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Abstract: Bengamide E is a bioactive natural product that was isolated from Jaspidae sponges by Crews and co-workers in 1989. It displays a wide range of biological activities, including antitumor, antibiotic, and anthelmintic properties. With the aim of investigating the structural feature essential for their activity, several total syntheses of Bengamide E and its analogues have been reported in the literature. Nevertheless, no synthesis of the stereoisomer with modification of its configuration at C-4 carbon has been reported so far. Here, we report the first total synthesis of the 4-*epi*-Bengamide E. Key reactions in the synthesis include a chemoenzimatic desymmetrization of biobased starting materials and a diastereoselective Passerini reaction using a chiral, enantiomerically pure aldehyde, and a lysine-derived novel isocyanide.

Keywords: biocatalysis; multicomponent reactions; natural products; total synthesis

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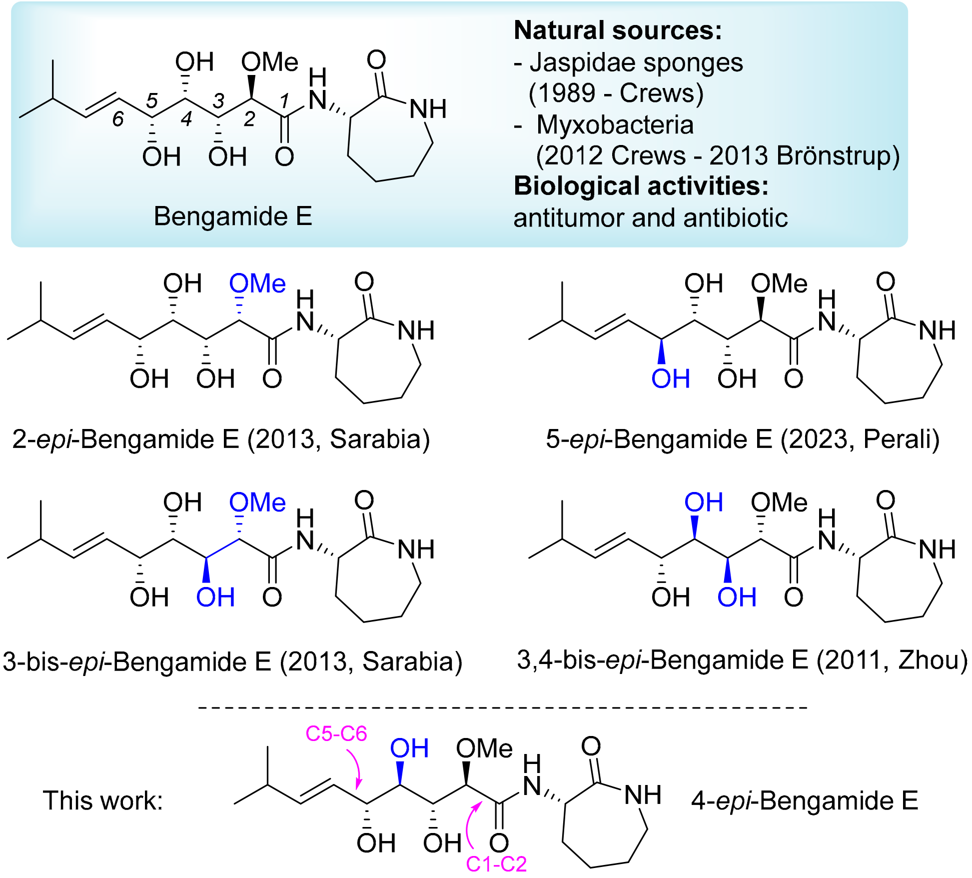
1. Introduction

Bengamides are a vast family of natural products of marine origin isolated by Crews and coworkers [1,2] in the late 1980s from an undescribed specimen of an orange sponge belonging to the Jaspidae family. Although a long time has passed since the discovery, their unique structures continue to attract huge interest of the synthetic community thanks to their prominent anticancer activity in humans [3,4]. For example, they can act as methionine aminopeptidase (MetAp1 and MetAp2) [5] and nuclear factor κB (NF-κB) [6] inhibitors. More recently, some members of bengamides have been isolated from terrestrial myxobacteria Myxococcus virescens by Crews [6] and Brönstrup [7].

Among the 21 different bengamides isolated from marine sponge and myxobacteria, Bengamide E consists of a carbon chain containing four contiguous stereocenters, a double bond with E configuration, and a secondary amide which binds an aminocaprolactamic unit (Scheme 1, top). Due to their interesting pharmacological applications, several total syntheses of Bengamide E and its analogues have been reported in the literature [8–27], and their cytotoxicity has been evaluated, showing the structural features that are essential for their activity. In 2013, Sarabia and coworkers published the total synthesis of 2-*epi* and 2,3-bis-*epi*-Bengamide E [25], while Zhou et al. reported the synthesis of the 3,4-bis-*epi*-Bengamide E [14]. All these stereochemical changes resulted in a complete loss of antitumor activity (Scheme 1, bottom). Very recently, the total synthesis of 5-*epi*-Bengamide E has been reported by Perali and coworkers, but the biological evaluation is still under investigation [28].

To our knowledge, no synthesis of the stereoisomer of Bengamide E with modification of chirality at C-4 carbon has been reported so far. In this paper, we present a new stereoselective approach to the unprecedent 4-*epi*-Bengamide E. Contrary to the previous syntheses, which were all target-oriented, we tried to develop a highly convergent, multicomponent reaction (MCR)-based approach to this structure, which may allow the easy introduction of diverse sidechains and the exploration of stereochemical diversity. As a first example, we will describe here the synthesis of an unprecedented isomer of natural Bengamide E.

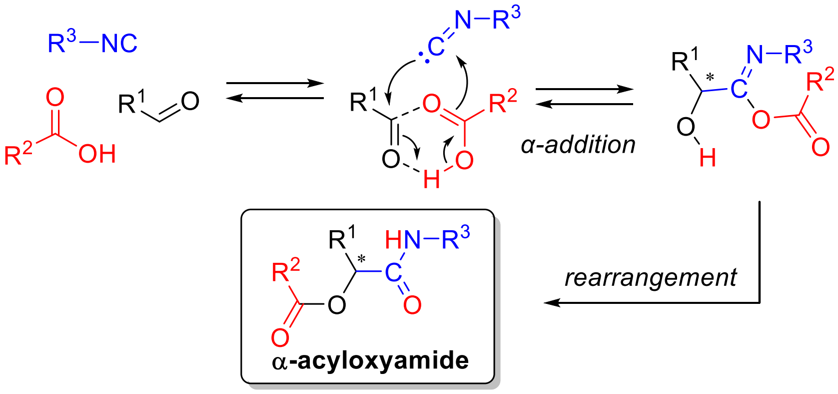


Scheme 1. Structures of natural Bengamide E and synthetic stereoisomers reported in the literature; 2-*epi* and 2,3-bis-*epi*-Bengamide E [25]; 3,4-bis-*epi*-Bengamide E [28]; 5-*epi*-Bengamide E [14].

The key step in our synthetic plan is a diastereoselective Passerini reaction using a chiral, enantiomerically pure aldehyde. The Passerini three-component reaction [29] involves an isocyanide, an aldehyde (or a ketone), and a carboxylic acid to produce an α-acyloxyamide (Scheme 2). It has recently emerged as a powerful method for the preparation of natural products and APIs [29–32], thanks to the advantages that multicomponent reactions in general possess, such as atom and step economy and experimental simplicity.

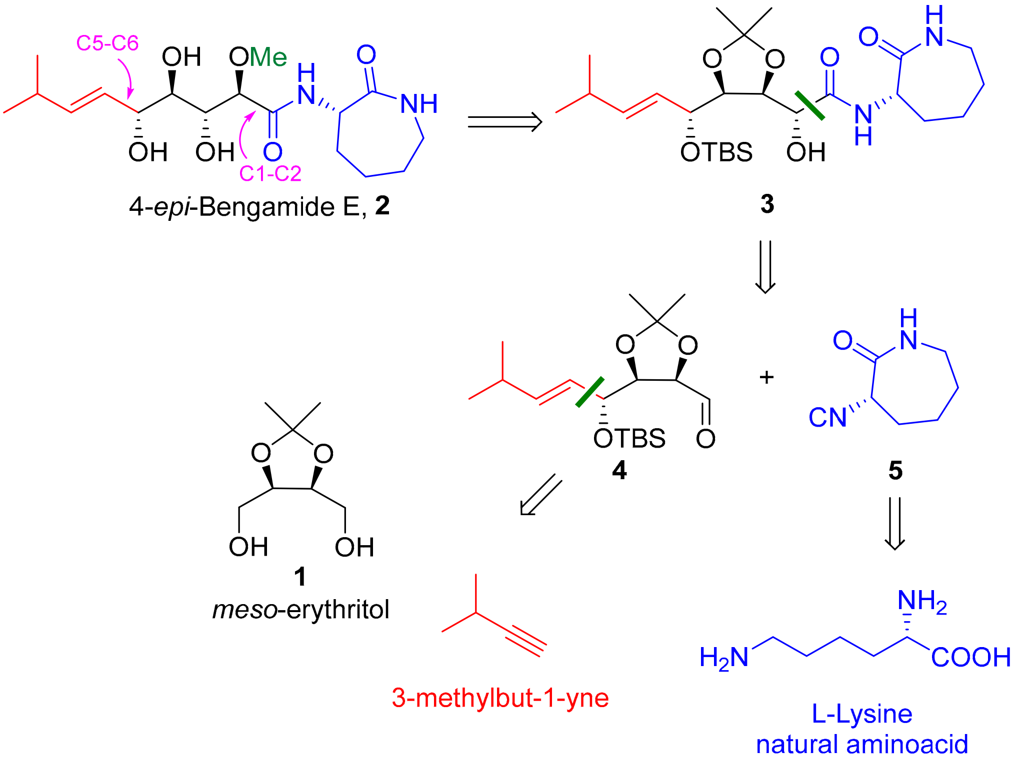
The main benefits of this strategy are (i) sustainability, thanks to the cooperation of multicomponent reactions with biocatalysis and/or with the use of renewable starting materials derived from biomass; (ii) the flexibility and convergence of the approach, which can allow the preparation of several analogs in a short and efficient manner.

In recent years, we have been particularly interested in the use of enantiopure chiral building blocks, synthesized using the chemoenzimatic treatment of biobased starting materials, and their use in diastereoselective Passerini reactions [33]. Actually, when aldehydes different from formaldehyde or unsymmetric ketones are used, this reaction generates a new stereogenic center, generally with poor diastereoselectivity. In this context, we have developed the diversity-oriented synthesis of chiral polysubstituted O- and N-heterocycles employing erythritol as the starting material [34–36].



Scheme 2. The Passerini reaction and its mechanism; * = new stereogenic centre.

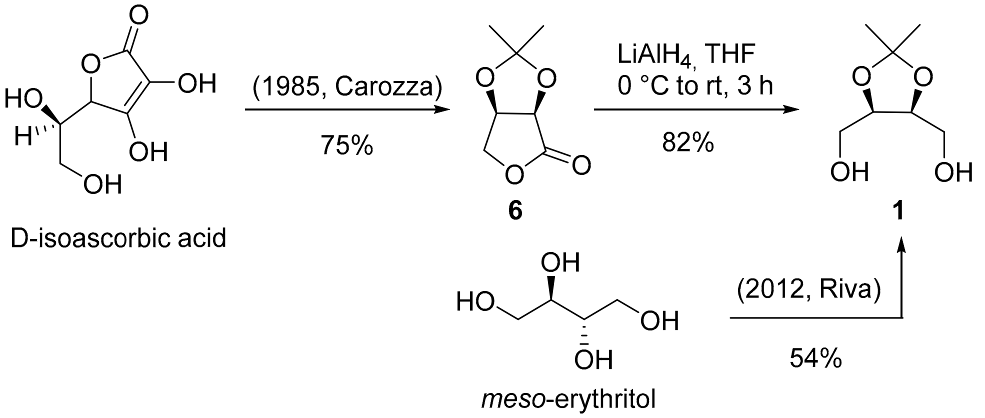
Herein, we present a different elaboration of *meso*-erythritol **1**, using it as a valuable biobased building block for the total synthesis of 4-*epi*-Bengamide E **2**. The convergent retrosynthetic strategy is depicted in Scheme 3 and stems from two key disconnections through the C1-C2 and C5-C6 bonds of the carbon chain. We envisioned constructing **2** through methylation and subsequent full deprotection of the advanced intermediate **3**, whose synthesis involves a diastereoselective Passerini reaction of chiral aldehyde **4** with chiral isocyanide **5** and acetic acid, followed by acetate hydrolysis. Enantiopure isocyanide **5** can be conveniently obtained starting from chiral pool compounds (L-lysine), while, for aldehyde **4**, a stepwise synthesis involving the chemoenzimatic desymmetrization of *meso*-diol **1** and the reaction with lithium acetylide of 3-methylbutyne was planned.



Scheme 3. Retrosynthetic analysis of 4-*epi*-Bengamide E, **2**.

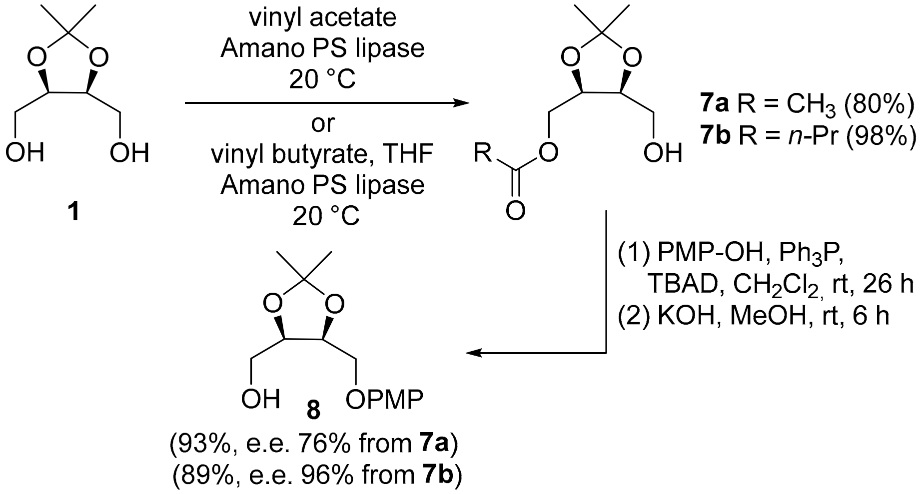
2. Results and Discussion

We first studied the enantioselective preparation of aldehyde **4** starting from *meso*-diol **1**, which can be conveniently obtained employing biobased materials (Scheme 4). As reported by us [36] and others [37], *meso*-erythritol can be converted in three straightforward steps in compound **1**. Alternatively, during this project, we found that the desired compound **1** could also be prepared starting from D-isoascorbic acid, the C-5 epimer of L-ascorbic acid, an important renewable materials produced through the microbial process from sugars [38]. Based on a procedure reported in the literature [39], D-isoascorbic acid was oxidized in the presence of hydrogen peroxide and subsequently protected as acetonide, affording lactone **6** high yield (75%), which was then reduced with $LiAlH_4$, giving **1** without need of further chromatographic purifications. Considering the operational simplicity, the greenness and cheapness of the starting material and reagents and the higher yield, this approach was found to be more sustainable and convenient.



Scheme 4. Synthesis of *meso*-diol **1** starting from renewable feedstocks; synthesis of **6** from D-isoascorbic acid [39]; synthesis of **1** from *meso*-erythritol [36].

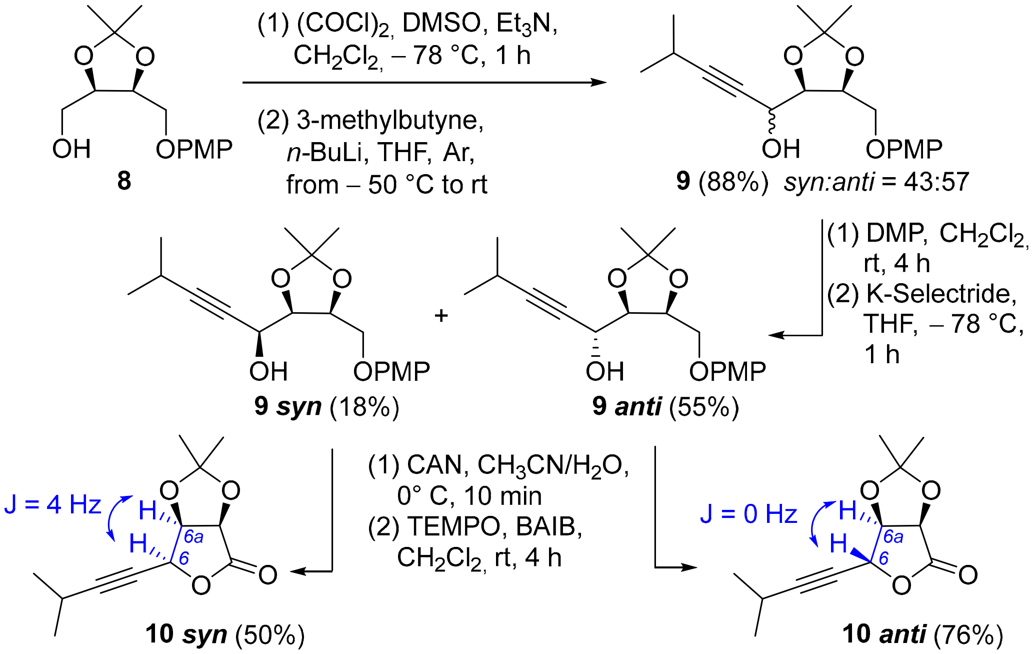
For the synthesis of alcohol **8**, bearing the appropriate protecting group, we initially used the enzymatic monoacetylation of diol **1** using vinyl acetate as the solvent, as previously reported by us [36], followed by a Mitsunobu reaction with *p*-methoxyphenol and a subsequent hydrolysis of the ester moiety under basic conditions (Scheme 5). The change in the protecting group is necessary, not only to obtain the desired enantiomer, but mainly because of the instability of the acyl group in the subsequent reactions, as demonstrated by previous studies in our lab (other protecting groups such as TBS or TBDPS resulted in instability during the following reduction of the triple bond).



Scheme 5. Chemoenzymatic synthesis of chiral alcohol **8**.

Thus, after careful evaluation, *p*-methoxyphenyl (PMP) was chosen as the protecting group, since it involves orthogonal cleavage conditions (reaction with ammonium cerium (IV) nitrate) with respect to the other protecting groups planned for the synthesis (acetonide and *t*-butyl-dimethyl-silyl (TBS) group are removed under acidic conditions). Unfortunately, chiral HPLC analysis of **8** revealed a low enantiomeric excess, probably due to a partial migration of the acetyl group when compound **7a** was reacted under the Mitsunobu conditions (see Figures S2 and S3 in the Supporting Information). After several unsuccessful attempts to find **8,** avoiding the Mitsunobu reaction (see Table S2 in the Supporting Information), we successfully solved this problem by performing the enzymatic desymmetrization with the more steric hindered vinyl butyrate. The enzymatic acylation was performed following the procedure reported in the literature [36], allowing us to isolate the monoacylated compound **7b** in excellent yield (98%). A mitsunobu reaction was carried out at room temperature in the presence of *p*-methoxyphenol (PMP-OH), triphenylphosphine, and di-*tert*-butyl azodicarboxylate (TBAD) and the crude residue was directly subjected to the next reaction with potassium hydroxide in MeOH to remove the acyl group. In this way, product **8** was obtained with a high yield (89%), even on a large scale (about 5 g), and the enantiomeric excess (96%) was completely retained. It is worth noting that the enantiomer of **7b** is easily available as well through enzymatic hydrolysis of the corresponding diacylated derivative [36].

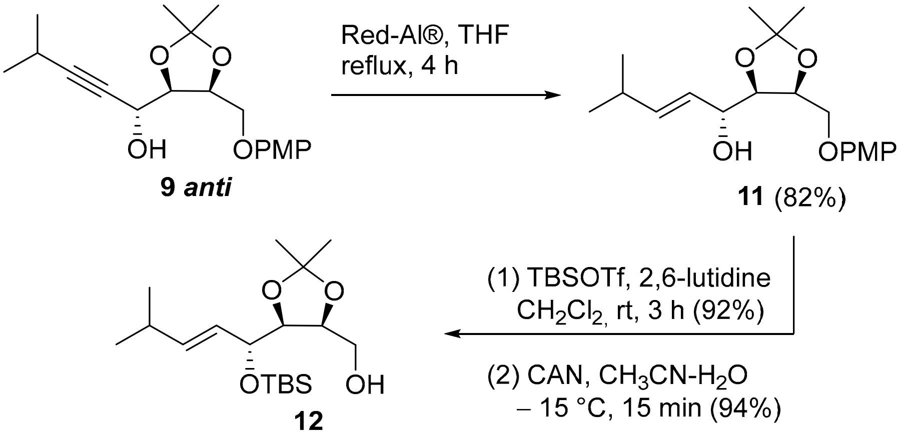
Alcohol **8** was then converted to the corresponding aldehyde using Swern oxidation. Initial attempts to directly introduce the olefinic residue, using organolithium or Grignard reagents did not lead to good results, due to the difficult preparation of the needed alkenyl reagents. Therefore, we decided to explore the nucleophilic addition of an acetylide instead (Scheme 6). This strategy leads to the formation of a propargyl alcohol, which can be selectively reduced to the *E*-allylic alcohol through treatment with aluminum hydrides, such as $LiAlH_4$ or Red-Al® [40–42]. This method presents two advantages: acetylides can be easily obtained from the corresponding terminal alkynes through a metalation reaction (lithium–hydrogen exchange), and, furthermore, many alkynes are commercially available, making the synthesis of a diversity-oriented library of analogs easier.



Scheme 6. Synthesis of chiral alcohols **9** and determination of the relative configuration of C-4.

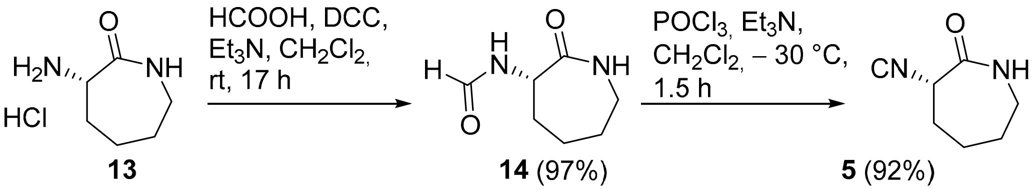
So, the addition of the lithium acetylide generated using treatment of the commercially available 1-methylbutyne with *n*-BuLi in THF, provided a mixture of separable diastereoisomers **9** with an excellent yield, but without any stereochemical induction. Therefore, in order to increase the d.r., we converted the mixture into the corresponding propargyl ketone via Dess–Martin Periodinane (DMP) oxidation followed by diastereoselective reduction with K-selectride at a low temperature to form the corresponding alcohols **9** as a 24:76 separable mixture of diastereomers, in which **9 *anti*** was the major product (55% isolated yield) [43]. The relative configuration of compounds **9** was determined with chemical conversion into the corresponding lactones **10** with treatment with cerium(IV) ammonium nitrate (CAN) to deprotect the PMP group and subsequent TEMPO/BAIB oxidation (Scheme 6). Since lactones **10** are rather rigid compounds, the examination of the J coupling relationship between H6 and H6a in the ^{1}H-NMR spectra allowed us to establish the relative configuration of the C-4 center: the *anti*-isomer shows a $J_{H6,H6a}$ around 0 Hz according to a dihedral angle close to 90°, while the $J_{H6,H6a}$ for the *syn*-isomer result are ~4 Hz. The detailed NMR studies are described in the Supporting Information.

Then, the allyl alcohol **11** was prepared using hydroalumination with sodium bis-(2-methoxyethoxy)-aluminumhydride (RED-Al®) on the single isomer **9 *anti*** (Scheme 7) [42,44,45]. The preliminary results obtained were not satisfactory, because of the presence of unreacted starting material, ending up with an only moderate yield (67% after 17 h). On the other hand, when the reaction was performed at reflux rather than at room temperature [46], the allylic alcohol **11** was isolated in excellent yield (82%) (Scheme 7). Finally, the secondary hydroxy group was protected as *tert*-butyldimethylsilyl (TBS) and the PMP residue was removed in order to obtain the key intermediate **12**, which was a useful precursor for the next step. As previously said, the choice of these two protecting groups was due to their orthogonal behavior. While the protection with TBS afforded the desired product in excellent yield under typical conditions [47,48], the subsequent PMP cleavage result was troublesome. Although the orthogonal PMP group removal in the presence of TBS ethers using CAN has already been reported in the literature [49–51], in this case, the acidic environment evidently promotes the concomitant removal of the silyl group. For this reason, the reaction must take place in a very short time, about 10–15 min, and it is extremely important to promptly quench it to avoid the formation of unprotected diol.



Scheme 7. Synthesis of chiral alcohol **12**.

With the key intermediate **12** in hand, we turned our attention to the synthesis of isocyanide **5** (Scheme 8).

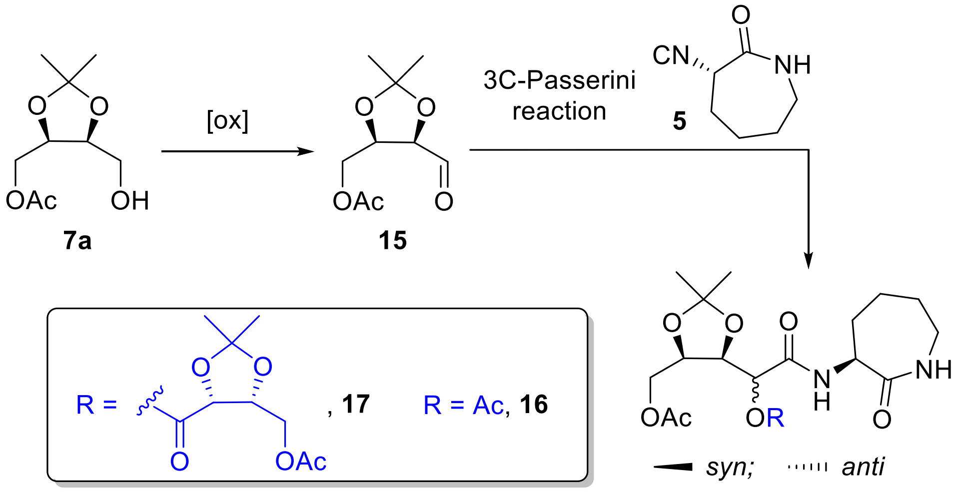


Scheme 8. Synthesis of isocyanide **5**.

Starting from commercially available L-(-)-α-amino-ε-caprolactam **13**, the formamide **14** was prepared through coupling with formic acid, in the presence of dicyclohexylcarbodiimide (DCC) and Et_3N. Since **14** presents high solubility in water, it must be isolated with filtration on celite to separate diclyclohexylurea, avoiding a difficult aqueous work up, and subsequent column chromatography. Then, the dehydration reaction was carried out to obtain the desired isocyanide. After careful optimization, $POCl_3$ was selected as the best dehydrating agent for the reaction, affording product **5** an excellent yield. Although the stereoconservative preparation of chiral α-isocyano amides from the corresponding formamides is less problematic than that of the corresponding esters [52], the use of an organic base such as Et_3N might lead to some epimerization. For this reason, we have checked the enantiopurity of isocyanide **5** both using chiral HPLC analysis and by employing it in a Passerini reaction with model compounds, demonstrating a substantial retention of e.e. (see Figures S7–S9 in the Supporting Information).

Since chiral isocyanide **5** has never been reported in the literature and used in a multicomponent reaction, we initially planned to check its reactivity in a Passerini reaction with the enantiopure alcohol **7a** as a simplified model compound. Thus, we investigated the oxidation of **7a** into the corresponding aldehyde **15** and the subsequent Passerini reaction between **15**, **5,** and acetic acid (Table 1).

Table 1. Investigation of the Passerini reaction between isocyanide **5**, acetic acid, and the model aldehyde **15**, obtained with oxidation of alcohol **7a**.



Entry	Reaction Conditions [a]	16 *syn*/16 *anti* [e]	Yield of 16 [f]	Yield of 17 [f]
1 [b]	TEMPO (0.2 equiv), BAIB (1.1 equiv), CH_2Cl_2, rt, 4 h; then **5**, rt, o.n.	19:81	54%	16%
2 [b]	TEMPO (0.2 equiv), BAIB (1.1 equiv), CH_2Cl_2, rt, 4 h; then **5**, $ZnBr_2$ (0.4 equiv), rt, 3 h	--	-- [d]	--
3 [c]	DMSO (2.5 equiv), $(COCl)_2$ (2.1 equiv), Et_3N (4.7 equiv), CH_2Cl_2, −78 °C, 1 h; then **5**, AcOH (1.1 equiv), rt, 7 h	20:80	69%	--
4 [c]	DMSO (2.5 equiv), $(COCl)_2$ (2.1 equiv), Et_3N (4.7 equiv), CH_2Cl_2, −78 °C, 1 h; then **5**, $Zn(OAc)_2$ (1.1 equiv), rt, 7 h	19:81	36%	--

[a] The two-step synthesis was carried out using alcohol **7a** (1 equiv) and isocyanide **5** (1.1 equiv) following different methods; [b] the synthetic procedure was carried out in one-pot manner without isolation of the aldehyde; [c] after Swern oxidation, the reaction mixture was worked up using liquid–liquid extraction, and the crude aldehyde directly used in the Passerini reaction; [d] no products were obtained due to substrates degradation; [e] d.r. calculated using HPLC-UV analysis of purified **16**; [f] isolated yield of **16** (***anti***+***syn***) or **17** (***anti***+***syn***) after column chromatography.

Initially, following our previous work on *meso*-erythritol derivatives [34], we used a one-pot protocol, in which **7a** was oxidized with catalytic TEMPO and stoichiometric $PhI(OAc)_2$ and subsequently treated with isocyanide **5**. In this one-pot process, the acetic acid is generated in situ as a by-product of $PhI(OAc)_2$ decomposition. Isocyanide **5** proved to be poorly reactive, affording product **16** in moderate yield, even with good diastereoselectivity, with **16** ***anti*** prevailing (entry 1, Table 1). Furthermore, a certain amount of formamide **14** has been isolated, demonstrating the tendency of **5** to hydrate.

Based on our previous experience with a diastereoselective Passerini reaction employing biobased-derived aldehydes [34,35], we repeated the reaction in the presence of a substechiometric amount of $ZnBr_2$, which proved to be very efficient in increasing d.r. in similar reactions (entry 2, Table 1). Unfortunately, in this case, the addition of the Lewis acid led to complete degradation of the substrates. Moreover, we noted the formation of the side-products **17**, where the carboxylic acid originated by the overoxidation of aldehyde **15**, reacted instead of acetic acid in the multicomponent reaction.The easy overoxidation of such *meso*-erythritol-derived compounds strongly affects the yield and makes the purification of the desired products extremely difficult.

For these reasons, we decided to perform the oxidation of **7a** under Swern conditions (entry 3, Table 1), which completely suppresses overoxidation. After a work-up under slightly acidic conditions, aldehyde **15** was used as such, avoiding chromatography, because of its known instability over silica gel. When **15**, **5,** and acetic acid were submitted to a traditional Passerini reaction, we isolated **16** with a good (69%) overall yield and diastereomeric ratio (*syn*/*anti* 20:80).

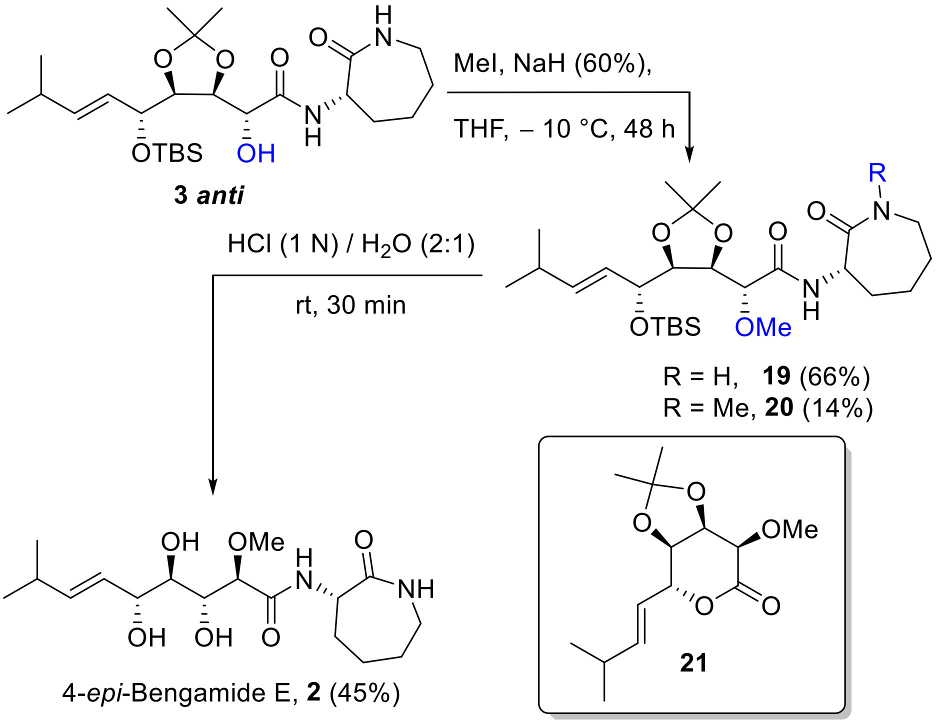
With the aim to improve the d.r., we tried the modified Passerini reaction using zinc dicarboxylates. Employing $Zn(OAc)_2$, the yield diminished considerably without any improvement in d.r. (entry 4, Table 1).

In view of these results, we selected the two-step protocol involving Swern oxidation for further studies with aldehyde **4** (Table 2).

Since the poor reactivity of **5** and its tendency to rehydrate during the long reaction time, we initially carried out the Passerini reaction with the consecutive addition of small aliquots of **5** (entry 1, Table 2), or using slow addition through a syringe pump (entry 2, Table 2). In both cases, the yields were not satisfactory, even if excellent d.r.ss were detected. However, the careful HPLC-UV analysis of the products obtained revealed the presence of a mixture of so-called 'truncated Passerini products' **3**, although they were formed in small amounts (5–10%). Since compounds **3** are the desired products of the next step, their formation should not be a problem. Nevertheless, the presence of **3** posed major difficulty in the analysis of the reaction outcome and purification of the products, making the d.r. values erratic. This suggested we should perform Swern oxidation, a Passerini reaction, and deacetylation in a sequential process, isolating directly deacetylated Passerini products **3**. In this way, the d.r.ss were determined through HPLC-UV analysis of compounds **3** after the tree steps (entries 3–8, Table 2). A series of solvent screening experiments was then performed. While the solvent seems not to affect the diastereoselection (entries 3–5, Table 2), a remarkable increase in the yield was obtained using $i\mathrm{Pr}_2\mathrm{O}$ (entry 4) instead of CH_2Cl_2 (entry 3) or THF (entry 5). These good results prompted us to investigate the effect of the Lewis acid additive, but again without any advantage (entries 6–8, Table 2). In conclusion, key intermediate **3** was obtained with a satisfactory yield over three steps (72%) and good stereoselectivity, employing iPr_2O as a solvent in the Passerini reaction and without any additive.

The selective O-methylation of **3** ***anti*** was particularly troublesome, due to the concomitant N-alkylation of the caprolactam unit. Careful optimization needed to be carried out, and the best conditions turned out to be MeI as the alkylating agent and a slight excess of NaH as the base at −10 °C in THF. Under these conditions, we were able to isolate the desired compound **19** in a 66% yield, together with **20**, where the O- and N-methylations had occurred (Scheme 9). It is noteworthy that the chemical elaboration of compound **20** would lead to the epimer of Bengamide F, another member of the bengamide family.

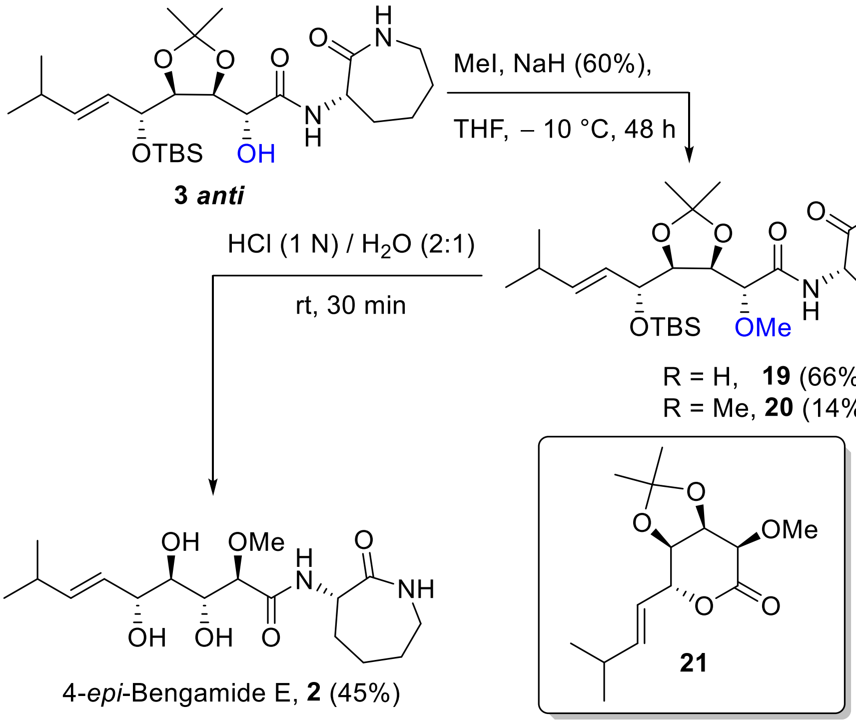
Table 2. Investigation of the Passerini reaction between isocyanide **5**, acetic acid, and aldehyde **4**.



Entry	Solvent [a]	Additive [b]	Yield of 18 [c] (*syn*/*anti*) [d]	Yield of 3 [c] (*syn*/*anti*) [d]
1 [e]	CH_2Cl_2	--	39% (9:91)	
2 [f]	CH_2Cl_2	--	41% (13:87)	
3	CH_2Cl_2	--		52% (23:77)
4	*i*Pr_2O	--		74% (20:80)
5	THF	--		63% (23:77)
6	*i*Pr_2O	$ZnBr_2$		19% (18:82)
7 [g]	*i*Pr_2O	$ZnBr_2$		14% (20:80)
8	THF	$ZnBr_2$		20% (33:67)

[a] Conditions for Passerini reaction: **4** (1 equiv), **5** (2 equiv), AcOH (2 equiv), solvent (0.2 M), rt, 20 h; [b] additive for the Passerini reaction: $ZnBr_2$ (0.4 equiv); [c] isolated yield of **18** (***anti***+***syn***) or **3** (***anti***+***syn***) after column chromatography; [d] d.r. calculated using HPLC-UV analysis of purified **18** or **3**; [e] isocyanide **5** and AcOH were added in three rates (0.6 + 0.6 + 0.8 equiv) every 6 h; [f] isocyanide **5** in CH_2Cl_2 was slowly added (1 h) to the reaction mixture using a syringe pump; [g] aldehyde **4** and AcOH in iPr_2O were slowly added (1 h) to the reaction mixture using a syringe pump.

For the conversion of **19** to 4-*epi*-Bengamide **2**, many acid catalyzing deprotection methods were evaluated. While the use of a mixture of TFA/THF/water [36] resulted in complete decomposition, the stepwise removal of the TBS group with TBAF, and the subsequent reaction with AcOH (70% aqueous solution) [24,26], furnished **2**, even produced a very poor yield (6%). Actually, lactone **21** was isolated as a major compound (Scheme 9, box). The formation of this product is probably due to the spatial proximity between the OH in position five and the amide carbonyl group, which favors intramolecular attack, expelling the amino-caprolactam unit. Finally, the aqueous HCl (1 N) and THF (2:1) [53] mixture gave the best results, providing **2** with a 45% isolated yield (Scheme 9).



Scheme 9. Regioselective methylation of compound **3** ***anti*** and the final deprotection.

3. Materials and Methods

^{1}H and ^{13}C NMR spectra were recorded with a Varian Mercury 300 (at 300 MHz, and 75 MHz, respectively) or a JEOL 400 (at 400 MHz and 101 MHz, respectively).

Unless otherwise stated, NMR spectra were recorded using residual solvent as the internal standard ^{1}H NMR: TMS = 0.00; $(CD_3)_2SO$ = 2.50; and ^{13}C NMR: $CDCl_3$ = 77.16; $(CD_3)_2SO$ = 39.52. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), integration, multiplicity, and coupling constants (Hz). Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ ppm). Interpretation of spectra has been made also with the aid of gCOSY, gHSQC, and gHMBC experiments. The following abbreviations are used to indicate the multiplicity in NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

IR spectra were recorded directly on solid, oil, or foamy samples, with the ATR (attenuated total reflectance) technique, using a FT Perkin Elmer Spectrum 65 spectrophotometer. TLC analyses were carried out on silica gel plates, viewed at UV (ν = 254 nm) and developed with Hanessian stain (dipping into a solution of $(NH_4)4MoO_4 \cdot 4H_2O$ (21 g) and $Ce(SO_4)_2 \cdot 4H_2O$ (1 g) in H_2SO_4 (31 mL) and H_2O (469 mL) and warming. Rf values were measured after an elution of 7–9 cm. Chiral HPLC analyses for the determination of enantiomeric excess were performed on a Daicel Chiral Pak AD 250 × 4.6 mm column, at 25–26 °C with a flow of about 0.8 mL/min (UV detection at ν = 220 nm). HPLC-MS analyses were performed on Synergi Hydro RP 150 × 3 mm column, at 30 °C with a flow of 0.5 mL/min (where not otherwise stated). For MS, the ESI+ ionization method was used. HPLC-UV analyses were carried out on a HP-1100 system (Agilent, Santa Clara, CA, USA) equipped with (a) a HYDRO RP column (150 × 3 mm, 4 μ) at 25 °C with flow = 0.5 mL/min and isocratic elution (CH_3CN/H_2O 50:50). Detection was conducted with UV at 220 nm; (b) a C6 PHENYLIC RP column (150 × 3 mm, 3 μ) at 25 °C with flow = 0.38 mL/min and gradient H_2O/CH_3CN, A = CH_3CN—B = H_2O, 0 min B = 70%, 20 min B = 0%. HRMS: samples, provided at 10 mM in DMSO, were diluted at 50 μM with acetonitrile/water 1:1, and analyzed on a UPLC Acquity system coupled to a Synapt G2 QToF mass spectrometer. MS signals were acquired from 50 to 1200 *m*/*z* ESI positive ionization mode. UPLC was carried out with H_2O–CH_3CN–HCO_2H with an Acquity UPLC BEH C18, 1.7 μM, 2.1 × 50 mm column at 45 °C. Column chromatography was performed with the "flash" methodology using 220–400 mesh silica. Melting points were determined with an electrothermal apparatus (Büchi B-535). Petroleum ether (40–60 °C) is abbreviated as PE. All reactions employing dry solvents were carried out under a nitrogen atmosphere. After extractions, the aqueous phases were always re-extracted three times with the appropriate organic solvent, and the organic extracts were always dried over Na_2SO_4 and filtered before evaporation to dryness.

((4R,5S)-5-((4-methoxyphenoxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol 8: from **7a**: To a solution of **7a** (110 mg, 0.50 mmol), triphenylphosphine (193 mg, 0.73 mmol) and *p*-methoxyphenol (182 mg, 1.50 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was added to *tert*-butyl azodicarboxylate (175 mg, 0.74 mmol). The mixture was stirred at room temperature for 37 h. Then, the reaction mixture was concentrated and filtered through a short column of silica gel with PE/CH_2Cl_2/Et_2O (1:1:1). The residue was directly diluted with MeOH (2 mL) and treated with KOH (0.80 mL, 6 M in MeOH). The reaction mixture was stirred at room temperature for 6 h, then diluted with saturated NH_4Cl aq, extracted with Et_2O, dried (Na_2SO_4), and concentrated. The crude residue was eluted from a column of silica gel with PE/AcOEt 3:1 to give **8** (152 mg, 93%, e.e. 76%) as a colorless oil.

From **7b**: To a solution of **7b** (4.71 g, 21.57 mmol), triphenylphosphine (8.49 g, 32.35 mmol) and *p*-methoxyphenol (8.03 g, 64.70 mmol) in dry CH_2Cl_2 (215 mL) at 0 °C was added to *tert*-butyl azodicarboxylate (7.45 g, 32.36 mmol). The mixture was stirred at room temperature for 37 h. Then, the reaction mixture was concentrated and filtered through a short column of silica gel with PE/CH_2Cl_2/Et_2O (1:1:1). The residue was directly diluted with MeOH (108 mL) and treated with KOH (32 mL, 1 M in MeOH). The reaction mixture was stirred at room temperature for 6 h, then diluted with saturated NH_4Cl aq, extracted with Et_2O, dried (Na_2SO_4), and concentrated. The crude residue was eluted from a column of silica gel with PE/AcOEt (from 2:1 to 1:1) to give **8** (5.16 g, 89%, e.e. 95%) as a colorless oil. The enantiomeric excess was determined using HPLC on a chiral stationary phase. Conditions: column Daicel Chiral Pak AD (250 × 4.6 mm); detector DAD (220 nm); flow 0.8 mL min^{-1}. Isocratic elution with *n*-hexane/isopropanol 90: 10. Temperature: 25 °C. Rt 14.3 min. (4R,5S) and 17.0 min (4S,5R). R_f = 0.27 (PE/AcOEt 2:1); $[\alpha]_D^{20} = +8.2$ (*c* 1.0, $CHCl_3$); m.p. 52.3–54.2 °C (CH_2Cl_2); IR (ATR): ν = 3519, 3058, 2988, 2938, 2887, 2836, 1509, 1460, 1374, 1335, 1289, 1216, 1182, 1164, 1111, 1089, 1050, 1035, 996, 907, 845, 830, 818, 803, 751, 715, 650 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.91–6.78 (m, 4H, aromatic H), 4.55 (q, *J* = 6.3 Hz, 1H, $\underline{CH}$-CH_2OPMP), 4.40 (q, *J* = 6.3 Hz, 1H, $\underline{CH}$-CH_2OH), 4.08–4.01 (m, 2H, $\underline{CH_2}$OPMP), 3.88–3.74 (m, 2H, $\underline{CH_2}OH$), 3.77 (s, 3H, OCH_3), 2.22 (q, *J* = 6.4 Hz, 1H, OH), 1.50 (s, 3H, CH_3 of acetonide), 1.41 (s, 3H, CH_3 of acetonide); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 154.5 (Cq Ar), 152.3 (Cq Ar), 115.7 (2 CH Ar), 114.8 (2 CH Ar), 109.0 (Cq acetonide), 77.4 ($\underline{CH}$-CH_2OH), 75.0 ($\underline{CH}$-CH_2OPMP), 67.2 ($\underline{CH_2}$OPMP), 61.1 ($\underline{CH_2}OH$), 55.8 (OCH_3), 27.9 (CH_3 acetonide), 25.3 (CH_3 acetonide); HRMS (ESI+) *m*/*z*: $[M + Na]^+$ Calcd for $C_{14}H_{20}NaO_5^+$: 291.1203; Found: 291.1106.

1-((4R,5S)-5-((4-methoxyphenoxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-methylpent-2-yn-1-ol (9): To a solution of DMSO (1.1 mL, 15.08 mmol), in dry CH_2Cl_2 (36 mL), at −70 °C, under a nitrogen atmosphere, a solution of oxalyl chloride in dry CH_2Cl_2 (1.43 M, 9.8 mL) was added. The solution was stirred for approximately 10 min, until effervescence ceased. A solution of **8** (1.50 g, 5.59 mmol) in dry CH_2Cl_2 (20 + 10 + 6 mL) was added dropwise, and the solution was stirred for 10 min at −70 °C. NEt_3 (4.3 mL, 30.73 mmol) was then added, and the solution was stirred for 2 h at −70 °C. After this time, the reaction mixture was poured into a mixture of 5% aq $(NH_4)H_2PO_4$ (90 mL) and 1 M HCl (10 mL) (final pH 4) and extracted with Et_2O (100 + 30 mL). The organic layer was washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The resulting crude aldehyde was rapidly solubilized in THF (20 mL) under Ar and used as such for the next reaction. To a solution of 2,2′-bipyridine (catalytic amount) in dry THF (30 mL) under Ar, at −50 °C, *n*-BuLi (11 mL, 1.6 M in hexane) was added, until a deep red color persisted. Then, 3-methyl-1-butyne (2 mL, 19.55 mmol) was added, and the mixture was stirred for 25 min. After this time, the temperature was kept at −70 °C, and the solution of aldehyde was slowly added to the mixture. The reaction was stirred for 1 h at −50 °C and overnight at room temperature. The reaction was diluted with saturated NH_4Cl aq., extracted with AcOEt, dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with PE/Et_2O 3:1 to give **9** (1.64 g, 88%) as a 57:43 mixture of diastereoisomers (PHENYLIC RP column 150 × 3 mm, 3 μm, temp 25 °C, flow = 0.38 mL/min, mobile phase H_2O/CH_3CN, A = CH_3CN—B = H_2O, 0 min B = 90%, 30 min B = 0%. R_t (*syn*) = 12.0 min, R_t (anti) = 12.4 min).

Oxidation and diastereoselective reduction to give 9 *anti*: To a solution of **9** (969 mg, 2.90 mmol), in dry CH_2Cl_2 (22 mL), under a nitrogen atmosphere, Dess Martin periodinane (1.35 g, 3.19 mmol) was added at 0 °C, and the reaction was stirred at room temperature for 4.5 h. The mixture was quenched with $NaHCO_3$ (5% *w*/*v* aqueous solution)/$Na_2S_2O_3$ (0.4 M in water) (1:1), extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated to afford the corresponding ketone, which was used as such for the next reaction. To a solution of ketone in dry THF (29 mL) at −78 °C under a nitrogen atmosphere, K-Selectride (1 M in THF, 2.9 mL) was added. After stirring at room temperature for 5 h, the reaction was diluted with saturated NH_4Cl (saturated aqueous solution), extracted with AcOEt, washed with brine, dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with PE/AcOEt 3:1 to give first **9 *anti*** (529 mg, 55%) as a white solid and **9 *syn*** (168 mg, 18%) as a pale-yellow oil. The diastereoisomeric ratio (76:24) was determined on the crude after the reduction with HPLC (PHENYLIC RP column 150 × 3 mm, 3 μm, temp 25 °C, flow = 0.38 mL/min, mobile phase H_2O/CH_3CN, A = CH_3CN—B = H_2O, 0 min B = 90%, 30 min B = 0%. R_t (*syn*) = 12.0 min, R_t (*anti*) = 12.4 min).

9 *anti*: R_f = 0.73 (PE/AcOEt 6:4); $[\alpha]_D^{25}$ = −13.0 (*c* 1.0, $CHCl_3$); m.p. 85.8–88.3 °C ($CHCl_3$); IR (ATR): ν = 3455, 3222, 2970, 2934, 2835, 1507, 1458, 1381, 1319, 1289, 1228, 1214, 1167, 1125, 1106, 1082, 1038, 884, 856, 824, 727, 639 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.93–6.86 (m, 2H, 2 CH Ar), 6.86–6.79 (m, 2H, 2 CH Ar), 4.65–4.55 (m, 2H, CH-4 and $\underline{\text{CH}}$OH), 4.36 (dd, *J* = 10.2, 5.2 Hz, 1H, 1 H of CH_2), 4.31 (dd, *J* = 6.5, 5.1 Hz, 1H, CH-5), 4.20 (dd, *J* = 10.1, 6.2 Hz, 1H, 1 H of CH_2), 3.77 (s, 3H, OCH_3), 2.70 (d, *J* = 5.7 Hz, 1H, OH), 2.57 (pd, *J* = 6.9, 1.8 Hz, 1H, CH of *i*Pr), 1.55 (s, 3H, CH_3 of acetonide), 1.42 (s, 3H, CH_3 of acetonide), 1.14 (d, *J* = 6.9 Hz, 6H, 2 CH_3 of *i*Pr); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 154.1 (Cq Ar), 152.4 (Cq Ar), 115.6 (2 CH Ar), 114.5 (2 CH Ar), 109.1 (Cq acetonide), 92.6 (Cq alkyne), 79.3 (CH-5), 77.2 (Cq alkyne), 75.5 (CH-4), 67.3 (CH_2), 61.7 (CHOH), 55.6 (OCH_3), 27.3 (CH_3 acetonide), 25.2 (CH_3 acetonide), 22.6 (2 CH_3 of *i*Pr), 20.4 (CH of *i*Pr); HRMS (ESI+) *m*/*z*: $[M + Na]^+$ Calcd for $C_{19}H_{26}NaO_5^+$: 357.1672; Found: 357.1670.

9 *syn*: R_f = 0.65 (PE/AcOEt 6:4); $[\alpha]_D^{20}$= −76.3 (*c* 1.0, $CHCl_3$); IR (ATR): ν = 3455, 3222, 2970, 2934, 2835, 1507, 1458, 1381, 1319, 1289, 1228, 1214, 1167, 1125, 1106, 1082, 1038, 884, 856, 824, 727, 639 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.92–6.79 (m, 4H. 4 CH Ar), 4.57 (td, *J* = 6.5, 4.4 Hz, 1H, CH-5), 4.53–4.48 (m, 1H, $\underline{\text{CH}}$-OH), 4.30 (dd, *J* = 10.1, 4.4 Hz, 1H, 1 H of CH_2), 4.26 (dd, *J* = 7.3, 6.3 Hz, 1H, CH-4), 4.10 (dd, *J* = 10.0, 6.6 Hz, 1H, 1 H of CH_2), 3.77 (s, 3H, OCH_3), 2.55 (pd, *J* = 7.4, 1.9 Hz, 1H, CH of *i*Pr), 2.53 (bs, 1H, OH), 1.54 (s, 3H, C*H*$_3$ of acetonide), 1.44 (s, 3H, C*H*$_3$ of acetonide), 1.13 (d, *J* = 6.9 Hz, 3H, C*H*$_3$ of acetonide), 1.13 (d, *J* = 6.9 Hz, 3H, C*H*$_3$ of acetonide); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 154.2 (Cq Ar), 152.7 (Cq Ar), 115.7 (2 CH Ar), 114.7 (2 CH Ar), 109.6 (Cq acetonide), 93.0 (Cq alkyne), 79.8 (CH-5), 76.8 (Cq alkyne), 75.6 (CH-4), 67.2 (CH_2), 61.3 (CHOH), 55.8 (OCH_3), 27.8 (CH_3 acetonide), 25.4 (CH_3 acetonide), 22.8 (2 CH_3 *i*Pr), 20.6 (CH *i*Pr); HRMS (ESI+) *m*/*z*: $[M + Na]^+$ Calcd for $C_{19}H_{26}NaO_5^+$: 357.1672; Found: 357.1670.

(3aR,6R,6aR)-2,2-dimethyl-6-(3-methylbut-1-yn-1-yl)dihydrofuro[3,4-d][1,3]dioxol-4(3aH)-one (10 *anti*): To a solution of **9 *anti*** (30 mg, 0.09 mmol), in CH_3CN (1.5 mL) and H_2O (450 μL), at 0 °C, CAN (123 mg, 0.22 mmol) was added. After 10 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated to afford the crude diol, which was directly used for the next reaction. To a solution of crude diol in CH_2Cl_2 (1 mL), under a nitrogen atmosphere, TEMPO (5 mg, 0.03 mmol) and BAIB (155 mg, 0.48 mmol) were added. After stirring for 4 h at room temperature, the reaction mixture was diluted with CH_2Cl_2, washed with $Na_2S_2O_3$ (0.4 M in water), dried (Na_2SO_4), and concentrated. The residue was purified with chromatography using PE/AcOEt 8:1 to create **10 *anti*** (15 mg, 74%) as a pale-yellow oil. R_f = 0.86 (PE/AcOEt = 3:2); $[\alpha]_D^{20}$ = +50.4 (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 5.14 (dt, *J* = 2.0, 0.5 Hz, 1H, propargylic CH), 4.86 (d, *J* = 5.2 Hz, 1H, CH-4), 4.75 (d, *J* = 5.3 Hz, 1H, CH-3), 2.59 (heptd, *J* = 6.9, 2.0 Hz, 1H, CH of *i*Pr), 1.47 (s, 3H, CH_3 of acetonide), 1.39 (s, 3H, CH_3 of acetonide), 1.17 (d, *J* = 6.9 Hz, 6H, 2 CH_3 of $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.7 (Cq of lactone), 114.6 (Cq of acetonide), 96.8 (Cq alkyne), 80.9 (CH-3), 75.0 (CH-4), 73.0 (Cq alkyne), 71.8 (propargylic CH), 26.9 (CH_3 acetonide), 26.1 (CH_3 acetonide), 22.5 (2 CH_3 of *i*Pr), 20.6 (CH of *i*Pr); HRMS (ESI+) *m/z*: $[M + Na]^+$ Calcd for $C_{12}H_{16}NaO_4^+$: 247.0941; Found: 247.0940.

(3aR,6S,6aR)-2,2-dimethyl-6-(3-methylbut-1-yn-1-yl)dihydrofuro[3,4-d][1,3]dioxol-4(3aH)-one (10 *syn*): Compound **10 *syn*** was obtained as a white foam (18 mg, 50%), starting from **9 *syn***, using the same procedure as above described for **10 *anti***. R_f = 0.70 (PE/AcOEt = 3:2); $[\alpha]_D^{20}$ = +87.9 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 5.17 (dd, *J* = 3.6, 1.8 Hz, 1H, propargylic CH), 4.81 (dd, *J* = 5.6, 3.6 Hz, 1H, CH-4), 4.78 (d, *J* = 5.6 Hz, 1H, CH-3), 2.67 (heptd, *J* = 6.9, 1.9 Hz, 1H, CH of *i*Pr), 1.51 (s, 3H, CH_3 of acetonide), 1.44 (s, 3H, CH_3 of acetonide), 1.21 (dd, *J* = 6.9, 1.0 Hz, 6H, 2 CH_3 of *i*Pr); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.1 (Cq lactone), 114.7 (Cq acetonide), 97.4 (Cq alkyne), 76.9 (CH-4), 75.7 (CH-3), 71.1 (propargylic CH), 70.4 (Cq alkyne), 26.9 (CH_3 acetonide), 26.3 (CH_3 acetonide), 22.6 (2 CH_3 of *i*Pr), 20.8 (CH of *i*Pr); HRMS (ESI+) *m/z*: $[M + Na]^+$ Calcd for $C_{12}H_{16}NaO_4^+$: 247.0941; Found: 247.0940.

(R,E)-1-((4R,5S)-5-((4-methoxyphenoxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-methylpent-2-en-1-ol (11): To a solution of **9 *anti*** (556 mg, 1.66 mmol), in dry THF (17 mL), under an argon atmosphere, Red-Al® (3.5 M in toluene, 1.2 mL) was added dropwise at 0 °C and the reaction was stirred under reflux for 4 h. Then, it was cooled to 0 °C and carefully quenched with 1:1 Rochelle salt (30% aqueous solution) and saturated NH_4Cl aqueous solution. The mixture was stirred for 1 h and then extracted with AcOEt. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The crude residue was purified using silica gel column chromatography (PE/Et_2O 3:1) to afford **11** (451 mg, 82%) as a white solid. R_f = 0.55 (PE/AcOEt 4:1); $[\alpha]_D^{25}$ = +4.9 (*c* 1.2, $CHCl_3$). m.p. 44.6–47.1 °C; IR (ATR): ν = 3487, 2990, 2957, 2939, 2883, 2867, 2837, 1858, 1670, 1624, 1591, 1506, 1458, 1441, 1412, 1379, 1367, 1329, 1302, 1290, 1250, 1220, 1183, 1167, 1137, 1113, 1081, 1039, 1013, 971, 958, 936, 923, 906, 861, 822, 799, 778, 721, 669, 659, 642, 605 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* = 6.93–6.79 (m, 4H, 4 CH Ar), 5.79 (ddd, *J* = 15.6, 6.5, 1.2 Hz, 1H, *i*Pr-$\underline{CH}$=), 5.57 (ddd, *J* = 15.6, 5.7, 1.3 Hz, 1H, *i*Pr-CH=$\underline{CH}$), 4.55 (dt, *J* = 6.7, 5.6 Hz, 1H, $\underline{CH}$-CH_2OPMP), 4.38–4.25 (m, 1H, $\underline{CH}$OH), 4.19 (dd, *J* = 9.8, 6.8 Hz, 1H, 1 H of CH_2), 4.13 (dd, *J* = 7.8, 5.7 Hz, 1H, $\underline{CH}$-CHOH), 4.02 (dd, *J* = 9.7, 5.5 Hz, 1H, 1 H of CH_2), 3.77 (s, 3H, OCH_3), 2.72 (d, *J* = 3.6 Hz, 1H, OH), 2.33 (hept, *J* = 6.9 Hz, 1H, CH of *i*Pr), 1.47 (s, 3H, CH_3 of acetonide), 1.39 (s, 3H, CH_3 of acetonide), 1.01 (dd, *J* = 6.8, 1.1 Hz, 6H, 2 CH_3 of *i*Pr); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* = 154.6 (Cq Ar), 152.2 (Cq Ar), 140.6 (*i*Pr-$\underline{CH}$=), 125.9 (*i*Pr-CH=$\underline{CH}$), 115.8 (2 CH Ar), 114.8 (2 CH Ar), 109.0 (Cq acetonide), 80.2 ($\underline{CH}$-CHOH), 75.7 ($\underline{CH}$-CH_2), 70.3 ($\underline{CH}$OH), 67.8 (CH_2), 55.9 (OCH_3), 31.0 (CH of *i*Pr), 28.1 (CH_3 acetonide), 25.5 (CH_3 acetonide), 22.4 (CH_3 of *i*Pr), 22.3 (CH_3 of *i*Pr); HRMS (ESI+) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{28}NaO_5^+$: 359.1829; Found: 359.1816.

((4S,5S)-5-((R,E)-1-((tert-butyldimethylsilyl)oxy)-4-methylpent-2-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (12): A solution of **11** (381 mg, 1.13 mmol), in dry CH_2Cl_2 (6 mL), under a nitrogen atmosphere was treated with 2,6-lutidine (527 μL, 4.53 mmol) and TBS-OTf (624 μL, 2.72 mmol) at 0 °C. After stirring at room temperature for 3 h, the reaction was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated and the crude residue was filtered through a short column of silica gel (PE/Et_2O 8:1) and the free alcohol obtained (470 mg, 92%) is directly subjected to the next reaction. To a solution of free alcohol (75 mg, 0.17 mmol) in CH_3CN (3 mL), a solution of CAN in deionized water (1 mL, 0.4 M) was added dropwise at −15 °C. After stirring for 15 min at −15 °C, the mixture was diluted with $NaHCO_3$ (5% *w*/*v* aqueous solution)/$Na_2S_2O_3$ (0.4 M in water) (1:1) and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated, and the crude residue was purified with silica gel column chromatography (PE/CH_2Cl_2/Et_2O 4:1:0.5) to afford **12** (54 mg, 94%) as a pale-yellow oil. R_f = 0.18 (PE/CH_2Cl_2/Et_2O 4:1:0.5); $[\alpha]_D^{25}$= −17.8 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.66 (dd, *J* = 15.3, 6.8 Hz, 1H, *i*Pr-CH=), 5.39 (ddd, *J* = 15.4, 7.2, 1.3 Hz, 1H, *i*Pr-CH=CH), 4.44 (dd, *J* = 7.1, 5.5 Hz, 1H, CH-OTBS), 4.19 (q, *J* = 5.8 Hz, 1H, CH-CH_2OH), 4.01 (t, *J* = 5.6 Hz, 1H, CH-CHOTBS), 3.75 (ddd, *J* = 11.8, 7.7, 5.8 Hz, 1H, 1 H of CH_2OH), 3.67 (ddd, *J* = 11.9, 6.2, 5.7 Hz, 1H, 1 H of CH_2OH), 2.95 (dd, *J* = 7.6, 6.2 Hz, 1H, OH), 2.33 (hept, *J* = 6.7 Hz, 1H, CH of *i*Pr), 1.45 (s, 3H, CH_3 acetonide), 1.34 (s, 3H, CH_3 acetonide), 1.00 (dd, *J* = 6.8, 1.8 Hz, 6H, 2 CH_3 of *i*Pr), 0.90 (s, 9H, 3 CH_3 of TBS), 0.12 (s, 3H, CH_3 of TBS), 0.08 (s, 3H, CH_3 of TBS); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 141.4 (*i*Pr-CH=CH), 126.2 (*i*Pr-CH=CH), 108.1 (Cq of acetonide), 79.8 (CH-CHOTBS), 77.8 (CH-CH_2OH), 72.9 (CHOTBS), 61.7 (CH_2OH), 30.9 (CH of *i*Pr), 27.9 (CH_3 acetonide), 26.0 (3 CH_3 of TBS), 25.8 (CH_3 acetonide), 22.2 (CH_3 of *i*Pr), 22.0 (CH_3 of *i*Pr), 18.3 (Cq of TBS), −3.7 (CH_3 of TBS), −4.4 (CH_3 of TBS).; HRMS (ESI+) *m*/*z*: [M+Na]+ Calcd for $C_{18}H_{36}NaO_4Si^+$: 367.2275; Found: 367.2322.

(S)-N-(2-oxoazepan-3-yl)formamide (14): To a solution of L -(−)-α-amino-ε-caprolactam hydrochloride **13** (502 mg, 3.05 mmol) in dry CH_2Cl_2 (15 mL), Et_3N (593 μL, 4.25 mmol), formic acid (183 μL, 4.86 mmol), and DCC (877 mg, 4.25 mmol) were added at 0 °C, and the reaction was stirred at room temperature for 19 h. The mixture was filtered through a pad of celite, washing it with CH_2Cl_2, and the solvent was removed under reduced pressure. The residue was purified using silica gel column chromatography (from AcOEt + 2% MeOH to AcOEt + 10% MeOH) to afford **14** as a white amorphous solid (460 mg, 97%). The optical purity of formamide was checked using chiral HPLC analysis on Daicel Chiralpak AD 250 × 4.6 mm column, after standardization with a racemic sample. Flow 1.0 mL/min; isocratic elution with *n*-hexane/*i*PrOH 90:10; temp.: 25 °C; UV detection at 220 nm. Rt 23.4 min (D) and 27.6 min (L). R_f = 0.42 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{20}$ = +80.04 (*c* 1.01, $CHCl_3$); IR (ATR): ν = 3268, 3089, 2972, 2912, 2866, 2850, 1695, 1628, 1517, 1482, 1437, 1381, 1370, 1361, 1335, 1316, 1292, 1278, 1222, 1212, 1122, 1092, 1057, 1043, 978, 946, 910, 851, 835, 804, 759 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.20 (s, 1H, CHO), 7.14 (bs, 1H, NH), 6.50 (bs, 1H, NH), 4.61 (dd, *J* = 11.2, 6.1 Hz, 1H, CH), 3.52–3.12 (m, 2H, CH_2C=O), 2.35–1.96 (m, 2H, 2 H of CH_2), 1.96–1.72 (m, 2H, 2 H of CH_2), 1.62–1.34 (m, 2H, 2 H of CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.2 (C=O caprolactame), 160.3 (C=O formamide), 51.2 (CH), 42.2 (CH_2), 31.6 (CH2), 28.9 (CH_2), 28.0 (CH_2); HRMS (ESI+) *m*/*z*: [M + Na]$^+$ Calcd for $C_7H_{12}N_2NaO_2^+$: 179.0791: Found: 179.0802.

(S)-3-isocyanoazepan-2-one (5): To a solution of **14** (122 mg, 0.78 mmol), in dry CH_2Cl_2 (4 mL), Et_3N (512 μL, 3.67 mmol) and $POCl_3$ (179 μL, 1.17 mmol) were added dropwise at −30 °C. After stirring for 90 min at −30 °C, the reaction was diluted with saturated $NaHCO_3$ aq, extracted with AcOEt, dried (Na_2SO_4), and concentrated. The crude residue was purified using silica gel column chromatography (PE/AcOEt 1:5) to afford **5** as a white amorphous solid (98 mg, 91%). The optical purity of isocyanide was not confirmed in this crude product due to the presence of unresolved peaks in the chromatogram. Therefore, the optical purity was checked on model compounds **16** derived from a Passerini reaction of **5** and **7a** (See Supporting Information). R_f = 0.63 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{25}$= −11.2 (*c* 1.0, $CHCl_3$); IR (ATR): ν = 3328, 3223, 3099, 2992, 2948, 2925, 2858, 2148, 1670, 1478, 1466, 1436, 1428, 1359, 1331, 1323, 1291, 1274, 1248, 1111, 1092, 1075, 1038, 1015, 964, 944, 885, 823, 789, 776, 687 cm^{-1}: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.50 (bs, 1H, NH), 4.49 (dd, *J* = 9.6, 2.2 Hz, 2H, CH), 3.50–3.32 (m, 1H, 1 H of CH_2NH), 3.13 (dddd, *J* = 15.5, 10.1, 5.7, 1.3 Hz, 1H, 1 H of CH_2NH), 2.08 (dtt, *J* = 17.4, 11.0, 3.4 Hz, 3H, 3 H of CH_2), 1.90–1.67 (m, 2H, 2 H of CH_2), 1.66–1.49 (m, 1H, 1 H of CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.1 (C=O), 159.5 (NC), 57.8 (CH), 41.7 (CH_2), 31.3 (CH_2), 28.5 (CH_2), 26.8 (CH_2); HRMS (ESI+) *m*/*z*: [M + Na]$^+$ Calcd for $C_7H_{10}N_2NaO_2^+$: 161.0685; Found: 161.0694.

((4R,5R)-5-(1-acetoxy-2-oxo-2-(((S)-2-oxoazepan-3-yl)amino)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate (16): To a solution of DMSO (44 μL, 0.61 mmol), in dry CH_2Cl_2 (3 mL), at −70 °C, under a nitrogen atmosphere, a solution of oxalyl chloride in dry CH_2Cl_2 (2 M, 0.26 mL) was added. The solution was stirred for approximately 10 min, until effervescence ceased. A solution of **7a** (50 mg, 0.24 mmol) in dry CH_2Cl_2 (1 + 1 + 0.5 mL) was added dropwise, and the solution was stirred for 10 min at −70 °C. NEt_3 (160 µL, 1.15 mmol) was then added, and the solution was stirred for 2 h at −50 °C. After this time, the reaction mixture was poured into a mixture of 5% aq $(NH_4)H_2PO_4$ (5 mL) and 1 M HCl (0.1 mL) (final pH 4) and extracted with Et_2O (20 + 10 mL). The organic layer was washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The resulting crude aldehyde **15** was rapidly solubilized in CH_2Cl_2 (1 mL) under N_2 and isocyanide **5** (37 mg, 0.27 mmol) and acetic acid (15 µL, 0.27 mmol) were added. After stirring for 7 h at room temperature, the solvent was removed and the residue was filtered on silica gel (PE/Acetone 3:2) to give **16** (68 mg, 69%) as a 20:80 (*syn*/*anti*) mixture of diastereoisomers (Colonna Hydro RP (2) 150 × 3 mm, 4 micron; flow = 0.5 mL/min; Vinj 5 µL; Temp: 26 °C Term. ON, VWD = 210 nm; MS: FullScan 100–800 *m*/*z* Positive, tic volt: 750V, Gradient A = H_2O+0.1%FA C = MeOH+0.1% FA, 0 min A = 80%, 30 min A = 0%. R_t (*anti*) = 12.9 min, R_t (*syn*) = 13.3 min). **16 *anti*** and **16 *syn*** can be separated performing column chromatography on silica gel with PE/Acetone (from 1:1 to 3:2).

16 *anti*: amorphous solid; R_f = 0.14 (PE/Acetone 2:1); $[\alpha]_D^{25}$ = +26.47 (*c* 0.85, $CHCl_3$): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.57 (bd, *J* = 5.8 Hz, 1H, $\underline{NH}CH$), 6.25 (bt, *J* = 6.4 Hz, 1H, $\underline{NH}CH_2$), 5.21 (d, *J* = 7.6 Hz, 1H, CHOAc), 4.57 (dd, *J* = 7.6, 5.8 Hz, 1H, $\underline{CH}$-CHOAc), 4.54–4.43 (m, 2H, $\underline{CH}$-CH_2OAc and $\underline{CH}$NH), 4.41 (dd, *J* = 11.4, 3.8 Hz, 2H, 1 H of $\underline{CH_2}$OAc), 4.11 (dd, *J* = 11.4, 6.8 Hz, 1H, 1 H of $\underline{CH_2}$OAc), 3.36–3.19 (m, 2H, $\underline{CH_2}$NH), 2.17 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.20–1.95 (m, 2H, 2 H of CH_2), 1.90–1.74 (m, 2H, 2 H of CH_2), 1.51 (s, 3H, CH_3 acetonide), 1.56–1.30 (m, 2H, 2 H of CH_2), 1.38 (s, 3H, CH_3 acetonide); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.0 (C=O), 170.8 (C=O), 169.5 (C=O), 166.3 (C=O), 109.7 (Cq acetonide), 75.3 (CHNH), 75.3 ($\underline{CH}$-CHOAc), 71.4 ($\underline{CH}$-OAc), 62.4 ($\underline{CH_2}$OAc), 52.6 ($\underline{CH}$-CH_2OAc), 42.3 (CH_2NH), 31.1 (CH_2), 29.0 (CH_2), 28.0 (CH_2), 27.7 (CH_3 acetonide), 25.3 (CH_3 acetonide), 21.0 (CH_3 of Ac), 20.8 (CH_3 of Ac); HRMS (ESI+) *m*/*z*: $[M + Na]^+$ Calcd for $C_{18}H_{28}N_2NaO_8{}^+$: 423.1738; Found: 423.1736.

16 *syn*: colorless oil; R_f = 0.15 (PE/Acetone 2:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.46 (bd, *J* = 6.3 Hz, 1H, $CH\underline{NH}$), 6.02 (bt, *J* = 6.4 Hz, 1H, $CH_2\underline{NH}$), 5.27 (d, *J* = 3.5 Hz, 1H, CHOAc), 4.62 (dd, *J* = 6.5, 3.5 Hz, 1H, $\underline{CH}$-CHOAc), 4.53–4.39 (m, 2H, $\underline{CH}$NH and $\underline{CH}$-CH_2OAc), 4.23 (dd, *J* = 11.4, 5.2 Hz, 1H, 1 H of CH_2OAc), 4.15 (dd, *J* = 11.4, 6.9 Hz, 1H, 1 H of CH_2OAc), 3.31–3.20 (m, 2H, $\underline{CH_2}$NH), 2.23 (s, 3H, OAc), 2.16–1.96 (m, 2H, CH_2), 2.08 (s, 3H, OAc), 1.91–1.78 (m, 2H, CH_2), 1.52 (s, 3H, CH_3 acetonide), 1.48–1.37 (m, 2H, CH_2), 1.35 (s, 3H, CH_3 acetonide); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.9 (C=O), 170.8 (C=O), 169.7 (C=O), 166.8 (C=O), 109.7 (Cq acetonide), 75.8 ($\underline{CH}$-CHOAc), 74.8 ($\underline{CH}$-CH_2OAc), 71.8 (CHOAc), 62.8 ($\underline{CH_2}$OAc), 52.4 (CHNH), 42.3 (CH_2NH), 31.3 (CH_2), 29.0 (CH_2), 28.0 (CH_2), 27.2 (OAc), 25.4 (OAc), 21.0 (CH_3 acetonide), 20.9 (CH_3 acetonide); HRMS (ESI+) *m*/*z*: $[M + Na]^+$ Calcd for $C_{18}H_{28}N_2NaO_8{}^+$: 423.1738; Found: 423.1736.

2-((4S,5S)-5-((R,E)-1-((tert-butyldimethylsilyl)oxy)-4-methylpent-2-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxy-N-((S)-2-oxoazepan-3-yl)acetamide (3): To a solution of DMSO (37 µL, 0.52 mmol), in dry CH_2Cl_2 (3 mL), at −70 °C, under a nitrogen atmosphere, a solution of oxalyl chloride in dry CH_2Cl_2 (1.43 M, 0.33 mL) was added. The solution was stirred for approximately 10 min, until effervescence ceased. A solution of 12 (67 mg, 0.19 mmol) in dry CH_2Cl_2 (1 + 0.5 mL) was added dropwise, and the solution was stirred for 10 min at −70 °C. NEt_3 (160 µL, 1.15 mmol) was then added, and the solution was stirred for 2 h at −50 °C. After this time, the reaction mixture was poured into a mixture of 5% aq $(NH_4)H_2PO_4$ (5 mL) and 1 M HCl (0.1 mL) (final pH 4) and extracted with Et_2O (20 + 10 mL). The organic layer was washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The resulting crude aldehyde **4** was rapidly solubilized in *i*Pr_2O (500 µL) under N_2, and isocyanide **5** (53 mg, 0.38 mmol) and acetic acid (22 µL, 0.38 mmol) were added. After stirring for 48 h at room temperature, the solvent was removed and the residue was filtered on silica gel (PE/AcOEt 3:4) to give a mixture of products **18** and **3** (73 mg), which was treated with MeOH/H_2O/Et_3N (5:1:1) and stirred at room temperature for 48 h. Then, the solvent was removed. The diastereomeric ratio was determined as

80:20 (*anti*:*syn*) using reverse-phase HPLC on the crude mixture (C6 PHENYLIC RP column (150 × 3 mm, 3 μ) at 30 °C with flow = 0.34 mL/min and gradient H$_2$O/MeOH, A = MeOH + 0.1% FA—B = H$_2$O + 0.1% FA, 0 min B = 30%, 20 min B = 20%. Detection was carried out with UV at 210 nm, R$_t$ (*anti*) = 13.2 min, R$_t$ (*syn*) = 15.6 min). The crude residue was purified with column chromatography of silica gel (PE/Et$_2$O 1:20) to give **3** ***anti*** (55 mg, 58%) and **3** ***syn*** (14 mg, 16%). **3** ***anti***: pale-yellow oil, R$_f$ = 0.35 (Et$_2$O/PE 20:1); $[\alpha]_D^{20}$ = +16.9 (*c* 1.0, CHCl$_3$); IR (ATR): ν = 3462, 3346, 2956, 2931, 2858, 1685, 1598, 1525, 1463, 1375, 1254, 1215, 1168, 1069, 1045, 974, 834, 800, 777, 667 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.79 (bd, *J* = 6.5 Hz, 1H, NHCH), 6.20 (bs, 1H, NHCH$_2$), 5.63 (dd, *J* = 15.5, 6.6 Hz, 1H, *i*Pr-CH=CH), 5.47 (dd, *J* = 15.5, 7.8 Hz, 1H, *i*Pr-CH=CH), 4.64–4.53 (m, 3H, OH, NHCH and CH-OTBS), 4.30–4.19 (m, 2H, CHOH and CH-CHOH), 4.06 (t, *J* = 4.5 Hz, 1H, CH-CHOTBS), 3.38–3.15 (m, 2H, CH$_2$NH), 2.31 (h, *J* = 6.6 Hz, 1H, CH of *i*Pr), 2.21–2.06 (m, 1H, 1 H of CH$_2$), 2.07–1.94 (m, 1H, 1 H of CH$_2$), 1.93–1.70 (m, 2H, 2 H of CH$_2$), 1.62–1.47 (m, 1H, 1 H of CH$_2$), 1.52 (s, 3H, CH$_3$ acetonide), 1.47–1.36 (m, 1H, 1 H of CH$_2$), 1.33 (s, 3H, CH$_3$ acetonide), 1.005 (d, *J* = 6.7 Hz, 3H, CH$_3$ of *i*Pr), 1.00 (d, *J* = 6.8 Hz, 3H, CH$_3$ of *i*Pr), 0.90 (s, 9H, 3 CH$_3$ of TBS), 0.14 (s, 3H, CH$_3$ of TBS), 0.11 (s, 3H, CH$_3$ of TBS); ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 175.5 (C=O), 170.6 (C=O), 142.0 (*i*Pr-CH=CH), 125.9 (*i*Pr-CH=CH), 108.5 (Cq acetonide), 80.8 (CH-CHOTBS), 77.9 (CHOH), 73.6 (CHOTBS), 70.2 (CH-CHOH), 52.2 (CHNH), 42.1 (CH$_2$NH), 31.4 (CH$_2$), 30.8 (CH of *i*Pr), 29.0 (CH$_2$), 28.0 (CH$_2$), 27.7 (CH$_3$ acetonide), 25.9 (3 CH$_3$ of TBS), 25.6 (CH$_3$ acetonide), 22.1 (CH$_3$ of *i*Pr), 21.9 (CH$_3$ of *i*Pr), 18.3 (Cq of TBS), −3.9 (CH$_3$ of TBS), −4.3 (CH$_3$ of TBS); HRMS (ESI+) *m*/*z*: [M + Na]$^+$ Calcd for $C_{25}H_{46}N_2NaO_6Si^+$: 521.3017; Found: 521.3018. **3** ***syn***: pale-yellow foam R$_f$ = 0.25 ((Et$_2$O/PE 20:1); $[\alpha]_D^{20}$ = −33.7 (*c* 1.2, CHCl$_3$); IR (ATR): ν = 3462, 3346, 2956, 2931, 2858, 1685, 1598, 1525, 1463, 1375, 1254, 1215, 1168, 1069, 1045, 974, 834, 800, 777, 667 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.98 (d, *J* = 7.0 Hz, 1H, NHCH), 6.16 (bs, 1H, NHCH$_2$), 5.72 (dd, *J* = 15.6, 6.9 Hz, 1H, *i*Pr-CH=CH), 5.38 (dd, *J* = 15.5, 6.1 Hz, 1H, *i*Pr-CH=CH), 4.68 (t, *J* = 4.9 Hz, 1H, CH-OTBS), 4.64–4.56 (m, 2H, NHCH and CH-CHOH), 4.54 (d, *J* = 2.6 Hz, 1H, OH), 4.29 (d, *J* = 2.2 Hz, 1H, CHOH), 4.17 (dd, *J* = 6.5, 4.4 Hz, 1H, CH-CHOTBS), 3.40–3.13 (m, 2H, CH$_2$NH), 2.31 (h, *J* = 6.9 Hz, 1H, CH of *i*Pr), 2.13–1.92 (m, 2H, 2 H of CH$_2$), 1.92–1.64 (m, 2H, 2 H of CH$_2$), 1.61–1.51 (m, 1H, 1 H of CH$_2$), 1.49 (s, 3H, CH$_3$ acetonide), 1.32 (s, 3H, CH$_3$ acetonide), 0.99 (d, *J* = 6.7 Hz, 6H, 2 CH$_3$ of *i*Pr), 0.92 (s, 9H, 3 CH$_3$ of TBS), 0.14 (s, 3H, CH$_3$ of *i*Pr), 0.11 (s, 3H, CH$_3$ of *i*Pr); ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 175.6 (C=O), 170.8 (C=O), 141.2 (*i*Pr-CH=CH), 124.6 (*i*Pr-CH=CH), 108.3 (Cq acetonide), 79.2 (CH-CHOTBS), 77.8 (CH-CHOH), 72.5 (CHOTBS), 71.5 (CHOH), 51.9 (CHNH), 42.3 (CH$_2$NH), 31.9 (CH$_2$), 31.0 (CH of *i*Pr), 29.2 (CH$_2$), 28.2 (CH$_2$), 26.4 (CH$_3$ acetonide), 26.0 (3 CH$_3$ of *i*Pr), 25.5 (CH$_3$ acetonide), 22.3 (CH$_3$ of *i*Pr), 22.2 (CH$_3$ of *i*Pr), 18.6 (Cq TBS), −4.2 (CH$_3$ of TBS), −4.7 (CH$_3$ of TBS); HRMS (ESI+) *m*/*z*: [M + Na]$^+$ Calcd for $C_{25}H_{46}N_2NaO_6Si^+$: 521.3017; Found: 521.3018.

(R)-2-((4R,5S)-5-((R,E)-1-((tert-butyldimethylsilyl)oxy)-4-methylpent-2-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methoxy-N-((S)-2-oxoazepan-3-yl)acetamide (19): A solution of **3** ***anti*** (64 mg, 0.128 mmol) in dry THF (1 mL) under a N$_2$ atmosphere was cooled at −10 °C. NaH (60% in silicon oil, 8 mg, 0.199 mmol) was added and the mixture was stirred for 30 min. Then, MeI (17 μL, 0.265 mmol) was added and the reaction was stirred at −10 °C for 48 h. The reaction mixture was diluted with saturated NH$_4$Cl solution, extracted with CH$_2$Cl$_2$, dried (Na$_2$SO$_4$), and concentrated. The crude residue was purified using silica gel column chromatography (PE/Et$_2$O 1:20) to give **20** (14 mg, 14%) and **19** (59 mg, 66%) both as a colorless oil. **19**: R$_f$ = 0.31 (Et$_2$O + 2% AcOEt); $[\alpha]_D^{20}$ = +6.2 (*c* 1.7, CHCl$_3$); IR (ATR): ν = 3383, 3292, 2955, 2930, 2858, 1714, 1662, 1504, 1474, 1435, 1362, 1334, 1250, 1217, 1169, 1103, 1073, 1047, 1017, 972, 941, 899, 875, 834, 808, 776, 754, 666 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.53 (d, *J* = 6.2 Hz, 1H, NHCH), 6.02 (t, *J* = 6.6 Hz, 1H, NHCH$_2$), 5.66 (dd, *J* = 15.6, 5.8 Hz, 1H, *i*Pr-CH=CH), 5.56 (dd, *J* = 15.6, 6.7 Hz, 1H, *i*Pr-CH=CH), 4.75–4.52 (m, 2H, CHOTBS and NHCH), 4.22 (dd, *J* = 7.1, 6.2 Hz, 1H, CH-CHOCH$_3$), 4.09 (dd, *J* = 6.1, 4.6 Hz, 1H, CH-CHOTBS), 4.05 (d, *J* = 7.0 Hz, 1H, CHOCH$_3$), 3.34 (s, 3H, OCH$_3$), 3.32–3.20 (m, 2H, CH$_2$NH), 2.32 (h, *J* = 6.1 Hz, 1H, CH of *i*Pr), 2.22–2.08 (m, 1H, 1 H of CH$_2$), 2.04–1.94

(m, 1H, 1 H of CH_2), 1.91–1.78 (m, 2H, 2 H of CH_2), 1.60–1.40 (m, 2H, 2 H of CH_2), 1.41 (s, 3H, CH_3 acetonide), 1.29 (s, 3H, CH_3 acetonide), 1.02 (d, *J* = 6.7 Hz, 3H, CH_3 of *i*Pr), 1.00 (d, *J* = 6.7 Hz, 3H, CH_3 of *i*Pr), 0.90 (s, 9H, 3 CH_3 of TBS), 0.10 (s, 3H, CH_3 of TBS), 0.07 (s, 3H, CH_3 of TBS); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.3 (C=O), 169.7 (C=O), 140.9 (*i*Pr-$\underline{CH}$=CH), 127.3 (*i*Pr-CH=$\underline{CH}$), 108.5 (Cq acetonide), 81.0 ($\underline{CH}$-CHOTBS), 80.9 ($\underline{CH}OCH_3$), 77.6 ($\underline{CH}$-$CHOCH_3$), 73.3 ($\underline{CH}$OTBS), 57.4 (OCH_3), 52.0 (CHNH), 42.2 ($NHCH_2$), 31.5 (CH_2), 30.9 (CH of *i*Pr), 29.1 (CH_2), 28.0 (CH_2), 27.2 (CH_3 acetonide), 26.1 (3 CH_3 of TBS), 25.3 (CH_3 acetonide), 22.4 (CH_3 of *i*Pr), 22.0 (CH_3 of *i*Pr), 18.5 (Cq of TBS), −3.5 (CH_3 of TBS), −4.3 (CH_3 of TBS); HRMS (ESI+) *m*/*z*: $[M + Na]^+$ Calcd for $C_{25}H_{46}N_2NaO_6Si^+$: 535.3174; Found: 535.3177.

(R)-2-((4R,5S)-5-((R,E)-1-((tert-butyldimethylsilyl)oxy)-4-methylpent-2-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methoxy-N-((S)-1-methyl-2-oxoazepan-3-yl)acetamide (20): colorless oil; R_f = 0.38 (Et_2O + 2% AcOEt); $[\alpha]_D^{20}$ = +1.6 (*c* 0.6, $CHCl_3$); IR (ATR): ν = 3388, 2955, 2930, 2858, 2246, 1648, 1495, 1461, 1403, 1381, 1370, 1339, 1251, 1214, 1157, 1138, 1102, 1075, 1047, 1016, 973, 910, 879, 834, 808, 777, 729, 646 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.61 (bd, *J* = 6.0 Hz, 1H, $\underline{NH}$CH), 5.78–5.46 (m, 2H, CH=CH), 4.70 (dd, *J* = 9.5, 6.3 Hz, 1H, NH$\underline{CH}$), 4.56 (dd, *J* = 6.4, 4.3 Hz, 1H, CHOTBS), 4.20 (dd, *J* = 7.4, 6.2 Hz, 1H, CH-CHOMe), 4.08 (dd, *J* = 6.0, 4.2 Hz, 1H, CH-CHOTBS), 4.02 (d, *J* = 7.5 Hz, 1H, CHOMe), 3.61 (dd, *J* = 15.3, 11.6 Hz, 1H, 1 H of CH_2-N), 3.33 (s, 3H, OMe), 3.18 (dd, *J* = 15.0, 4.5 Hz, 1H, 1 H of CH_2-N), 3.04 (s, 3H, NMe), 2.31 (h, *J* = 6.0 Hz, 1H, CH of *i*Pr), 2.21–2.00 (m, 1H, 1 H of CH_2), 2.00–1.72 (m, 3H, 3 H of CH_2), 1.55–1.31 (m, 2H, 2 H of CH_2), 1.42 (s, 3H, CH_3 acetonide), 1.29 (s, 3H, CH_3 acetonide), 1.01 (d, *J* = 6.7 Hz, 3H, CH_3 of *i*Pr), 1.00 (d, *J* = 6.7 Hz, 3H, CH_3 of *i*Pr), 0.90 (s, 9H, 3 CH_3 of TBS), 0.10 (s, 3H, CH_3 of TBS), 0.07 (s, 3H, CH_3 of TBS); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.8 (C=O), 169.5 (C=O), 140.7 (CH=), 127.3 (C=H), 108.5 (Cq acetonide), 81.2 (CH-CHOTBS), 80.8 (CHOMe), 77.5 ($\underline{CH}$-CHOMe), 73.3 (CHOTBS), 57.3 (OMe), 51.9 (NHCH), 50.5 (CH_2N), 36.0 (NMe), 31.7 (CH_2), 30.9 (CH of *i*Pr), 27.8 (CH_2), 27.3 (CH_3 acetonide), 26.8 (CH_2), 26.2 (3 CH_3 of TBS), 25.3 (CH_3 acetonide), 22.4 (CH_3 of *i*Pr), 22.1 (CH_3 of *i*Pr), 18.5 (Cq of TBS), −3.6 (CH_3 of TBS), −4.3 (CH_3 of TBS); HRMS (ESI+) *m*/*z*: $[M + Na]^+$ Calcd for $C_{27}H_{50}N_2NaO_6Si^+$: 549.3330; found: 549.3299.

(2R,3R,4R,5R,E)-3,4,5-trihydroxy-2-methoxy-8-methyl-N-((S)-2-oxoazepan-3-yl)non-6-enamide (2): Pale-yellow foam; R_f = 0.42 (AcOEt + 2% MeOH); $[\alpha]_D^{20}$ = +34.5 (*c* 0.3, $CHCl_3$); IR (ATR): ν = 3334, 2956, 2930, 2868, 1639, 1519, 1483, 1437, 1361, 1334, 1291, 1261, 1066, 973, 943, 893, 800, 720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.63 (bd, *J* = 7.0 Hz, 1H, $\underline{NH}$CH), 6.22 (bt, *J* = 6.1 Hz, 1H, $\underline{NH}CH_2$), 5.78 (ddd, *J* = 15.6, 6.4, 0.9 Hz, 1H, *i*Pr-$\underline{CH}$=CH), 5.55 (ddd, *J* = 15.6, 7.2, 1.3 Hz, 1H, *i*Pr-CH=$\underline{CH}$), 4.59 (dd, *J* = 10.3, 7.0 Hz, 1H, NH$\underline{CH}$), 4.26 (bt, *J* = 5.3 Hz, 1H, CH-5), 4.07 (d, *J* = 3.3 Hz, 1H, CH-2), 4.07–3.95 (m, 1H, CH-3), 3.77 (d, *J* = 4.7 Hz, 1H, OH), 3.62 (dt, *J* = 8.2, 4.4 Hz, 1H, CH-4), 3.49 (s, 3H, OMe), 3.49–3.47 (m, 1H, OH), 3.39–3.18 (m, 2H, NH$\underline{CH_2}$), 2.77 (bs, 1H, OH), 2.32 (h, *J* = 6.3 Hz, 1H, CH of *i*Pr), 2.11–2.00 (m, 2H, 2 H of CH_2), 1.94–1.71 (m, 2H, 2 H of CH_2), 1.61–1.36 (m, 2H, 2 H of CH_2), 1.01 (d, *J* = 6.8 Hz, 6H, 2 CH_3 of *i*Pr); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.2 (C=O), 170.7 (C=O), 141.8 (*i*Pr-$\underline{CH}$=CH), 125.3 (*i*Pr-CH=$\underline{CH}$), 82.6 (CH-2), 74.7 (CH-5), 74.0 (CH-4), 73.0 (CH-3), 58.9 (OMe), 52.5 (NHCH), 42.2 ($NHCH_2$), 31.0 (CH of *i*Pr), 30.8 (CH_2), 28.9 (CH_2), 28.1 (CH_2), 22.5 (CH_3 of *i*Pr), 22.3 (CH_3 of *i*Pr); HRMS (ESI+) *m*/*z*: $[M + Na]^+$ Calcd for $C_{17}H_{30}N_2NaO_6^+$: 381.1996; Found: 381.1993.

(3aR,4R,7R,7aR)-7-methoxy-2,2-dimethyl-4-((E)-3-methylbut-1-en-1-yl)tetrahydro-6H-[1,3]dioxolo[4,5-c]pyran-6-one (21): Colorless oil; R_f = 0.69 (AcOEt + 10% MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.82 (ddd, *J* = 15.8, 6.8, 2.1 Hz, 1H, *i*Pr-$\underline{CH}$=CH), 5.45 (ddd, *J* = 15.9, 4.1, 1.3 Hz, 1H, *i*Pr-CH=$\underline{CH}$), 5.07–4.98 (m, 1H, CH-5), 4.82 (dd, *J* = 7.6, 3.5 Hz, 1H, CH-3), 4.56 (dd, *J* = 7.6, 1.1 Hz, 1H, CH-4), 4.07 (d, *J* = 3.5 Hz, 1H, CH-2), 3.63 (s, 3H, OMe), 2.37 (sest, *J* = 6.8 Hz, 1H, CH of *i*Pr), 1.50 (s, 3H, CH_3 acetonide), 1.36 (s, 3H, CH_3 acetonide), 1.02 (d, *J* = 6.7 Hz, 6H, 2 CH_3 of *i*Pr); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.6 (C=O), 142.7 (*i*Pr-$\underline{CH}$=CH), 121.3 (*i*Pr-CH=$\underline{CH}$), 111.0 (Cq acetonide), 79.7 (CH-5), 76.2 (CH-2), 75.7 (CH-4), 74.8 (CH-3), 59.9 (OMe), 31.3 (CH of *i*Pr), 26.2 (CH_3 acetonide), 24.4

(CH_3 acetonide), 22.1 (CH_3 of *i*Pr), 22.0 (CH_3 of *i*Pr); HRMS (ESI+) *m*/*z*: $[M + Na]^+$ Calcd for $C_{14}H_{22}NaO_5^+$: 293.1359; Found: 293.1349.

4. Conclusions

In conclusion, we have reported herein the first total synthesis of 4-*epi*-Bengamide E with a 4.1% yield over 14 steps from D-isoascorbic acid (with a 6.6% yield over 12 steps from *meso*-diol **1**). Key features of our convergent synthesis included (a) a chemoenzimatic desymmetrization of a biobased achiral compound; (b) a nucleophilic addition of acetylides and subsequent selective reduction to form the *E*-allylic alcohol; and (c) a diastereoselective Passerini reaction. This strategy allows the easy variation of side-chains, using different alkynes or different isocyanoamides in the synthetic sequence. Regarding concerns for stereochemical diversity, we think that there will be future chances to explore it. For example, configuration at C-5 might be varied by developing a complementary *syn*-selective reduction of ketoalkyne. Configuration at C-2 can be inverted by performing a Mitsunobu inversion before methylation. Finally, it must be noted that the enantiomeric series is easily accessible, due to the availability of the enantiomer of **7b**. The main limitation of this approach, from the stereochemical point of view, is the fixed relative configuration between C-3 and C-4, which prevents access to Bengamide E itself. For the Bengamide E relative configuration, tartaric acid-derived building blocks are surely better suited, which is already demonstrated by some total syntheses. These synthetic efforts, as well as biological evaluations of the described bengamide analogues, are currently in progress and will be presented in due course.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/molecules29081715/s1. Figure S1: section of ^{1}H NMR spectra of compounds **10** ***syn*** and **10** ***anti***. Figure S2: chiral-HPLC for determination of e.e. of compound **8** synthesized from **7a**. Figure S3: chiral-HPLC for determination of e.e. of compound **8** synthesized from **7b**. Figure S4: HPLC for determination of d.r. of compounds **9** after addition of acetylide. Figure S5: HPLC for determination of d.r. of compounds **9** after diastereoselective reduction with K-selectride. Figure S6: chiral-HPLC of *rac*-**14**. Figure S7: chiral-HPLC for determination of e.e. of compound **14**. Figure S8: HPLC for determination of d.r. of compounds **16** using Swern Oxidation and Passerini reaction in classical conditions. Figure S9: HPLC for determination of e.e. of compounds **16** using Swern Oxidation and Passerini reaction in classical conditions. Figure S10: HPLC for determination of d.r. of compounds **3** after Swern oxidation on alcohol **12**, Passerini reaction with AcOH and isocyanide **5** and final deacetylation in basic conditions. Table S1: optimization of diastereoselective reduction of ketone **S1**. Table S2: alternative syntheses of compound **8** avoiding Mitsunobu reaction.

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References

1. Adamczeski, M.; Quinoa, E.; Crews, P. Novel sponge-derived amino acids. 11. The entire absolute stereochemistry of the bengamides. *J. Org. Chem.* **2002**, *55*, 240–242. [CrossRef]
2. Adamczeski, M.; Quinoa, E.; Crews, P. Novel sponge-derived amino acids. 5. Structures, stereochemistry, and synthesis of several new heterocycles. *J. Am. Chem. Soc.* **2002**, *111*, 647–654. [CrossRef]
3. Garcia-Pinel, B.; Porras-Alcala, C.; Cabeza, L.; Ortiz, R.; Prados, J.; Melguizo, C.; Cheng-Sanchez, I.; Lopez-Romero, J.M.; Sarabia, F. Bengamide Analogues Show a Potent Antitumor Activity against Colon Cancer Cells: A Preliminary Study. *Mar. Drugs* **2020**, *18*, 240. [CrossRef] [PubMed]
4. White, K.N.; Tenney, K.; Crews, P. The Bengamides: A Mini-Review of Natural Sources, Analogues, Biological Properties, Biosynthetic Origins, and Future Prospects. *J. Nat. Prod.* **2017**, *80*, 740–755. [CrossRef] [PubMed]
5. Towbin, H.; Bair, K.W.; DeCaprio, J.A.; Eck, M.J.; Kim, S.; Kinder, F.R.; Morollo, A.; Mueller, D.R.; Schindler, P.; Song, H.K.; et al. Proteomics-based target identification: Bengamides as a new class of methionine aminopeptidase inhibitors. *J. Biol. Chem.* **2003**, *278*, 52964–52971. [CrossRef] [PubMed]
6. Johnson, T.A.; Sohn, J.; Vaske, Y.M.; White, K.N.; Cohen, T.L.; Vervoort, H.C.; Tenney, K.; Valeriote, F.A.; Bjeldanes, L.F.; Crews, P. Myxobacteria versus sponge-derived alkaloids: The bengamide family identified as potent immune modulating agents by scrutiny of LC-MS/ELSD libraries. *Bioorg. Med. Chem.* **2012**, *20*, 4348–4355. [CrossRef] [PubMed]
7. Wenzel, S.C.; Hoffmann, H.; Zhang, J.; Debussche, L.; Haag-Richter, S.; Kurz, M.; Nardi, F.; Lukat, P.; Kochems, I.; Tietgen, H.; et al. Production of the Bengamide Class of Marine Natural Products in Myxobacteria: Biosynthesis and Structure-Activity Relationships. *Angew. Chem. Int. Ed.* **2015**, *54*, 15560–15564. [CrossRef] [PubMed]
8. Banwell, M.G.; McRae, K.J. A chemoenzymatic total synthesis of ent-bengamide E. *J. Org. Chem.* **2001**, *66*, 6768–6774. [CrossRef] [PubMed]
9. Boeckman, R.K., Jr.; Clark, T.J.; Shook, B.C. A practical enantioselective total synthesis of the bengamides B, E, and Z. *Org. Lett.* **2002**, *4*, 2109–2112. [CrossRef]
10. Broka, C.A.; Ehrler, J. Enantioselective total syntheses of bengamides B and E. *Tetrahedron Lett.* **1991**, *32*, 5907–5910. [CrossRef]
11. Chida, N.; Tobe, T.; Ogawa, S. Total synthesis of bengamide E. *Tetrahedron Lett.* **1991**, *32*, 1063–1066. [CrossRef]
12. Dhimane, H.; Alam, S. A Concise Synthesis of Bengamide E and Analogues via E-Selective Cross-Metathesis Olefination. *Synlett* **2010**, *2010*, 2923–2927. [CrossRef]
13. Kishimoto, H.; Ohrui, H.; Meguro, H. An enantioselective synthesis of bengamide E. *J. Org. Chem.* **2002**, *57*, 5042–5044. [CrossRef]
14. Liu, Q.J.; Li, H.; Chen, S.P.; Zhou, G.C. Synthesis of (3S,4R)-bengamide E. *Chin. Chem. Lett.* **2011**, *22*, 505–507. [CrossRef]
15. Liu, W.; Szewczyk, J.M.; Waykole, L.; Repič, O.; Blacklock, T.J. Total synthesis of bengamide E. *Tetrahedron Lett.* **2002**, *43*, 1373–1375. [CrossRef]
16. Marshall, J.A.; Luke, G.P. Stereoselective Synthesis of a Bengamide E Derivative Through SE′Addition of a Chiral γ-Alkoxy Allylic Stannane to a Tartrate-Derived α, β-Dialkoxy Aldehyde. *Synlett* **1992**, *1992*, 1007–1008. [CrossRef]
17. Marshall, J.A.; Luke, G.P. Stereoselective total synthesis of bengamide E from glyceraldehyde acetonide and a nonracemic.gamma.-alkoxy allylic stannane. *J. Org. Chem.* **2002**, *58*, 6229–6234. [CrossRef]
18. Martin-Galvez, F.; Garcia-Ruiz, C.; Sanchez-Ruiz, A.; Valeriote, F.A.; Sarabia, F. An array of bengamide E analogues modified at the terminal olefinic position: Synthesis and antitumor properties. *ChemMedChem.* **2013**, *8*, 819–831. [CrossRef] [PubMed]
19. Metri, P.K.; Schiess, R.; Prasad, K.R. Enantiospecific total synthesis of (-)-bengamide E. *Chem. Asian J.* **2013**, *8*, 488–493. [CrossRef]
20. Mukai, C.; Kataoka, O.; Hanaoka, M. A cobalt-complexed propyanl in organic synthesis: A highly stereoselective total synthesis of bengamide E. *Tetrahedron Lett.* **1994**, *35*, 6899–6902. [CrossRef]
21. Mukai, C.; Kataoka, O.; Hanaoka, M. An efficient method for the optical resolution of 3-hydroxy-2-substituted-4-alkynoates: A highly stereoselective total synthesis of (+)-bengamide E1. *J. Org. Chem.* **2002**, *60*, 5910–5918. [CrossRef]
22. Mukai, C.; Moharram, S.M.; Kataoka, O.; Hanaoka, M. Highly stereocontrolled total synthesis of (+)-bengamide E. *J. Chem. Soc. Perkin Trans. 1* **1995**, *22*, 2849–2854. [CrossRef]
23. Phi, T.D.; Mai, H.D.T.; Tran, V.H.; Vu, V.L.; Truong, B.N.; Tran, T.A.; Chau, V.M.; Pham, V.C. Synthesis of bengamide E analogues and their cytotoxic activity. *Tetrahedron Lett.* **2017**, *58*, 1830–1833. [CrossRef]
24. Sarabia, F.; Martin-Galvez, F.; Chammaa, S.; Martin-Ortiz, L.; Sanchez-Ruiz, A. Chiral sulfur ylides for the synthesis of bengamide E and analogues. *J. Org. Chem.* **2010**, *75*, 5526–5532. [CrossRef] [PubMed]
25. Sarabia, F.; Martin-Galvez, F.; Garcia-Ruiz, C.; Sanchez-Ruiz, A.; Vivar-Garcia, C. Epi-, epoxy-, and C2-modified bengamides: Synthesis and biological evaluation. *J. Org. Chem.* **2013**, *78*, 5239–5253. [CrossRef] [PubMed]
26. Sarabia, F.; Sanchez-Ruiz, A. Total synthesis of Bengamide E and analogues by modification at C-2 and at terminal olefinic positions. *J. Org. Chem.* **2005**, *70*, 9514–9520. [CrossRef] [PubMed]
27. Zhang, W.; Liang, Q.; Li, H.; Meng, X.; Li, Z. Concise synthesis and antitumor activity of Bengamide E and its analogs. *Tetrahedron* **2013**, *69*, 664–672. [CrossRef]
28. Gupta, A.; Ambati, P.; Perali, R.S. A simple and efficient pathway for the total synthesis of marine natural products: Bengamide E and 5-epi-bengamide E. *Org. Biomol. Chem.* **2023**, *21*, 5861–5865. [CrossRef]
29. Banfi, L.; Basso, A.; Lambruschini, C.; Moni, L.; Riva, R. The 100 facets of the Passerini reaction. *Chem. Sci.* **2021**, *12*, 15445–15472. [CrossRef]

30. Faure, S.; Hjelmgaard, T.; Roche, S.P.; Aitken, D.J. Passerini reaction-amine deprotection-acyl migration peptide assembly: Efficient formal synthesis of cyclotheonamide C. *Org. Lett.* **2009**, *11*, 1167–1170. [CrossRef]
31. Moni, L.; Banfi, L.; Basso, A.; Carcone, L.; Rasparini, M.; Riva, R. Ugi and Passerini reactions of biocatalytically derived chiral aldehydes: Application to the synthesis of bicyclic pyrrolidines and of antiviral agent telaprevir. *J. Org. Chem.* **2015**, *80*, 3411–3428. [CrossRef] [PubMed]
32. Vishwanatha, T.M.; Giepmans, B.; Goda, S.K.; Domling, A. Tubulysin Synthesis Featuring Stereoselective Catalysis and Highly Convergent Multicomponent Assembly. *Org. Lett.* **2020**, *22*, 5396–5400. [CrossRef] [PubMed]
33. Lambruschini, C.; Moni, L.; Banfi, L. Diastereoselectivity in Passerini Reactions of Chiral Aldehydes and in Ugi Reactions of Chiral Cyclic Imines. *Eur. J. Org. Chem.* **2020**, *2020*, 3766–3778. [CrossRef]
34. Moni, L.; Banfi, L.; Basso, A.; Martino, E.; Riva, R. Diastereoselective Passerini Reaction of Biobased Chiral Aldehydes: Divergent Synthesis of Various Polyfunctionalized Heterocycles. *Org. Lett.* **2016**, *18*, 1638–1641, Erratum in *Org. Lett.* **2016**, *18*, 3306. [CrossRef] [PubMed]
35. Vitali Forconesi, G.; Banfi, L.; Basso, A.; Lambruschini, C.; Moni, L.; Riva, R. Synthesis of Polyoxygenated Heterocycles by Diastereoselective Functionalization of a Bio-Based Chiral Aldehyde Exploiting the Passerini Reaction. *Molecules* **2020**, *25*, 3227. [CrossRef] [PubMed]
36. Cerulli, V.; Banfi, L.; Basso, A.; Rocca, V.; Riva, R. Diversity oriented and chemoenzymatic synthesis of densely functionalized pyrrolidines through a highly diastereoselective Ugi multicomponent reaction. *Org. Biomol. Chem.* **2012**, *10*, 1255–1274. [CrossRef] [PubMed]
37. Pottie, M.; De Lathauwer, G.; Vandewalle, M. Erythritol: A Versatile Precursor for C-4 Chiral Building Blocks. *Bull. Soc. Chim. Belg.* **2010**, *103*, 285–294. [CrossRef]
38. Pappenberger, G.; Hohmann, H.P. Industrial production of L-ascorbic Acid (vitamin C) and D-isoascorbic acid. *Adv. Biochem. Eng. Biotechnol.* **2014**, *143*, 143–188. [CrossRef] [PubMed]
39. Cohen, N.; Banner, B.L.; Laurenzano, A.J.; Carozza, L. 2,3-O-Isopropylidene-D-Erythronolactone. *Org. Synth.* **1985**, *63*, 127. [CrossRef]
40. Sydnes, L.K.; Holmelid, B.; Kvernenes, O.H.; Valdersnes, S.; Hodne, M.; Boman, K. Stereospecific synthesis of allylic and homoallylic alcohols from functionalized propargylic alcohols. *Arkivoc* **2008**, *2008*, 242–268. [CrossRef]
41. Ha, H.J.; Hong, M.C.; Ko, S.W.; Kim, Y.W.; Lee, W.K.; Park, J. Synthesis of constrained ceramide analogs and their potent antileukemic activities. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1880–1883. [CrossRef] [PubMed]
42. Baudouy, R.; Gore, J. Reduction d'alcools alleniques par l'hydrure et le methoxy hydrure de lithium et d'aluminium. *Tetrahedron* **1975**, *31*, 383–389. [CrossRef]
43. Younus, M.; Khan, M.A.; Moin, S.T.; Basha, F.Z. Engaging Diastereomeric syn- and anti-6-Bromo-4a-isopropyl-2-methyl-2,3,4,4a-tetrahydro-1H-carbazoles in Suzuki Coupling Reaction: Synthesis, Spectral Characterization and DFT Studies. *ChemistrySelect* **2023**, *8*, e202300649. [CrossRef]
44. Halvorsen, G.T.; Roush, W.R. Stereoselective Synthesis of the Decahydrofluorene Core of the Hirsutellones. *Tetrahedron Lett.* **2011**, *52*, 2072–2075. [CrossRef] [PubMed]
45. Denmark, S.E.; Jones, T.K. (E)-3-(Trimethylsilyl)-2-propen-1-ol. An improved preparation. *J. Org. Chem.* **1982**, *47*, 4595–4597. [CrossRef]
46. Kobayashi, Y.; Yamaguchi, K.; Morita, M. Regio- and stereoselective SN2′ reaction of an allylic picolinate in the synthesis of LY426965. *Tetrahedron* **2018**, *74*, 1826–1831. [CrossRef]
47. Yadav, J.S.; Thirupathaiah, B.; Singh, V.K.; Ravishashidhar, V. Total synthesis of (+)-synargentolide A. *Tetrahedron Asymmetry* **2012**, *23*, 931–937. [CrossRef]
48. Shiozaki, M.; Tashiro, T.; Koshino, H.; Nakagawa, R.; Inoue, S.; Shigeura, T.; Watarai, H.; Taniguchi, M.; Mori, K. Synthesis and biological activity of ester and ether analogues of alpha-galactosylceramide (KRN7000). *Carbohydr. Res.* **2010**, *345*, 1663–1684. [CrossRef] [PubMed]
49. Hara, A.; Morimoto, R.; Iwasaki, Y.; Saitoh, T.; Ishikawa, Y.; Nishiyama, S. Total Syntheses of Amphidinolides B, G, and H. *Angew. Chem. Int. Ed.* **2012**, *51*, 9877–9880. [CrossRef]
50. Moodie, L.W.K.; Larsen, D.S. A Ring-Closing Enyne Metathesis Approach to Functionalized Semicyclic Dienes: The Total Synthesis of (–)-Tetrangomycin. *Eur. J. Org. Chem.* **2014**, *2014*, 1684–1694. [CrossRef]
51. Xiong, Z.; Hale, K.J. Total Synthesis of the Antitumor Macrolides, (+)-Brefeldin A and 4-Epi-Brefeldin A from d-Glucose: Use of the Padwa Anionic Allenylsulfone [3 + 2]-Cycloadditive Elimination to Construct Trans-Configured Chiral Cyclopentane Systems. *Org. Lett.* **2016**, *18*, 4254–4257. [CrossRef] [PubMed]
52. Banfi, L.; Basso, A.; Riva, R. Chiral Nonracemic Isocyanides. In *Isocyanide Chemistry: Applications in Synthesis and Material Science*; Wiley: New York, NY, USA, 2012; pp. 1–33. [CrossRef]
53. Xu, D.D.; Waykole, L.; Calienni, J.V.; Ciszewski, L.; Lee, G.T.; Liu, W.; Szewczyk, J.; Vargas, K.; Prasad, K.; Repič, O.; et al. An Expedient Synthesis of LAF389, a Bengamide B Analogue. *Org. Process Res. Dev.* **2003**, *7*, 856–865. [CrossRef]