3 $[M+Na]^+$; calcd for $[2\,C_{21}H_{32}O_4+Na]^+$: 719.5; found: 718.3 $[2M+Na]^+$.

(2*S*,3*S*)-2-{(4*R*,5*R*)-5-[4-(*tert*-Butoxymethyl)phenyl]-2,2-dimethyl-1,3-dioxolan-4-yl}hex-5-en-3-ol (2d): The procedure is analogous to the one given for **2a**; starting from **16d**. Yield: 214 mg (73%); R_f=0.28 (hexane/EtOAc 4:1); $[\alpha]_D^{24}$ (0.96 g/100 mL, $CHCl_3$): −7.3; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.29–7.36 (m, 4H; Ar-*H*), 5.73 (dddd, J=14.2, 10.1, 9.9, 7.1 Hz, 1H; C$^{\beta}$*H*), 4.93–5.04 (m, 2H; C$^{\alpha}H_2$), 4.77 (d, J=8.9, 2.1 Hz, 1H; C$^{\eta}$*H*), 4.44 (s, 2H; CH_2O*t*Bu), 4.09 (dd, J=8.9, 2.1 Hz, 1H; C$^{\zeta}$*H*), 3.59 (m, 1H; C$^{\delta}$*H*), 2.32 (br s, 1H; O*H*), 2.26 (m, 1H; C$^{\gamma}H_A$), 2.13 (m, 1H; C$^{\gamma}H_B$), 1.74 (ddq, J=6.7, 1.9, 6.9 Hz, 1H; C$^{\varepsilon}$*H*), 1.55 (s, 3H; C(CH_3)$_2$), 1.49 (s, 3H; C(CH_3)$_2$), 1.29 (s, 9H; C(CH_3)$_3$), 1.06 ppm (d, J=7.0 Hz, 3H; C$^{\varepsilon}CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ=137.6, 136.4, 134.9, 127.6, 126.7, 117.8, 108.7, 82.6, 79.8, 73.7, 73.5, 63.8, 39.5, 36.2, 27.7, 27.2, 27.1, 10.7 ppm; IR (film): $\tilde{\nu}$=3477 (br m), 3074 (vw), 2976 (vs), 2933 (s), 1640 (w), 1516 (w), 1459 (m), 1421 (m), 1368 (s), 1236 (vs), 1196 (s), 1170 (m), 1082 (s), 1047 (s), 1020 (s) ,995 (m), 892 (m), 817 cm^{-1} (m); MS (ESI): m/z: calcd for $[C_{22}H_{34}O_4+Na]^+$: 385.2; found: 385.3 $[M+Na]^+$; calcd for $[2\,C_{22}H_{34}O_4+Na]^+$: 747.5; found: 746.2 $[2M+Na]^+$.

Partially protected DC fragment 19: The unit D building block **4** (5.000 g; 26.56 mmol) was dissolved in dry CH_2Cl_2 (60 mL) and a solution of unit C building block **5** (10.011 g; 39.84 mmol) in dry CH_2Cl_2 (45 mL) and dry NEt_3 (5.56 mL; 4.034 g; 39.87 mmol) was added at RT. The mixture was cooled to 0 °C and DMAP (2.596 g; 21.25 mmol) and EDC·HCl (8.147 g; 42.50 mmol) were added. The mixture was stirred for 30 min at 0 °C, 30 min warming to 5 °C and 18 h at RT. Then additional DMAP (649 mg; 5.31 mmol) and EDC·HCl (2.037 g; 10.63 mmol) were added at 0 °C and the mixture was stirred for a further 5 h at RT. The reaction mixture was diluted with Et_2O (500 mL), EtOAc (500 mL) and H_2O (250 mL). The layers were separated, and the aqueous layer was extracted three times with Et_2O/EtOAc 1:1 (100 mL). The combined organic layers were washed with 5% aqueous $KHSO_4$ solution (150 mL), saturated aqueous $NaHCO_3$ solution (150 mL) and brine (150 mL) and dried over $MgSO_4$. The solvent was removed in vacuum (40 °C) and high vacuum. The crude material was purified by flash chromatography on silica gel. The benzyloxycarbonyl-protected DC fragment was obtained as a colourless oil (10.613 g, 95%). R_f=0.23 (hexane/EtOAc 4:1); $[\alpha]_D^{24}$ (1.00 g/100 mL, $CHCl_3$): −26.0; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.24–7.39 (m, 5H; uC-Ar-*H*), 5.97 (m, 1H; N*H*), 5.11 (s, 2H; uC-CH_2Ph), 4.93 (m, 1H; uD-C$^{\alpha}H$), 3.30–3.42 (m, 2H; uC-C$^{\beta}H_2$), 1.68–1.84 (m, 2H; uD-C$^{\beta}H_A$ and uD-C$^{\gamma}H$), 1.57–1.66 (m, 1H; uD-C$^{\beta}H_B$), 1.45 (s, 9H; uD-C-(CH_3)$_3$), 1.24 (s, 3H; uC-C$^{\alpha}CH_3$), 1.22 (s, 3H; uC-C$^{\alpha}CH_3$), 0.96 (d, 3H; J=6.4 Hz, uD-C$^{\delta}H_3$), 0.92 ppm (d, J=6.5 Hz, 3H; uD-C$^{\delta}H_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ=176.2, 170.3, 157.0, 136.9, 128.4, 127.8, 127.6, 82.5, 71.4, 66.3, 49.3, 43.9, 39.5, 27.9, 24.8, 23.09, 23.07, 22.3, 21.6 ppm; IR

(film): $\tilde{\nu}$ = 3357 (w), 2964 (m), 2873 (w), 1730 (vs), 1525 (m), 1471 (w), 1393 (vw), 1369 (m), 1305 (w), 1249 (s), 1141 (s), 1073 (vw), 1043 (vw), 845 (vw), 775 (vw), 736 (w), 697 cm^{-1} (m); MS (ESI): *m/z*: calcd for $[C_{23}H_{35}NO_6+Na]^+$: 444.2; found: 444.2 $[M+Na]^+$; calcd for $[2\,C_{23}H_{35}NO_6+Na]^+$: 865.5; found: 864.7 $[2M+Na]^+$.

The benzyloxycarbonyl-protected DC fragment (2.500 g; 5.93 mmol) was dissolved in EtOAc (165 mL) and Pd/C 10% (690 mg) was added. The suspension was deoxygenated for 1 h with Ar, then H_2 was bubbled through the suspension for 1 h and the reaction mixture was stirred for 2 h under an H_2 atmosphere at RT. The reaction mixture was filtered through a pad of Celite and the solvent was removed in vacuum (40 °C), which gave the partially protected DC fragment **19** (1.672 g, 98%). $[\alpha]_D^{24}$ (1.00 g/100 mL, $CHCl_3$): −27.0; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.88 (m, 1H; uD-C$^{\alpha}$*H*), 2.89 (d, *J* = 13.3 Hz, 1H; uC-C$^{\beta}H_A$), 2.69 (d, *J* = 13.3 Hz, 1H; uC-C$^{\beta}H_B$), 1.71–1.84 (m, 2H; uD-C$^{\beta}H_A$ and uD-C$^{\gamma}$*H*), 1.61 (m, 1H; uD-C$^{\beta}H_B$), 1.46 (m, 11H; uD-C(CH_3)$_3$ and NH_2), 1.20 (s, 6H; uC-C$^{\alpha}$-(CH_3)$_2$), 0.97 (d, *J* = 6.5 Hz, 3H; uD-C$^{\delta}H_3$), 0.93 ppm (d, *J* = 6.5 Hz, 3H; uD-C$^{\delta}H_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.6, 170.0, 81.9, 71.3, 51.9, 44.7, 39.6, 28.0, 24.8, 23.14, 23.06, 22.4, 21.5 ppm; IR (film): $\tilde{\nu}$ = 3402 (w), 2962 (s), 2872 (m), 1735 (vs), 1472 (m), 1393 (m), 1369 (s), 1294 (m), 1247 (m), 1154 (vs), 1072 (m), 1012 (vw), 945 (vw), 902 (vw), 846 (m), 769 cm^{-1} (w); MS (ESI): *m/z*: calcd for $[C_{15}H_{29}NO_4+H]^+$: 288.2; found: 288.0 $[M+H]^+$; calcd for $[C_{18}H_{33}NO_4+H]^+$: 328.3; found: 328.1 $[M$(acetone imine)$+H]^+$; calcd for $[C_{18}H_{33}NO_4+Na]^+$: 350.2; found: 350.1 $[M$(acetone imine)$+Na]^+$.

Deprotected DCB fragment 20: The unit B building block **3** (873 mg; 3.08 mmol) was dissolved in dry CH_2Cl_2 (4.6 mL). The solution was cooled to 0 °C, then NEt_3 (980 µL; 710 mg; 7.04 mmol) was added. Freshly prepared, partially protected DC fragment **19** (631 mg, 2.20 mmol) in CH_2Cl_2 (17.6 mL) was added over 15 min. Then HOAt (419 mg; 3.08 mmol) was added as a solid. After complete dissolution, EDC·HCl (675 mg; 3.52 mmol) was added. The mixture was stirred in the dark and was allowed to gradually warm up to RT. After 19 h the amino component was completely consumed. The reaction mixture was diluted with Et_2O/EtOAc 1:1 (300 mL). The organic layer was washed with H_2O (30 mL), 5% aqueous $KHSO_4$ solution (30 mL) and saturated aqueous $NaHCO_3$ solution (30 mL). The individual aqueous layers from the washing steps were extracted with Et_2O/EtOAc 1:1 (20 mL). All organic layers were combined, washed with brine (30 mL) and dried over $MgSO_4$. The solvent was removed in vacuum (40 °C) and high vacuum. The crude product was purified by flash chromatography on silica gel. The protected DCB fragment was obtained as a colourless, amorphous solid (976 mg, 80%). R_f = 0.21 (hexane/EtOAc 1:1); $[\alpha]_D^{24}$ (1.00 g/100 mL, $CHCl_3$): −44.5; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (dd, *J* = 7.6, 4.8 Hz, 1H; N*H*), 7.21 (d, *J* = 2.0 Hz, 1H; uB-C$^{2'}$*H*), 7.05 (dd, *J* = 8.4, 2.1 Hz, 1H; uB-C$^{6'}$*H*), 6.81 (d, *J* = 8.4 Hz, 1H; uB-C$^{5'}$*H*), 6.68 (d, *J* = 7.9 Hz, 1H; N*H*), 6.26 (dd, *J* = 1.4, 17.0 Hz, 1H; uB-NHC(O)CH=CH_A), 6.10 (dd, *J* = 17.0, 10.3 Hz, 1H; uB-NHC(O)C*H*=CH$_2$), 5.61 (dd, *J* = 1.4, 10.2 Hz, 1H; uB-NHC(O)CH=CH_B), 4.97 (dd, *J* = 9.4, 3.9 Hz, 1H; uD-C$^{\alpha}$*H*), 4.77 (ddd, *J* = 7.7, 6.7, 6.6 Hz, 1H; uB-C$^{\alpha}$*H*), 3.85 (s, 3H; uB-C4′OCH_3), 3.56 (dd, *J* = 13.1, 8.0 Hz, 1H; uC-C$^{\beta}H_A$), 3.29 (dd, *J* = 13.0, 4.6 Hz, 1H; uC-C$^{\beta}H_B$), 3.07 (dd, *J* = 13.9, 6.6 Hz, 1H; uB-C$^{\beta}H_A$), 3.01 (dd, *J* = 13.8, 6.5 Hz, 1H; uB-C$^{\beta}H_B$), 1.66–1.78 (m, 2H; uD-C$^{\beta}H_A$ and uD-C$^{\gamma}$*H*), 1.56–1.65 (m, 1H; uD-C$^{\beta}H_B$), 1.51 (s, 9H; uD-C(CH_3)$_3$), 1.20 (s, 3H; uC-C$^{\alpha}$CH_3), 1.17 (s, 3H; uC-C$^{\alpha}$CH_3), 0.96 (d, *J* = 6.4 Hz, 3H; uD-C$^{\delta}H_3$), 0.92 ppm (d, *J* = 6.4 Hz, 3H; uD-C$^{\delta}H_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.7, 171.4, 171.0, 164.8, 153.8, 131.2, 130.6, 129.8, 128.6, 126.7, 122.1, 111.9, 83.4, 71.3, 56.0, 54.3, 47.5, 43.8, 39.5, 37.8, 28.1, 24.9, 23.3, 23.0, 22.3, 21.5 ppm; MS (ESI): *m/z*: calcd for $[C_{28}H_{41}ClN_2O_7+H]^+$: 553.3; found: 553.2 $[M+H]^+$; calcd for $[C_{28}H_{41}ClN_2O_7+Na]^+$: 575.3; found: 575.2 $[M+Na]^+$; calcd for $[C_{28}H_{41}ClN_2O_7-H]^-$: 551.3; found: 551.2 $[M-H]^-$; calcd for $[C_{28}H_{41}ClN_2O_7-Cl]^-$: 587.2; found: 587.2 $[M+Cl]^-$.

The protected DCB fragment (976 mg; 1.76 mmol) was dissolved in dry CH_2Cl_2 (15.8 mL) and cooled to 0 °C. Then CF_3CO_2H (7.9 mL) was added over 15 min and the mixture was stirred for 17 h in the dark, during which the reaction mixture was allowed to reach RT. After all the starting material was consumed according to TLC analysis, the reaction mixture was diluted with toluene (50 mL) and the solvent was removed in vacuum (40 °C) in the dark. The crude product was co-evaporated with toluene (50 mL) in vacuum (40 °C) twice, then the residue was dried in high vacuum. The deprotected DCB fragment **20** was obtained as slightly yellow, amorphous solid (877 mg, 100%). $[\alpha]_D^{24}$ (0.95 g/100 mL, $CHCl_3$): −54.8; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.09 (m, 2H; N*H* and CO_2H), 7.63 (dd, *J* = 7.4, 4.7 Hz, 1H; N*H*), 7.12 (d, *J* = 1.9 Hz, 1H; uB-C$^{2'}$*H*), 6.99 (dd, *J* = 8.3, 1.9 Hz, 1H; uB-C$^{6'}$*H*), 6.72 (d, *J* = 8.5 Hz, 1H; uB-C$^{5'}$*H*), 6.25 (dd, *J* = 1.9, 17.0 Hz, 1H; uB-NHC(O)CH=CH_A), 6.19 (dd, *J* = 17.1, 9.5 Hz, 1H; uB-NHC(O)C*H*=CH$_2$), 5.71 (dd, *J* = 1.8, 9.5 Hz, 1H; uB-NHC(O)CH=CH_B), 5.14–5.24 (m, 1H; uD-C$^{\alpha}$*H*), 4.73 (ddd, *J* = 7.1, 6.9, 6.9 Hz, 1H; uB-C$^{\alpha}$*H*), 3.80 (s, 3H; uB-C$^{4'}$OCH_3), 3.56 (dd, *J* = 13.4, 7.8 Hz, 1H; uC-C$^{\beta}H_A$), 3.27 (dd, *J* = 13.3, 4.4 Hz, 1H; uC-C$^{\beta}H_B$), 3.04 (dd, *J* = 14.1, 7.0 Hz, 1H; uB-C$^{\beta}H_A$), 3.00 (dd, *J* = 14.1, 6.3 Hz, 1H; uB-C$^{\beta}H_B$), 1.69–1.85 (m, 3H; uD-C$^{\beta}H_2$ and uD-C$^{\gamma}$*H*), 1.20 (s, 3H; uC-C$^{\alpha}$CH_3), 1.17 (s, 3H; uC-C$^{\alpha}$CH_3), 0.97 (d, *J* = 5.8 Hz, 3H; uD-C$^{\delta}H_3$), 0.93 ppm (d, *J* = 5.7 Hz, 3H; uD-C$^{\delta}H_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.6, 173.5, 170.8, 166.4, 153.9, 131.2, 130.0, 129.2, 128.7, 128.0, 122.0, 111.9, 70.8, 56.0, 54.7, 47.8, 43.8, 39.4, 37.4, 25.0, 23.4, 23.0, 22.4, 21.4 ppm; MS (ESI): *m/z*: calcd for $[C_{24}H_{33}ClN_2O_7+H]^+$: 497.2; found: 497.2 $[M+H]^+$; calcd for $[C_{24}H_{33}ClN_2O_7+Na]^+$: 519.2; found: 519.2 $[M+Na]^+$.

***seco*-ADCB fragment 21a (R = H)**: The deprotected DCB fragment **20** (100 mg; 0.20 mmol) was dissolved in dry THF (1.4 mL). NEt_3 (92 µL; 67 mg; 0.66 mmol) was added and the mixture was cooled to 0 °C. Then 2,4,6-trichlorobenzoic acid chloride (38 µL, 59 mg; 0.24 mmol) was added dropwise. The mixture was kept in the dark and was stirred for 30 min at 0 °C and 30 min while warming to RT. Then the mixture was cooled to 0 °C again and a solution of unit A building block **2a** (50 mg; 0.18 mmol) and DMAP (33 mg; 0.27 mmol) in a solution of THF (1.0 mL) was added over 15 min. The mixture was stirred for 70 min at 0 °C in the dark. Subsequently, the reaction was quenched by addition of saturated aqueous NH_4Cl solution (10 mL). The mixture was diluted with Et_2O (50 mL), EtOAc (50 mL) and H_2O (10 mL). The layers were separated, and the aqueous layer was extracted three times with Et_2O/EtOAc 1:1 (30 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuum (40 °C) in the dark, the residue was purified by flash chromatography on silica gel. The product **21a** was obtained as a colourless, amorphous solid (107 mg, 78%). R_f = 0.23 (hexane/EtOAc 1:1); $[\alpha]_D^{24}$ (0.96 g/100 mL, $CHCl_3$): −28.5; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.42 (m, 5H; uA-Ar-*H*), 7.17 (d, *J* = 1.7 Hz, 1H; uB-C$^{2'}$*H*), 7.11 (dd, *J* = 7.5, 4.6 Hz, 1H; N*H*), 7.02 (dd, *J* = 8.3, 1.5 Hz, 1H; uB-C$^{6'}$*H*), 6.80 (d, *J* = 8.4 Hz, 1H; uB-C$^{5'}$*H*), 6.42 (d, *J* = 7.7 Hz, 1H; N*H*), 6.25 (dd, *J* = 1.3, 17.0 Hz, 1H; uB-NHC(O)CH=CH_A), 6.08 (dd, *J* = 17.0, 10.3 Hz, 1H; uB-NHC(O)C*H*=CH$_2$), 5.61 (dd, *J* = 1.3, 10.3 Hz, 1H; uB-NHC(O)CH=CH_B), 5.54 (dddd, *J* = 17.1, 10.1, 7.1, 7.1 Hz, 1H; uA-C$^{\beta}$*H*), 4.94–5.03 (m, 3H; uA-C$^{\alpha}H_A$ and uA-C$^{\delta}$*H* and uD-C$^{\alpha}$*H*), 4.89 (dd, *J* = 1.3, 17.0 Hz, 1H; uA-C$^{\alpha}H_B$), 4.74 (ddd, *J* = 7.6, 6.5, 6.5 Hz, 1H; uB-C$^{\alpha}$*H*), 4.70 (d, *J* = 8.9 Hz, 1H; uA-C$^{\eta}$*H*), 3.87 (dd, *J* = 9.0, 1.8 Hz, 1H; uA-C$^{\zeta}$*H*), 3.85 (s, 3H; uB-C$^{4'}$OCH_3), 3.56 (dd, *J* = 13.3, 8.2 Hz, 1H; uC-C$^{\beta}H_A$), 3.24 (dd, *J* = 13.3, 4.4 Hz, 1H; uC-C$^{\beta}H_B$), 3.07 (dd, *J* = 13.9, 6.4 Hz, 1H; uB-C$^{\beta}H_A$), 2.98 (dd, *J* = 13.9, 6.2 Hz, 1H; uB-C$^{\beta}H_B$), 2.31 (ddm, *J* = 14.8, 10.9 Hz, 1H; uA-C$^{\gamma}H_A$), 2.24 (dd, *J* = 14.8, 7.4 Hz, 1H; uA-C$^{\gamma}H_B$), 1.92 (ddq, *J* = 6.7, 1.3, 6.7 Hz, 1H; uA-C$^{\varepsilon}$*H*), 1.63–1.73 (m, 2H; uD-C$^{\beta}H_A$ and uD-C$^{\gamma}$*H*), 1.52–1.61 (m, 1H; uD-C$^{\beta}H_B$), 1.51 (s, 3H; uA-C(CH_3)$_2$), 1.46 (s, 3H; uA-C(CH_3)$_2$), 1.17 (s, 3H; uC-C$^{\alpha}$CH_3), 1.14 (s, 3H; uC-C$^{\alpha}$CH_3), 1.11 (d, *J* = 6.9 Hz, 3H; uA-C$^{\varepsilon}$CH_3), 0.93 (d, *J* = 6.4 Hz, 3H; uD-C$^{\delta}H_3$), 0.87 ppm (d, *J* = 6.2 Hz, 3H; uD-C$^{\delta}H_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.6, 171.6, 170.8, 164.8, 153.9, 137.6, 132.4, 131.2, 130.6, 129.6, 128.7, 128.6, 128.5, 126.8, 126.7, 122.2, 118.6, 112.0, 109.0, 81.8, 80.3, 77.0, 70.8, 56.1, 54.3, 47.5, 43.8, 39.3, 37.6, 35.6, 35.0, 27.3, 27.1, 24.8, 23.3, 23.2, 22.3, 21.2, 9.8 ppm; MS (ESI): *m/z*: calcd for $[C_{41}H_{55}ClN_2O_9+H]^+$: 755.4; found: 755.2 $[M+H]^+$; calcd for $[C_{41}H_{55}ClN_2O_9+Na]^+$: 777.4; found: 777.3 $[M+Na]^+$; calcd for $[C_{41}H_{55}ClN_2O_9+Cl]^-$: 789.3; found: 789.3 $[M+Cl]^-$.

***seco*-ADCB fragment 21b (R = CH$_2$OMe)**: The procedure is analogous to the one given for **21a**; starting from unit A building block **2b**. Yield: 112 mg (88%); R_f = 0.24 (hexane/EtOAc 1:1); $[\alpha]_D^{24}$ (0.92 g/100 mL, $CHCl_3$): −27.2; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.44 (m, 4H; uA-

Ar-*H*), 7.20 (d, $J=1.9$ Hz, 1H; uB-C$^{2'}$*H*), 7.15 (dd, $J=7.5$, 4.9 Hz, 1H; N*H*), 7.04 (dd, $J=8.4$, 1.9 Hz, 1H; uB-C$^{6'}$*H*), 6.81 (d, $J=8.4$ Hz, 1H; uB-C$^{5'}$*H*), 6.62 (d, $J=7.9$ Hz, 1H; N*H*), 6.25 (dm, $J=17.0$ Hz, 1H; uB-NHC(O)CH=C*H*$_A$), 6.09 (dd, $J=17.0$, 10.3 Hz, 1H; uB-NHC(O)C*H*=CH$_2$), 5.60 (dd, $J=1.1$, 10.4 Hz, 1H; uB-NHC(O)CH=C*H*$_B$), 5.56 (ddm, $J=14.6$, 10.1 Hz, 1H; uA-C$^{\beta}$*H*), 4.95–5.05 (m, 3H; uA-C$^{\alpha}$*H*$_A$ and uA-C$^{\delta}$*H* and uD-C$^{\alpha}$*H*), 4.91 (dm, $J=17.0$ Hz, 1H; uA-C$^{\alpha}$*H*$_B$), 4.75 (ddd, $J=7.5$, 6.7, 6.7 Hz, 1H; uB-C$^{\alpha}$*H*), 4.71 (d, $J=8.9$ Hz, 1H; uA-C$^{\eta}$*H*), 4.44 (s, 2H; uA-C$^{4'}$C*H*$_2$), 3.87 (dd, $J=9.0$, 1.8 Hz, 1H; uA-C$^{\zeta}$*H*), 3.85 (s, 3H; uB-C$^{4'}$OC*H*$_3$), 3.55 (dd, $J=13.3$, 8.1 Hz, 1H; uC-C$^{\beta}$*H*$_A$), 3.38 (s, 3H; uA-CH$_2$OC*H*$_3$), 3.22 (dd, $J=13.4$, 4.4 Hz, 1H; uC-C$^{\beta}$*H*$_B$), 3.08 (dd, $J=13.9$, 6.2 Hz, 1H; uB-C$^{\beta}$*H*$_A$), 2.97 (dd, $J=13.9$, 6.5 Hz, 1H; uB-C$^{\beta}$*H*$_B$), 2.33 (dm, $J=14.9$ Hz, 1H; uA-C$^{\gamma}$*H*$_A$), 2.25 (ddd, $J=14.6$, 7.3, 7.3 Hz, 1H; uA-C$^{\gamma}$*H*$_B$), 1.91 (ddq, $J=6.6$, 1.7, 6.8 Hz, 1H; uA-C$^{\varepsilon}$*H*), 1.65–1.77 (m, 2H; uD-C$^{\beta}$*H*$_A$ and uD-C$^{\gamma}$*H*), 1.57 (m, 1H; uD-C$^{\beta}$*H*$_B$), 1.51 (s, 3H; uA-C(C*H*$_3$)$_2$), 1.45 (s, 3H; uA-C(C*H*$_3$)$_2$), 1.17 (s, 3H; uC-C$^{\alpha}$C*H*$_3$), 1.14 (s, 3H; uC-C$^{\alpha}$C*H*$_3$), 1.11 (d, $J=7.0$ Hz, 3H; uA-C$^{\varepsilon}$C*H*$_3$), 0.94 (d, $J=6.3$ Hz, 3H; uD-C$^{\delta}$*H*$_3$), 0.87 ppm (d, $J=6.3$ Hz, 3H; uD-C$^{\delta}$*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=175.6$, 171.5, 170.9, 164.9, 153.8, 138.5, 137.0, 132.4, 131.2, 130.6, 129.7, 128.6, 128.1, 126.8, 126.7, 122.1, 118.6, 111.9, 108.9, 81.7, 80.1, 76.9, 74.3, 70.8, 58.1, 56.0, 54.3, 47.4, 43.8, 39.4, 37.6, 35.6, 34.9, 27.2, 27.1, 24.8, 23.3, 23.2, 22.3, 21.2, 9.8 ppm; MS (ESI): *m*/*z*: calcd for $[C_{43}H_{59}ClN_2O_{10}+H]^+$: 799.4; found: 799.2 $[M+H]^+$; calcd for $[C_{43}H_{59}ClN_2O_{10}+Na]^+$: 821.4; found: 821.4 $[M+Na]^+$; calcd for $[C_{43}H_{59}ClN_2O_{10}+Cl]^-$: 833.4; found: 833.5 $[M+Cl]^-$.

***seco*-ADCB fragment 21c (R = CH$_2$O*i*Pr)**: The procedure is analogous to the one given for **21a**; starting from unit A building block **2c**. Yield: 109 mg (72%); $R_f=0.29$ (hexane/EtOAc 1:1); $[\alpha]_D^{24}$ (1.04 g/100 mL, $CHCl_3$): −25.8; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.34$ (m, 4H; uA-Ar-*H*), 7.18 (d, $J=1.6$ Hz, 1H; uB-C$^{2'}$*H*), 7.14 (dd, $J=7.4$, 4.4 Hz, 1H; N*H*), 7.03 (dd, $J=8.3$, 1.6 Hz, 1H; uB-C$^{6'}$*H*), 6.80 (d, $J=8.4$ Hz, 1H; uB-C$^{5'}$*H*), 6.47 (d, $J=7.8$ Hz, 1H; N*H*), 6.25 (dm, $J=17.0$ Hz, 1H; uB-NHC(O)CH=C*H*$_A$), 6.08 (dd, $J=17.0$, 10.2 Hz, 1H; uB-NHC(O)C*H*=CH$_2$), 5.61 (dm, $J=10.3$ Hz, 1H; uB-NHC(O)CH=C*H*$_B$), 5.48–5.67 (m, 1H; uA-C$^{\beta}$*H*), 4.89–5.08 (m, 4H; uA-C$^{\delta}$*H* and uA-C$^{\alpha}$*H*$_2$ and uD-C$^{\alpha}$*H*), 4.75 (ddd, $J=7.1$, 6.9, 6.7 Hz, 1H; uB-C$^{\alpha}$*H*), 4.70 (d, $J=8.8$ Hz, 1H; uA-C$^{\eta}$*H*), 4.49 (s, 2H; uA-C$^{4'}$C*H*$_2$), 3.85 (s, 3H; uB-C$^{4'}$OC*H*$_3$), 3.84–3.88 (m, 1H; uA-C$^{\zeta}$*H*), 3.67 (uA-C*H*(CH$_3$)$_2$), 3.56 (dd, $J=13.3$, 8.3 Hz, 1H; uC-C$^{\beta}$*H*$_A$), 3.24 (dd, $J=13.4$, 4.4 Hz, 1H; uC-C$^{\beta}$*H*$_B$), 3.08 (dd, $J=13.9$, 6.2 Hz, 1H; uB-C$^{\beta}$*H*$_A$), 2.98 (dd, $J=13.9$, 6.2 Hz, 1H; uB-C$^{\beta}$*H*$_B$), 2.34 (ddd, $J=14.5$, 5.2, 5.2 Hz, 1H; uA-C$^{\gamma}$*H*$_A$), 2.25 (ddd, $J=14.6$, 7.3, 7.3 Hz, 1H; uA-C$^{\gamma}$*H*$_B$), 1.90 (dqm, $J=8.1$, 6.9 Hz, 1H; uA-C$^{\varepsilon}$*H*), 1.63–1.77 (m, 2H; uD-C$^{\beta}$*H*$_A$ and uD-C$^{\gamma}$*H*), 1.56 (m, 1H; uD-C$^{\beta}$*H*$_B$), 1.50 (s, 3H; uA-C(C*H*$_3$)$_2$), 1.45 (s, 3H; uA-C(C*H*$_3$)$_2$), 1.21 (d, $J=6.0$ Hz, 6H; uA-CH(C*H*$_3$)$_2$), 1.18 (s, 3H; uC-C$^{\alpha}$C*H*$_3$), 1.14 (s, 3H; uC-C$^{\alpha}$C*H*$_3$), 1.11 (d, $J=7.0$ Hz, 3H; uA-C$^{\varepsilon}$C*H*$_3$), 0.94 (d, $J=6.2$ Hz, 3H; uD-C$^{\delta}$*H*$_3$), 0.87 ppm (d, $J=6.3$ Hz, 3H; uD-C$^{\delta}$*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=175.6$, 171.5, 170.8, 164.9, 153.9, 139.5, 136.7, 132.4, 131.2, 130.6, 129.6, 128.6, 127.9, 126.8, 126.7, 122.1, 118.6, 111.9, 108.9, 81.7, 80.1, 77.0, 71.0 70.8, 69.6, 56.0, 54.3, 47.4, 43.8, 39.3, 37.6, 35.7, 34.9, 27.3, 27.1, 24.8, 23.3, 23.2, 22.3, 22.11, 22.08, 21.2, 9.8 ppm; MS (ESI): *m*/*z*: calcd for $[C_{45}H_{63}ClN_2O_{10}+Na]^+$: 849.4; found: 849.5 $[M+Na]^+$; calcd for $[C_{45}H_{63}ClN_2O_{10}-H]^-$: 825.4; found: 825.5 $[M-H]^-$; calcd for $[C_{45}H_{63}ClN_2O_{10}+Cl]^-$: 861.4; found: 861.6 $[M+Cl]^-$.

***seco*-ADCB fragment 21d (R = CH$_2$O*t*Bu)**: The procedure is analogous to the one given for **21a**; starting from unit A building block **2d**. Yield: 176 mg (72%); $R_f=0.31$ (hexane/EtOAc 1:1); $[\alpha]_D^{24}$ (1.04 g/100 mL, $CHCl_3$): −29.3; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.26$–7.41 (m, 4H; uA-Ar-*H*), 7.17–7.26 (m, 2H; uB-C$^{2'}$*H* and N*H*), 7.05 (dm, $J=7.6$ Hz, 1H; uB-C$^{6'}$*H*), 6.85 (d, $J=7.8$ Hz, 1H; N*H*), 6.80 (d, $J=8.4$ Hz, 1H; uB-C$^{5'}$*H*), 6.24 (dm, $J=17.0$ Hz, 1H; uB-NHC(O)CH=C*H*$_A$), 6.10 (dd, $J=16.5$, 10.2 Hz, 1H; uB-NHC(O)C*H*=CH$_2$), 5.52–5.66 (m, 2H; uA-C$^{\beta}$*H* and uB-NHC(O)CH=C*H*$_B$), 4.88–5.11 (m, 4H; uA-C$^{\delta}$*H* and uA-C$^{\alpha}$*H*$_2$ and uD-C$^{\alpha}$*H*), 4.76 (dm, $J=6.6$ Hz, 1H; uB-C$^{\alpha}$*H*), 4.70 (d, $J=8.7$ Hz, 1H; uA-C$^{\eta}$*H*), 4.43 (s, 2H; uA-C$^{4'}$C*H*$_2$), 3.80–3.87 (m, 4H; uB-C$^{4'}$OC*H*$_3$ and uA-C$^{\zeta}$*H*), 3.55 (dd, $J=13.2$, 8.1 Hz, 1H; uC-C$^{\beta}$*H*$_A$), 3.28 (dd, $J=13.2$, 4.2 Hz, 1H; uC-C$^{\beta}$*H*$_B$), 3.08 (dd, $J=13.7$, 5.8 Hz, 1H; uB-C$^{\beta}$*H*$_A$), 2.96 (dd, $J=13.7$, 6.8 Hz, 1H; uB-C$^{\beta}$*H*$_B$), 2.32–2.41 (m, 1H; uA-C$^{\gamma}$*H*$_A$), 2.26 (ddd, $J=14.5$, 7.1, 7.2 Hz, 1H; uA-C$^{\gamma}$*H*$_B$), 1.89 (m, 1H; uA-C$^{\varepsilon}$*H*), 1.65–1.78 (m, 2H; uD-C$^{\beta}$*H*$_A$ and uD-C$^{\gamma}$*H*), 1.56 (m, 1H; uD-C$^{\beta}$*H*$_B$), 1.49 (s, 3H; uA-C(C*H*$_3$)$_2$), 1.44 (s, 3H; uA-C(C*H*$_3$)$_2$), 1.28 (s, 9H; uA-C(C*H*$_3$)$_3$), 1.18 (s, 3H; uC-C$^{\alpha}$C*H*$_3$), 1.15 (s, 3H; uC-C$^{\alpha}$C*H*$_3$), 1.10 (d, $J=6.8$ Hz, 3H; uA-C$^{\varepsilon}$C*H*$_3$), 0.95 (d, $J=6.0$ Hz, 3H; uD-C$^{\delta}$*H*$_3$), 0.88 ppm (d, $J=6.2$ Hz, 3H; uD-C$^{\delta}$*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=175.6$, 171.4, 171.2, 165.0, 153.8, 140.2, 136.4, 132.4, 131.2, 130.6, 129.8, 128.6, 127.7, 126.6, 122.0, 118.6, 111.9, 108.8, 81.7, 80.0, 76.9, 73.5, 70.8, 63.8, 56.0, 54.4, 47.4, 43.8, 39.3, 37.6, 35.7, 34.8, 27.7, 27.2, 27.1, 24.8, 23.3, 23.2, 22.3, 21.2, 9.7 ppm; MS (ESI): *m*/*z*: calcd for $[C_{46}H_{65}ClN_2O_{10}+Na]^+$: 863.4; found: 863.6 $[M+Na]^+$.

Cyclic, acetonide-protected depsipeptide 22a (R = H): The *seco*-ADCB fragment (R = H) **21a** (494 mg; 0.65 mmol) was dissolved in dry CH_2Cl_2 (65 mL). The commercially available Grubbs second-generation catalyst (28 mg; 0.033 mmol; 5 mol%) was added and the reaction mixture was heated at reflux for 6 h. Then the solvent was removed in vacuum (40 °C). The residue was purified by flash chromatography on silica gel. The product was obtained as an amorphous solid (397 mg, 85%). $R_f=0.25$ (hexane/EtOAc 1:2); $[\alpha]_D^{24}$ (0.96 g/100 mL, $CHCl_3$): +14.6; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.30$–7.43 (m, 5H; uA-Ar-*H*), 7.20 (m, 1H; N*H*), 7.19 (d, $J=1.8$ Hz, 1H; uB-C$^{2'}$*H*), 7.05 (dd, $J=8.3$, 1.8 Hz, 1H; uB-C$^{6'}$*H*), 6.83 (d, $J=8.4$ Hz, 1H; uB-C$^{5'}$*H*), 6.63 (ddd, $J=15.0$, 10.7, 4.3 Hz, 1H; uA-C$^{\beta}$*H*), 5.67 (d, $J=15.2$ Hz, 1H; uA-C$^{\alpha}$*H*), 5.60 (d, $J=7.8$ Hz, 1H; N*H*), 5.04 (ddd, $J=10.7$, 7.4, 1.0 Hz, 1H; uA-C$^{\delta}$*H*), 4.79 (dd, $J=10.3$, 3.5 Hz, 1H; uD-C$^{\alpha}$*H*), 4.72 (ddm, $J=7.6$, 5.7 Hz, 1H; uB-C$^{\alpha}$*H*), 4.70 (d, $J=8.9$ Hz, 1H; uA-C$^{\eta}$*H*), 3.87 (s, 3H; uB-C$^{4'}$OC*H*$_3$), 3.79 (dd, $J=8.8$, 1.8 Hz, 1H; uA-C$^{\zeta}$*H*), 3.38 (dd, $J=13.4$, 8.4 Hz, 1H; uC-C$^{\beta}$*H*$_A$), 3.13 (dd, $J=13.7$, 3.3 Hz, 1H; uC-C$^{\beta}$*H*$_B$), 3.11 (dd, $J=14.2$, 4.9 Hz, 1H; uB-C$^{\beta}$*H*$_A$), 3.02 (dd, $J=14.4$, 7.7 Hz, 1H; uB-C$^{\beta}$*H*$_B$), 2.47 (dm, $J=14.3$ Hz, 1H; uA-C$^{\gamma}$*H*$_A$), 2.22 (ddd, $J=14.2$, 11.2, 11.2 Hz, 1H; uA-C$^{\gamma}$*H*$_B$), 1.84 (ddq, $J=6.8$, 1.6, 6.8 Hz, 1H; uA-C$^{\varepsilon}$*H*), 1.75 (ddd, $J=13.9$, 10.4, 5.0 Hz, 1H; uD-C$^{\beta}$*H*$_A$), 1.65 (m, 1H; uD-C$^{\gamma}$*H*), 1.50 (s, 3H; uA-C(C*H*$_3$)$_2$), 1.46 (s, 3H; uA-C(C*H*$_3$)$_2$), 1.35 (ddd, $J=13.7$, 9.0, 3.7 Hz, 1H; uD-C$^{\beta}$*H*$_B$), 1.22 (s, 3H; uC-C$^{\alpha}$C*H*$_3$), 1.15 (s, 3H; uC-C$^{\alpha}$C*H*$_3$), 1.13 (d, $J=6.9$ Hz, 3H; uA-C$^{\varepsilon}$C*H*$_3$), 0.92 (d, $J=6.6$ Hz, 3H; uD-C$^{\delta}$*H*$_3$), 0.83 ppm (d, $J=6.6$ Hz, 3H; uD-C$^{\delta}$*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=177.9$, 170.4, 170.2, 165.1, 154.1, 142.4, 137.6, 130.9, 129.6, 128.8, 128.6, 128.3, 126.6, 124.4, 122.5, 112.3, 109.1, 82.4, 80.2, 75.8, 71.2, 56.1, 54.4, 46.5, 42.8, 39.5, 36.8, 35.8, 35.3, 27.2, 27.0, 24.7, 23.0, 22.9, 22.7, 21.4, 9.7 ppm; MS (ESI): *m*/*z*: calcd for $[C_{39}H_{51}ClN_2O_9\text{-}C_3H_6O+H]^+$: 669.3; found: 669.2 $[M-C_3H_6O+H]^+$; calcd for $[C_{39}H_{51}ClN_2O_9+H]^+$: 727.3; found: 727.2 $[M+H]^+$; calcd for $[C_{39}H_{51}ClN_2O_9+Na]^+$: 749.3; found: 749.2 $[M+Na]^+$; calcd for $[C_{39}H_{51}ClN_2O_9+Cl]^-$: 761.3; found: 761.4 $[M+Cl]^-$.

Cyclic, acetonide-protected depsipeptide 22b (R = CH$_2$OMe): The procedure is analogous to the one given for **22a**; starting from **21b**. Yield: 76 mg (71%); $R_f=0.22$ (hexane/EtOAc 1:2); $[\alpha]_D^{24}$ (0.91 g/100 mL, $CHCl_3$): +9.6; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=7.30$–7.37 (m, 4H; uA-Ar-*H*), 7.22 (dd, $J=8.0$, 3.4 Hz, 1H; N*H*), 7.19 (m, 1H; uB-C$^{2'}$*H*), 7.05 (dm, $J=8.4$ Hz, 1H; uB-C$^{6'}$*H*), 6.83 (d, $J=8.4$ Hz, 1H; uB-C$^{5'}$*H*), 6.64 (ddd, $J=15.0$, 10.7, 4.3 Hz, 1H; uA-C$^{\beta}$*H*), 5.75 (d, $J=7.8$ Hz, 1H; N*H*), 5.67 (d, $J=15.2$ Hz, 1H; uA-C$^{\alpha}$*H*), 5.03 (ddm, $J=10.2$, 7.8 Hz, 1H; uA-C$^{\delta}$*H*), 4.79 (dd, $J=10.2$, 3.3 Hz, 1H; uD-C$^{\alpha}$*H*), 4.71 (m, 1H; uB-C$^{\alpha}$*H*), 4.70 (d, $J=8.6$ Hz, 1H; uA-C$^{\eta}$*H*), 4.45 (s, 2H; uA-C$^{4'}$C*H*$_2$), 3.86 (s, 3H; uB-C$^{4'}$OC*H*$_3$), 3.79 (dm, $J=8.7$ Hz, 1H; uA-C$^{\zeta}$*H*), 3.39 (dm, $J=8.8$ Hz, 1H; uC-C$^{\beta}$*H*$_A$), 3.37 (s, 3H; uA-CH$_2$OC*H*$_3$), 3.14 (dd, $J=10.9$, 2.3 Hz, 1H; uC-C$^{\beta}$*H*$_B$), 3.12 (dd, $J=13.3$, 4.4 Hz, 1H; uB-C$^{\beta}$*H*$_A$), 3.01 (dd, $J=14.5$, 8.0 Hz, 1H; uB-C$^{\beta}$*H*$_B$), 2.48 (dm, $J=13.4$ Hz, 1H; uA-C$^{\gamma}$*H*$_A$), 2.22 (ddd, $J=14.0$, 11.4, 11.4 Hz, 1H; uA-C$^{\gamma}$*H*$_B$), 1.82 (dqm, $J=6.7$, 6.8 Hz, 1H; uA-C$^{\varepsilon}$*H*), 1.76 (ddd, $J=13.9$, 10.4, 4.9 Hz, 1H; uD-C$^{\beta}$*H*$_A$), 1.67 (m, 1H; uD-C$^{\gamma}$*H*), 1.50 (s, 3H; uA-C(C*H*$_3$)$_2$), 1.45 (s, 3H; uA-C(C*H*$_3$)$_2$), 1.37 (ddd, $J=13.9$, 8.9, 3.3 Hz, 1H; uD-C$^{\beta}$*H*$_B$), 1.22 (s, 3H; uC-C$^{\alpha}$C*H*$_3$), 1.15 (s, 3H; uC-C$^{\alpha}$C*H*$_3$), 1.12 (d, $J=6.8$ Hz, 3H; uA-C$^{\varepsilon}$C*H*$_3$), 0.92 (d, $J=6.6$ Hz, 3H; uD-C$^{\delta}$*H*$_3$), 0.83 ppm (d, $J=6.5$ Hz, 3H; uD-C$^{\delta}$*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=177.8$, 170.5, 170.2, 165.2, 154.0, 142.3, 138.7, 137.0, 130.9, 129.8, 128.3, 128.1, 126.7, 124.4, 122.5, 112.3, 109.1, 82.3, 79.9, 75.9, 74.3, 71.1, 58.2, 56.1, 54.5, 46.5, 42.8, 39.5, 36.7, 35.8, 35.3, 27.2, 27.0, 24.7, 23.0, 22.9, 22.7, 21.4, 9.6 ppm; MS (ESI): *m*/*z*: calcd for $[C_{41}H_{55}ClN_2O_{10}+H]^+$: 771.4; found: 771.6 $[M+H]^+$; calcd for $[C_{41}H_{55}ClN_2O_{10}+Na]^+$: 793.3; found: 793.6 $[M+Na]^+$; calcd for $[C_{41}H_{55}ClN_2O_{10}+Cl]^-$: 805.3; found: 805.5 $[M+Cl]^-$.

Cyclic, acetonide-protected depsipeptide 22c (R = CH_2OiPr): The procedure is analogous to the one given for **22a**; starting from **21c**. Yield: 49 mg (75%); R_f = 0.25 (hexane/EtOAc 1:2); $[\alpha]_D^{24}$ (0.90 g/100 mL, $CHCl_3$): +4.1; H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.39 (m, 4H; uA-Ar-*H*), 7.21 (dd, *J* = 8.3, 3.6 Hz, 1H; N*H*), 7.19 (d, *J* = 1.9 Hz, 1H; uB-C$^{2'}$*H*), 7.05 (dd, *J* = 8.4, 1.9 Hz, 1H; uB-C$^{6'}$*H*), 6.83 (d, *J* = 8.4 Hz, 1H; uB-C$^{5'}$*H*), 6.66 (ddd, *J* = 15.0, 10.7, 4.3 Hz, 1H; uA-C$^{\beta}$*H*), 5.68 (d, *J* = 15.5 Hz, 1H; uA-C$^{\alpha}$*H*), 5.66 (d, *J* = 7.9 Hz, 1H; N*H*), 5.02 (ddd, *J* = 10.7, 7.5, 1.0 Hz, 1H; uA-C$^{\delta}$*H*), 4.79 (dd, *J* = 10.4, 3.4 Hz, 1H; uD-C$^{\alpha}$*H*), 4.72 (ddd, *J* = 7.7, 7.7, 5.0 Hz, 1H; uB-C$^{\alpha}$*H*), 4.69 (d, *J* = 8.9 Hz, 1H; uA-C$^{\eta}$*H*), 4.50 (s, 2H; uA-C$^{4'}CH_2$), 3.87 (s, 3H; uB-C$^{4'}OCH_3$), 3.78 (dd, *J* = 8.8, 1.5 Hz, 1H; uA-C$^{\zeta}$*H*), 3.67 (m, 1H; uA-C*H*$(CH_3)_2$), 3.39 (dd, *J* = 13.4, 8.4 Hz, 1H; uC-C$^{\beta}H_A$), 3.07–3.18 (m, 2H; uC-C$^{\beta}H_B$ and uB-C$^{\beta}H_A$), 3.02 (dd, *J* = 14.5, 7.9 Hz, 1H; uB-C$^{\beta}H_B$), 2.52 (dm, *J* = 14.5 Hz, 1H; uA-C$^{\gamma}H_A$), 2.22 (dm, *J* = 14.3 Hz, 1H; uA-C$^{\gamma}H_B$), 1.82 (dqm, *J* = 1.6, 6.8 Hz, 1H; uA-C$^{\varepsilon}$*H*), 1.76 (ddd, *J* = 14.1, 10.3, 4.8 Hz, 1H; uD-C$^{\beta}H_A$), 1.66 (m, 1H; uD-C$^{\gamma}$*H*), 1.49 (s, 3H; uA-C(CH_3)$_2$), 1.45 (s, 3H; uA-C(CH_3)$_2$), 1.36 (ddd, *J* = 13.9, 9.0, 3.6 Hz, 1H; uD-C$^{\beta}H_B$), 1.22 (s, 3H; uC-C$^{\alpha}CH_3$), 1.21 (d, *J* = 6.1 Hz, 6H; uA-CH(CH_3)$_2$), 1.16 (s, 3H; uC-C$^{\alpha}CH_3$), 1.12 (d, *J* = 6.9 Hz, 3H; uA-C$^{\varepsilon}CH_3$), 0.93 (d, *J* = 6.7 Hz, 3H; uD-C$^{\delta}H_3$), 0.83 ppm (d, *J* = 6.6 Hz, 3H; uD-C$^{\delta}H_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.8, 170.4, 170.2, 165.1, 154.0, 142.4, 139.6, 136.6, 130.9, 129.7, 128.3, 127.9, 126.6, 124.3, 122.5, 112.3, 109.0, 82.2, 79.9, 75.9, 71.12, 71.11, 69.6, 56.1, 54.4, 46.5, 42.8, 39.5, 36.5, 35.9, 35.3, 27.2, 27.0, 24.7, 23.0, 22.8, 22.7, 22.11, 22.08, 21.3, 9.6 ppm; MS (ESI): *m*/*z*: calcd for $[C_{43}H_{59}ClN_2O_{10}+H]^+$: 799.4; found: 799.6 $[M+H]^+$; calcd for $[C_{43}H_{59}ClN_2O_{10}+Na]^+$: 821.4; found: 821.6 $[M+Na]^+$; calcd for $[C_{43}H_{59}ClN_2O_{10}+Cl]^-$: 833.4; found: 833.5 $[M+Cl]^-$.

Cyclic, acetonide-protected depsipeptide 22d (R = CH_2OtBu): The procedure is analogous to the one given for **22a**; starting from **21d**. Yield: 131 mg (76%); R_f = 0.37 (hexane/EtOAc 1:2); $[\alpha]_D^{24}$ (1.19 g/100 mL, $CHCl_3$): +3.0; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24–7.39 (m, 5H; uA-Ar-*H* and N*H*), 7.19 (m, 1H; uB-C$^{2'}$*H*), 7.05 (dm, *J* = 7.9 Hz, 1H; uB-C$^{6'}$*H*), 6.82 (d, *J* = 8.4 Hz, 1H; uB-C$^{5'}$*H*), 6.67 (ddd, *J* = 14.4, 10.9, 3.7 Hz, 1H; uA-C$^{\beta}$*H*), 6.01 (d, *J* = 7.6 Hz, 1H; N*H*), 5.72 (d, *J* = 15.1 Hz, 1H; uA-C$^{\alpha}$*H*), 5.01 (m, 1H; uA-C$^{\delta}$*H*), 4.79 (dd, *J* = 10.3, 2.6 Hz, 1H; uD-C$^{\alpha}$*H*), 4.66–4.74 (m, 2H; uB-C$^{\alpha}$*H* and uA-C$^{\eta}$*H*), 4.43 (s, 2H; uA-C$^{4'}CH_2$), 3.85 (s, 3H; uB-C$^{4'}OCH_3$), 3.77 (dm, *J* = 8.6 Hz, 1H; uA-C$^{\zeta}$*H*), 3.40 (dd, *J* = 13.2, 8.7 Hz, 1H; uC-C$^{\beta}H_A$), 3.08–3.18 (m, 2H; uC-C$^{\beta}H_B$ and uB-C$^{\beta}H_A$), 2.96 (dd, *J* = 14.3, 8.4 Hz, 1H; uB-C$^{\beta}H_B$), 2.54 (dm, *J* = 13.6 Hz, 1H; uA-C$^{\gamma}H_A$), 2.14–2.29 (m, 1H; uA-C$^{\gamma}H_B$), 1.71–1.86 (m, 2H; uD-C$^{\beta}H_A$ and uA-C$^{\varepsilon}$*H*), 1.66 (m, 1H; uD-C$^{\gamma}$*H*), 1.48 (s, 3H; uA-C(CH_3)$_2$), 1.44 (s, 3H; uA-C(CH_3)$_2$), 1.35 (ddd, *J* = 12.8, 9.8, 2.7 Hz, 1H; uD-C$^{\beta}H_B$), 1.28 (s, 9H; uA-C(CH_3)$_2$), 1.22 (s, 3H; uC-C$^{\alpha}CH_3$), 1.15 (s, 3H; uC-C$^{\alpha}CH_3$), 1.11 (d, *J* = 6.7 Hz, 3H; uA-C$^{\varepsilon}CH_3$), 0.93 (d, *J* = 6.4 Hz, 3H; uD-C$^{\delta}H_3$), 0.83 ppm (d, *J* = 6.4 Hz, 3H; uD-C$^{\delta}H_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.8, 170.6, 170.1, 165.3, 153.9, 142.4, 140.3, 136.4, 130.8, 129.9, 128.2, 127.7, 126.5, 124.3, 122.4, 112.3, 109.0, 82.2, 79.8, 76.0, 73.5, 71.0, 63.7, 56.1, 54.6, 46.5, 42.8, 39.5, 36.3, 36.0, 35.3, 27.7, 27.2, 27.0, 24.7, 23.0, 22.9, 22.7, 21.3, 9.5 ppm; MS (ESI): *m*/*z*: calcd for $[C_{44}H_{61}ClN_2O_{10}+Na]^+$: 835.4; found: 835.5 $[M+Na]^+$; calcd for $[C_{44}H_{61}ClN_2O_{10}+Cl]^-$: 847.4; found: 847.6 $[M+Cl]^-$.

Deprotected cyclic depsipeptide 23a (R = H): The acetonide-protected depsipeptide (R = H) **22a** (368 mg; 0.51 mmol) was dissolved in H_2O (3.5 mL) and CH_3CN (7.5 mL). The solution was cooled to 0°C, then CF_3CO_2H (0.58 mL) was added dropwise. The reaction mixture was allowed to reach RT. After complete conversion (TLC control; 36 h) the reaction mixture was lyophilised and the residue was purified by flash chromatography on silica gel. The product was obtained as an amorphous solid (246 mg, 71%). R_f = 0.31 (EtOAc); $[\alpha]_D^{24}$ (0.97 g/100 mL, MeOH): −30.3; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.38 (m, 5H; uA-Ar-*H*), 7.24 (dd, *J* = 7.7, 3.7 Hz, 1H; N*H*), 7.18 (d, *J* = 2.0 Hz, 1H; uB-C$^{2'}$*H*), 7.04 (dd, *J* = 8.4, 2.0 Hz, 1H; uB-C$^{6'}$*H*), 6.82 (d, *J* = 8.5 Hz, 1H; uB-C$^{5'}$*H*), 6.71 (ddd, *J* = 15.1, 10.8, 4.2 Hz, 1H; uA-C$^{\beta}$*H*), 5.99 (d, *J* = 6.9 Hz, 1H; N*H*), 5.72 (dm, *J* = 15.1 Hz, 1H; uA-C$^{\alpha}$*H*), 5.07 (m, 1H; uA-C$^{\delta}$*H*), 4.86 (dd, *J* = 10.1, 3.5 Hz, 1H; uD-C$^{\alpha}$*H*), 4.70 (ddd, *J* = 7.7, 7.7, 5.2 Hz, 1H; uB-C$^{\alpha}$*H*), 4.57 (d, *J* = 8.5 Hz, 1H; uA-C$^{\eta}$*H*), 3.87 (s, 3H; uB-C$^{4'}OCH_3$), 3.79 (d, *J* = 8.8 Hz, 1H; uA-C$^{\zeta}$*H*), 3.34 (dd, *J* = 13.5, 8.1 Hz, 1H; uC-C$^{\beta}H_A$), 3.17 (dd, *J* = 13.4, 3.5 Hz, 1H; uC-C$^{\beta}H_B$) 3.10 (dd, *J* = 14.5, 4.9 Hz, 1H; uB-C$^{\beta}H_A$), 2.95 (dd, *J* = 14.1, 7.9 Hz, 1H; uB-C$^{\beta}H_B$; and m, 2H; O*H*), 2.44 (dm, *J* = 14.2 Hz, 1H; uA-C$^{\gamma}H_A$), 2.23 (ddd, *J* = 14.2, 11.2, 11.2 Hz, 1H; uA-C$^{\gamma}H_B$), 1.79 (ddd, *J* = 14.1, 10.0, 4.9 Hz, 1H; uD-C$^{\beta}H_A$), 1.64 (m, 1H; uD-C$^{\gamma}$*H*), 1.46 (m, 2H; uA-C$^{\varepsilon}$*H* and uD-C$^{\beta}H_B$), 1.23 (s, 3H; uC-C$^{\alpha}CH_3$), 1.16 (s, 3H; uC-C$^{\alpha}CH_3$), 0.99 (d, *J* = 7.0 Hz, 3H; uA-C$^{\varepsilon}CH_3$), 0.93 (d, *J* = 6.7 Hz, 3H; uD-C$^{\delta}H_3$), 0.87 ppm (d, *J* = 6.6 Hz, 3H; uD-C$^{\delta}H_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.7, 170.8, 170.6, 165.5, 154.0, 142.7, 140.6, 130.9, 129.7, 128.7, 128.4, 128.2, 126.9, 124.4, 122.4, 112.3, 76.5, 75.8, 74.9, 71.2, 56.1, 54.6, 46.5, 42.8, 39.6, 38.0, 36.1, 35.2, 24.8, 23.0, 22.8, 21.5, 9.6 ppm; MS (ESI): *m*/*z*: calcd for $[C_{36}H_{47}ClN_2O_9+H]^+$: 687.3; found: 687.4 $[M+H]^+$; calcd for $[C_{36}H_{47}ClN_2O_9+Na]^+$: 709.3; found: 709.4 $[M+Na]^+$.

Deprotected cyclic depsipeptide 23b (R = CH_2OMe): The procedure is analogous to the one given for **23a**; starting from **22b**. Yield: 52 mg (72%); R_f = 0.29 (EtOAc); $[\alpha]_D^{24}$ (0.48 g/100 mL MeOH): −31.5, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27–7.35 (m, 4H; uA-Ar-*H*), 7.24 (dd, *J* = 7.8, 3.9 Hz, 1H; N*H*), 7.19 (d, *J* = 1.9 Hz, 1H; uB-C$^{2'}$*H*), 7.05 (dd, *J* = 8.4, 1.9 Hz, 1H; uB-C$^{6'}$*H*), 6.83 (d, *J* = 8.5 Hz, 1H; uB-C$^{5'}$*H*), 6.71 (ddd, *J* = 15.0, 10.8, 4.2 Hz, 1H; uA-C$^{\beta}$*H*), 5.97 (d, *J* = 7.7 Hz, 1H; N*H*), 5.72 (d, *J* = 15.2 Hz, 1H; uA-C$^{\alpha}$*H*), 5.06 (ddm, *J* = 10.5, 7.8 Hz, 1H; uA-C$^{\delta}$*H*), 4.87 (dd, *J* = 10.1, 3.4 Hz, 1H; uD-C$^{\alpha}$*H*), 4.72 (ddd, *J* = 7.8, 7.7, 5.2 Hz, 1H; uB-C$^{\alpha}$*H*), 4.56 (d, *J* = 8.5 Hz, 1H; uA-C$^{\eta}$*H*), 4.44 (s, 2H; uA-C$^{4'}CH_2$), 3.86 (s, 3H; uB-C$^{4'}OCH_3$), 3.78 (d, *J* = 8.4 Hz, 1H; uA-C$^{\zeta}$*H*), 3.39 (s, 3H; uA-CH_2OCH_3), 3.35 (dd, *J* = 13.5, 8.1 Hz, 1H; uC-C$^{\beta}H_A$; and m, 2H; O*H*), 3.17 (dd, *J* = 13.5, 3.7 Hz, 1H; uC-C$^{\beta}H_B$), 3.10 (dd, *J* = 14.5, 4.9 Hz, 1H; uB-C$^{\beta}H_A$), 2.95 (dd, *J* = 14.5, 8.2 Hz, 1H; uB-C$^{\beta}H_B$), 2.42 (dm, *J* = 14.3 Hz, 1H; uA-C$^{\gamma}H_A$), 2.22 (ddd, *J* = 14.1, 11.3, 11.3 Hz, 1H; uA-C$^{\gamma}H_B$), 1.81 (ddd, *J* = 14.1, 10.0, 4.8 Hz, 1H; uD-C$^{\beta}H_A$), 1.67 (dm, *J* = 6.6 Hz, 1H; uD-C$^{\gamma}$*H*), 1.41–1.52 (m, 2H; uA-C$^{\varepsilon}$*H* and uD-C$^{\beta}H_B$), 1.23 (s, 3H; uC-C$^{\alpha}CH_3$), 1.17 (s, 3H; uC-C$^{\alpha}CH_3$), 0.98 (d, *J* = 7.0 Hz, 3H; uA-C$^{\varepsilon}CH_3$), 0.94 (d, *J* = 6.6 Hz, 3H; uD-C$^{\delta}H_3$), 0.88 ppm (d, *J* = 6.6 Hz, 3H; uD-C$^{\delta}H_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.6, 170.7, 170.6, 165.5, 154.0, 142.6, 140.1, 138.4, 130.8, 129.8, 128.2, 182.0, 127.0, 124.4, 122.4, 112.3, 76.4, 75.5, 74.7, 74.4, 71.1, 58.3, 56.1, 54.5, 46.5, 42.7, 39.6, 37.9, 36.2, 35.2, 24.8, 23.1, 23.0, 22.8, 21.5, 9.7 ppm; MS (ESI): *m*/*z*: calcd for $[C_{38}H_{51}ClN_2O_{10}+H]^+$: 731.3; found: 730.7 $[M+H]^+$.

Deprotected cyclic depsipeptide 23c (R = CH_2OiPr): The procedure is analogous to the one given for **23a**; starting from **22c**. Yield: 111 mg (100%); R_f = 0.31 (EtOAc); $[\alpha]_D^{24}$ (0.48 g/100 mL, MeOH): −30.2, ^{1}H NMR (600 MHz, CD_3OD): δ = 8.41 (d, *J* = 7.7 Hz, 0.4H; N*H*), 7.75 (dd, *J* = 9.4, 1.2 Hz, 1H; N*H*), 7.32–7.39 (m, 4H; uA-Ar-*H*), 7.27 (d, *J* = 1.6 Hz, 1H; uB-C$^{2'}$*H*), 7.16 (dd, *J* = 8.4, 1.4 Hz, 1H; uB-C$^{6'}$*H*), 6.97 (d, *J* = 8.5 Hz, 1H; uB-C$^{5'}$*H*), 6.68 (ddd, *J* = 15.1, 11.4, 3.6 Hz, 1H; uA-C$^{\beta}$*H*), 5.84 (d, *J* = 15.2 Hz, 1H; uA-C$^{\alpha}$*H*), 5.08 (m, 1H; uA-C$^{\delta}$*H*), 4.91 (dd, *J* = 10.2, 3.2 Hz, 1H; uD-C$^{\alpha}$*H*), 4.55 (d, *J* = 8.5 Hz, 1H; uA-C$^{\eta}$*H*), 4.53 (s, 2H; uA-C$^{4'}CH_2$), 4.49 (dd, *J* = 11.1, 3.6 Hz, 1H; uB-C$^{\alpha}$*H*), 3.84 (s, 3H; uB-C$^{4'}OCH_3$), 3.74 (m, 1H; uA-C*H*$(CH_3)_2$), 3.70 (dm, *J* = 8.4 Hz, 1H; uA-C$^{\zeta}$*H*), 3.46 (dd, *J* = 13.5, 9.8 Hz, 1H; uC-C$^{\beta}H_A$) 3.17 (dd, *J* = 14.5, 3.4 Hz, 1H; uB-C$^{\beta}H_A$), 3.11 (dd, *J* = 13.2, 1.4 Hz, 1H; uC-C$^{\beta}H_B$), 2.74 (dd, *J* = 14.3, 11.6 Hz, 1H; uB-C$^{\beta}H_B$), 2.63 (dm, *J* = 14.3 Hz, 1H; uA-C$^{\gamma}H_A$), 2.12 (ddd, *J* = 14.2, 11.6, 11.6 Hz, 1H; uA-C$^{\gamma}H_B$), 1.83 (ddd, *J* = 14.1, 10.2, 4.7 Hz, 1H; uD-C$^{\beta}H_A$), 1.73 (m, 1H; uD-C$^{\gamma}$*H*), 1.58 (ddd, *J* = 13.9, 9.1, 3.4 Hz, 1H; uD-C$^{\beta}H_B$), 1.46 (m, 1H; uA-C$^{\varepsilon}$*H*), 1.20–1.25 (m, 9H; uA-CH(CH_3)$_2$ and uC-C$^{\alpha}CH_3$), 1.20 (s, 3H; uC-C$^{\alpha}CH_3$), 1.03 (d, *J* = 6.7 Hz, 3H; uD-C$^{\delta}H_3$), 1.00 (d, *J* = 7.1 Hz, 3H; uA-C$^{\varepsilon}CH_3$), 0.98 ppm (d, *J* = 6.5 Hz, 3H; uD-C$^{\delta}H_3$); ^{13}C NMR (151 MHz, CD_3OD): δ = 179.7, 174.6, 172.6, 169.1, 156.2, 145.1, 143.5, 140.9, 133.0, 132.3, 130.1, 129.8, 129.0, 125.8, 124.1, 114.3, 77.9, 77.7, 76.7, 73.6, 73.3, 71.8, 58.4, 57.4, 48.4, 45.0, 41.8, 40.6, 38.5, 37.3, 27.0, 24.33, 24.27, 24.2, 23.4, 23.3, 22.8, 10.6 ppm; HRMS (ESI): *m*/*z*: calcd for $[C_{40}H_{55}ClN_2O_{10}+Na]^+$: 781.34374; found: 781.34490 $[M+Na]^+$, calcd for $[2C_{40}H_{55}ClN_2O_{10}+Na]^+$: 1539.69827; found: 1539.70059 $[2M+Na]^+$.

Deprotected cyclic depsipeptide 23d (R = CH_2OtBu): The procedure is analogous to the one given for **23a**; starting from **22d**. Yield: 116 mg (94%); R_f = 0.33 (EtOAc); $[\alpha]_D^{24}$ (0.97 g/100 mL, MeOH): −30.6, ^{1}H NMR (600 MHz, CD_3OD): δ = 7.29–7.35 (m, 4H; uA-Ar-*H*), 7.25 (d, *J* = 2.1 Hz, 1H; uB-C$^{2'}$*H*), 7.14 (dd, *J* = 8.4, 2.1 Hz, 1H; uB-C$^{6'}$*H*), 6.96 (d, *J* = 8.5 Hz, 1H; uB-C$^{5'}$*H*), 6.66 (ddd, *J* = 15.1, 11.3, 3.8 Hz, 1H; uA-C$^{\beta}$*H*), 5.81 (d, *J* = 15.1, 1.7 Hz, 1H; uA-C$^{\alpha}$*H*), 5.06 (ddd, *J* = 10.9, 9.0, 1.7 Hz,

1H; uA-C$^{\delta}H$), 4.89 (dd, J=8.4, 3.3 Hz, 1H; uD-C$^{\alpha}H$), 4.52 (d, J=8.5 Hz, 1H; uA-C$^{\eta}H$), 4.47 (s, 2H; uA-C$^{4'}CH_2$), 4.45 (ddd, J=7.7, 3.8, 1.5 Hz, 1H; uB-C$^{\alpha}H$), 3.82 (s, 3H; uB-C$^{4'}OCH_3$), 3.67 (dd, J=8.5, 1.5 Hz, 1H; uA-C$^{\zeta}H$), 3.44 (dd, J=13.6, 9.8 Hz, 1H; uC-C$^{\beta}H_A$), 3.15 (dd, J=14.5, 3.6 Hz, 1H; uB-C$^{\beta}H_A$), 3.07 (dd, J=13.6, 2.3 Hz, 1H; uC-C$^{\beta}H_B$), 2.70 (dd, J=14.5, 11.4 Hz, 1H; uB-C$^{\beta}H_B$), 2.60 (ddd, J=14.5, 3.5, 1.7, 1.7 Hz, 1H; uA-C$^{\gamma}H_A$), 2.06 (ddd, J=14.5, 11.4, 11.4 Hz, 1H; uA-C$^{\gamma}H_B$), 1.80 (ddd, J=14.2, 10.3, 4.7 Hz, 1H; uD-C$^{\beta}H_A$), 1.69 (m, 1H; uD-C$^{\gamma}H$), 1.55 (ddd, J=14.1, 9.0, 3.4 Hz, 1H; uD-C$^{\beta}H_B$), 1.41 (ddq, J=7.4, 1.1, 7.1 Hz, 1H; uA-C$^{\varepsilon}H$), 1.29 (s, 9H; uA-C(CH_3)$_3$), 1.20 (s, 3H; uC-C$^{\alpha}CH_3$), 1.15 (s, 3H; uC-C$^{\alpha}CH_3$), 1.00 (d, J=6.7 Hz, 3H; uD-C$^{\delta}H_3$), 0,96 (d, J=7.1 Hz, 3H; uA-C$^{\varepsilon}CH_3$), 0.94 ppm (d, J=6.6 Hz, 3H; uD-C$^{\delta}H_3$); ^{13}C NMR (151 MHz, CD_3OD): δ=179.2, 174.0, 172.1, 168.5, 155.7, 144.6, 142.7, 141.0, 132.4, 131.8, 129.6, 129.2, 128.3, 125.3, 123.5, 113.7, 77.3, 77.2, 76.1, 75.3, 72.7, 65.3, 57.9, 56.9, 47.8, 44.4, 41.2, 40.0, 38.0, 36.7, 28.2, 26.4, 23.8, 23.7, 23.6, 22.2, 10.0 ppm; MS (ESI): m/z: calcd for $[C_{41}H_{57}ClN_2O_{10}+Na]^+$: 795.4; found: 795.5 $[M+Na]^+$.

Cryptophycin-52 (R=H) (1): The deprotected cyclic depsipeptide (R=H) **23a** (20 mg; 0.029 mmol) and pyridinium *p*-toluenesulfonate (PPTS, 6 mg; 0.023 mmol) were dissolved in dry CH_2Cl_2 (1.9 mL) and trimethyl orthoformate (0.6 mL) was added. The reaction mixture was stirred until all the starting material was consumed (HPLC monitoring, about 2 h). Then the reaction mixture was diluted with CH_2Cl_2 (5 mL) and filtered through a pad of silica gel (washing with CH_2Cl_2/EtOAc 1:1, 180 mL). The solvent was removed in vacuum (40 °C) and subsequently in high vacuum. The residue was dissolved in dry CH_2Cl_2 (0.4 mL) and a 0.85 M solution of AcBr in dry CH_2Cl_2 (68 μL; 0.058 mmol; 2 equiv) was added. The reaction was stirred until the starting material was consumed (HPLC monitoring, about 4 h). In the case of incomplete conversion, additional AcBr solution (0.5 equiv) was added. Then the reaction mixture was diluted with dry CH_2Cl_2 (5.0 mL) and the mixture was cooled to below 0 °C and a mixture of saturated aqueous $NaHCO_3$ (1.0 mL) solution and H_2O (1.0 mL) was added. The frozen mixture was melted by warming in cold water, then the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2 (20 mL). All organic layers were immediately combined and dried over Na_2SO_4. The solvent was removed in vacuum (40 °C) and high vacuum. The residue was treated with an emulsion (0.7 mL) of dried K_2CO_3 (829 mg; 6 mmol), dry 1,2-dimethoxyethane (DME; 20 mL) and dry ethylene glycol (10 mL), which was stored over a molecular sieve 3 Å (0.9 g). The reaction mixture was stirred for 3 min at RT. Then the reaction was quenched by addition of a mixture of CH_2Cl_2 (7 mL), H_2O (7 mL) and 5% $KHSO_4$ solution (0.3 mL). The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2 (10 mL). All organic layers were immediately combined and dried over Na_2SO_4. The solvent was removed in vacuum (40 °C) and high vacuum. The residue was immediately purified by flash chromatography on silica gel. Cryptophycin-52 (**1**) was obtained as an amorphous solid (16 mg, 83%). R_f=0.30 (hexane/EtOAc 1:3); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.22–7.44 (m, 5H; uA-Ar-*H*), 7.18 (d, J=1.8 Hz, 1H; uB-C$^{2'}H$), 7.04 (dd, J=8.3, 1.9 Hz, 1H; uB-C$^{6'}H$), 6.84 (d, J=8.3 Hz, 1H; uB-C$^{5'}H$), 6.76 (ddd, J=15.0, 10.7, 4.2 Hz, 1H; uA-C$^{\beta}H$), 5.73 (dm, J=15.1 Hz, 1H; uA-C$^{\alpha}H$), 5.65 (d, J=7.7 Hz, 1H; N*H*), 5.20 (ddd, J=11.0, 4.8, 1.2 Hz, 1H; uA-C$^{\delta}H$), 4.83 (dd, J=10.2, 3.4 Hz, 1H; uD-C$^{\alpha}H$), 4.74 (ddd, J=7.6, 7.4, 5.3 Hz, 1H; uB-C$^{\alpha}H$), 4.29 (s, 1H; N*H*), 3.87 (s, 3H; uB-C$^{4'}OCH_3$), 3.68 (d, J=1.5 Hz, 1H; uA-C$^{\eta}H$), 3.41 (dd, J=13.6, 8.6 Hz, 1H; uC-C$^{\beta}H_A$), 3.07–3.14 (m, 2H; uC-C$^{\beta}H_B$ and uB-C$^{\beta}H_A$), 3.03 (dd, J=14.5, 7.6 Hz, 1H; uB-C$^{\beta}H_B$), 2.92 (dd, J=7.5, 1.8 Hz, 1H; uA-C$^{\zeta}H$), 2.58 (ddd, J=14.5, 1.9, 1.9 Hz, 1H; uA-C$^{\gamma}H_A$), 2.45 (ddd, J=14.4, 11.2, 11.2 Hz, 1H; uA-C$^{\gamma}H_B$), 1.79 (dqm, J=12.5, 6.9 Hz, 1H; uA-C$^{\varepsilon}H$), 1.71 (ddd, J=14.1, 10.3, 4.7 Hz, 1H; uD-C$^{\beta}H_A$), 1.67 (m, 1H; uD-C$^{\gamma}H$), 1.32 (ddd, J=13.6, 9.0, 3.6 Hz, 1H; uD-C$^{\beta}H_B$), 1.22 (s, 3H; uC-C$^{\alpha}CH_3$), 1.16 (s, 3H; uC-C$^{\alpha}CH_3$), 1.14 (d, J=6.9 Hz, 3H; uA-C$^{\varepsilon}CH_3$), 0.84 (d, J=6.5 Hz, 3H; uD-C$^{\delta}H_3$), 0.83 ppm (d, J=6.5 Hz, 3H; uD-C$^{\delta}H_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ=178.0, 170.5, 170.3, 165.0, 154.1, 141.9, 136.8, 130.9, 129.5, 128.7, 128.6, 128.3, 125.6, 124.6, 122.5, 112.3, 75.9, 71.2, 63.1, 59.1, 56.1, 54.4, 46.4, 42.8, 40.7, 39.3, 36.9, 35.3, 24.6, 22.88, 22.86, 22.7, 21.2, 13.6 ppm; MS (ESI): m/z: calcd for $[C_{36}H_{45}ClN_2O_8+H]^+$: 669.3; found: 669.3 $[M+H]^+$; calcd for $[C_{36}H_{45}ClN_2O_8+Na]^+$: 691.3; found: 691.3 $[M+Na]^+$; calcd for $[C_{36}H_{45}ClN_2O_8+Cl]^-$: 703.3; found: 703.4 $[M+Cl]^-$.

***para*-Methoxymethyl-cryptophycin-52 (R=CH$_2$OMe) (24b)**: The procedure is analogous to the one given for **1**; starting from **23b**. Yield: 15 mg (64%); R_f=0.22 (hexane/EtOAc 1:3); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.30–7.37 (m, 2H; uA-Ar-*H*), 7.20–7.25 (m, 3H; uA-Ar-*H* and N*H*), 7.19 (d, J=1.4 Hz, 1H; uB-C$^{2'}H$), 7.05 (dd, J=8.4, 1.7 Hz, 1H; uB-C$^{6'}H$), 6.84 (d, J=8.4 Hz, 1H; uB-C$^{5'}H$), 6.76 (ddd, J=15.0, 10.7, 4.2 Hz, 1H; uA-C$^{\beta}H$), 5.71 (d, J=15.2 Hz, 1H; uA-C$^{\alpha}H$), 5.57 (d, J=7.7 Hz, 1H; N*H*), 5.20 (ddm, J=10.9, 3.7 Hz, 1H; uA-C$^{\delta}H$), 4.83 (dd, J=10.1, 3.3 Hz, 1H; uD-C$^{\alpha}H$), 4.74 (ddd, J=7.4, 7.4, 5.3 Hz, 1H; uB-C$^{\alpha}H$), 4.46 (s, 2H; uA-C$^{4'}CH_2$), 3.87 (s, 3H; uB-C$^{4'}OCH_3$), 3.68 (d, J=1.3 Hz, 1H; uA-C$^{\eta}H$), 3.42 (dd, J=13.6, 8.6 Hz, 1H; uC-C$^{\beta}H_A$), 3.40 (s, 3H; uA-CH$_2$OCH_3), 3.08–3.14 (m, 2H; uC-C$^{\beta}H_B$ and uB-C$^{\beta}H_A$), 3.04 (dd, J=14.5, 7.6 Hz, 1H; uB-C$^{\beta}H_B$), 2.91 (dd, J=7.5, 1.3 Hz, 1H; uA-C$^{\zeta}H$), 2.56 (dm, J=14.5 Hz, 1H; uA-C$^{\gamma}H_A$), 2.44 (ddd, J=14.3, 11.1, 11.1 Hz, 1H; uA-C$^{\gamma}H_B$), 1.78 (dqm, J=12.3, 6.9 Hz, 1H; uA-C$^{\varepsilon}H$), 1.60–1.73 (m, 2H; uD-C$^{\beta}H_A$ and uD-C$^{\gamma}H$), 1.34 (ddd, J=13.5, 9.2, 3.8 Hz, 1H; uD-C$^{\beta}H_B$), 1.22 (s, 3H; uC-C$^{\alpha}CH_3$), 1.16 (s, 3H; uC-C$^{\alpha}CH_3$), 1.14 (d, J=6.9 Hz, 3H; uA-C$^{\varepsilon}CH_3$), 0.86 (d, J=6.6 Hz, 3H; uD-C$^{\delta}H_3$), 0.84 ppm (d, J=6.5 Hz, 3H; uD-C$^{\delta}H_3$); ^{13}C NMR (151 MHz, $CDCl_3$): δ=178.0, 170.5, 170.3, 165.0, 154.1, 141.8, 138.8, 136.2, 130.9, 129.5, 128.3, 128.0, 125.7, 124.7, 122.6, 112.4, 75.9, 74.3, 71.2, 63.1, 58.9, 58.2, 56.2, 54.4, 46.5, 42.8, 40.7, 39.4, 36.9, 35.3, 24.6, 22.9, 22.7, 21.3, 13.6 ppm; HRMS (ESI): m/z: calcd for $[C_{38}H_{49}ClN_2O_9+Na]^+$: 735.30188; found: 735.30320 $[M+Na]^+$.

***para*-Isopropoxymethyl-cryptophycin-52 (R=CH$_2$O*i*Pr) (24c)**: The procedure is analogous to the one given for **1**; starting from **23c**. Yield: 63 mg (78%); R_f=0.35 (hexane/EtOAc 1:3); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.33–7.37 (m, 2H; uA-Ar-*H*), 7.20–7.25 (m, 3H; uA-Ar-*H* and N*H*), 7.19 (d, J=1.5 Hz, 1H; uB-C$^{2'}H$), 7.05 (dd, J=8.4, 1.7 Hz, 1H; uB-C$^{6'}H$), 6.84 (d, J=8.4 Hz, 1H; uB-C$^{5'}H$), 6.75 (ddd, J=15.0, 10.8, 4.2 Hz, 1H; uA-C$^{\beta}H$), 5.71 (d, J=15.2 Hz, 1H; uA-C$^{\alpha}H$), 5.56 (d, J=7.8 Hz, 1H; N*H*), 5.20 (dd, J=10.7, 3.9 Hz, 1H; uA-C$^{\delta}H$), 4.83 (dd, J=10.2, 3.3 Hz, 1H; uD-C$^{\alpha}H$), 4.74 (ddd, J=7.3, 7.3, 5.4 Hz, 1H; uB-C$^{\alpha}H$), 4.51 (s, 2H; uA-C$^{4'}CH_2$), 3.87 (s, 3H; uB-C$^{4'}OCH_3$), 3.65–3.73 (m, 2H; uA-C$^{\eta}H$ and uA-CH(CH_3)$_2$), 3.42 (dd, J=13.5, 8.7 Hz, 1H; uC-C$^{\beta}H_A$), 3.07–3.13 (m, 2H; uC-C$^{\beta}H_B$ and uB-C$^{\beta}H_A$), 3.04 (dd, J=14.5, 7.6 Hz, 1H; uB-C$^{\beta}H_B$), 2.90 (dd, J=7.5, 1.3 Hz, 1H; uA-C$^{\zeta}H$), 2.56 (dm, J=14.5 Hz, 1H; uA-C$^{\gamma}H_A$), 2.44 (ddd, J=14.2, 11.3, 11.2 Hz, 1H; uA-C$^{\gamma}H_B$), 1.77 (dqm, J=12.8, 6.8 Hz, 1H; uA-C$^{\varepsilon}H$), 1.62–1.74 (m, 2H; uD-C$^{\beta}H_A$ and uD-C$^{\gamma}H$), 1.34 (ddd, J=13.5, 9.1, 3.7 Hz, 1H; uD-C$^{\beta}H_B$), 1.21–1.24 (m, 9H; uA-CH(CH_3)$_2$ and uC-C$^{\alpha}CH_3$), 1.16 (s, 3H; uC-C$^{\alpha}CH_3$), 1.14 (d, J=6.8 Hz, 3H; uA-C$^{\varepsilon}CH_3$), 0.86 (d, J=6.6 Hz, 3H; uD-C$^{\delta}H_3$), 0.84 ppm (d, J=6.5 Hz, 3H; uD-C$^{\delta}H_3$); ^{13}C NMR (151 MHz, $CDCl_3$): δ=178.0, 170.5, 170.3, 165.0, 154.1, 141.8, 139.7, 135.9, 130.9, 129.5, 128.3, 127.9, 125.6, 124.7, 122.6, 112.4, 75.9, 71.2, 71.1, 69.6, 63.1, 59.0, 56.1, 54.4, 46.5, 42.8, 40.7, 39.4, 36.9, 35.3, 24.6, 22.9, 22.7, 22.1, 21.3, 13.6 ppm; HRMS (ESI): m/z: calcd for $[C_{40}H_{53}ClN_2O_9+H]^+$: 741.35124; found: 741.35050 $[M+H]^+$; calcd for $[C_{40}H_{53}ClN_2O_9+Na]^+$: 763.33318; found: 763.33159 $[M+Na]^+$.

***para-tert*-Butoxymethyl-cryptophycin-52 (R=CH$_2$O*t*Bu) (24d)**: The procedure is analogous to the one given for **1**; starting from **23d**. Yield: 18.8 mg (64%); R_f=0.34 (hexane/EtOAc 1:3); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.31–7.37 (m, 2H; uA-Ar-*H*), 7.17–7.23 (m, 3H; uA-Ar-*H* and uB-C$^{2'}H$), 7.05 (dm, J=7.9 Hz, 1H; uB-C$^{6'}H$), 6.84 (d, J=8.3 Hz, 1H; uB-C$^{5'}H$), 6.75 (ddd, J=14.4, 10.9, 3.7 Hz, 1H; uA-C$^{\beta}H$), 5.71 (d, J=15.0 Hz, 1H; uA-C$^{\alpha}H$), 5.54 (d, J=7.6 Hz, 1H; N*H*), 5.19 (ddm, J=10.5, 2.9 Hz, 1H; uA-C$^{\delta}H$), 4.83 (dd, J=10.0, 2.8 Hz, 1H; uD-C$^{\alpha}H$), 4.74 (dd, J=12.2, 7.0 Hz, 1H; uB-C$^{\alpha}H$), 4.44 (s, 2H; uA-C$^{4'}CH_2$), 3.87 (s, 3H; uB-C$^{4'}OCH_3$), 3.67 (m, 1H; uA-C$^{\eta}H$), 3.42 (dd, J=13.3, 8.8 Hz, 1H; uC-C$^{\beta}H_A$), 3.07–3.15 (m, 2H; uC-C$^{\beta}H_B$ and uB-C$^{\beta}H_A$), 3.04 (dd, J=14.4, 7.6 Hz, 1H; uB-C$^{\beta}H_B$), 2.89 (dm, J=7.0 Hz, 1H; uA-C$^{\zeta}H$), 2.55 (dm, J=13.9 Hz, 1H; uA-C$^{\gamma}H_A$), 2.44 (ddd, J=13.9, 11.3, 11.3 Hz, 1H; uA-C$^{\gamma}H_B$), 1.62–1.81 (m, 3H; uD-C$^{\beta}H_A$ and uD-C$^{\gamma}H$ and uA-C$^{\varepsilon}H$), 1.30 (s, 9H; uA-C(CH_3)$_3$), 1.27–1.37 (m, 1H; uD-C$^{\beta}H_B$), 1.22 (s, 3H; uC-C$^{\alpha}CH_3$), 1.16 (s, 3H; uC-C$^{\alpha}CH_3$), 1.14 (d, J=6.7 Hz, 3H; uA-C$^{\varepsilon}CH_3$), 0.86 (d, J=6.3 Hz, 3H; uD-C$^{\delta}H_3$), 0.84 ppm (d, J=6.3 Hz, 3H; uD-C$^{\delta}H_3$); ^{13}C NMR (151 MHz, $CDCl_3$): δ=178.0, 170.5, 170.3, 164.9, 154.1, 141.8, 140.4, 135.6, 130.9, 129.5, 128.3, 127.8, 125.5, 124.7, 122.5, 112.3, 75.9, 73.6, 71.2, 63.8, 63.2, 59.1, 56.1, 54.4, 46.4, 42.7, 40.7, 39.4, 37.0, 35.3, 27.7, 24.6, 22.9,

22.8, 22.7, 21.3, 13.7 ppm; HRMS (ESI): *m/z*: calcd for $[C_{41}H_{55}ClN_2O_9+Na]^+$: 777.34994; found: 777.34762 $[M+Na]^+$.

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Asymmetric Synthesis

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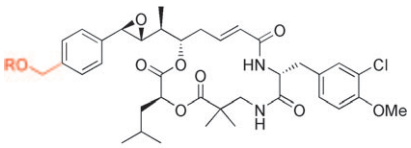
Efficient Synthesis of Cryptophycin-52 and Novel *para*-Alkoxymethyl Unit A Analogues



para-alkoxymethyl cryptophycin-52 analogues
R = Me, *i*Pr, *t*Bu

Taking a new route: Cryptophycin-52 and three new *para*-alkoxymethyl analogues (see scheme) were synthesized using an atom-economic ring-closing metathesis approach. The highly stereoselective synthesis of unit A was achieved in only six steps with 45% overall yield, which represents the shortest and most versatile route to a unit A precursor known to date.

