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Unified Synthesis of Densely Functionalized Amino Acid Building Blocks for the Preparation of Caprazamycin Nucleoside Antibiotics

Ruth Linder,[a] and Christian Ducho*[a]

Abstract: Naturally occurring caprazamycin nucleoside antibiotics are promising lead structures for the development of novel antimicrobial agents. However, efficient synthetic access to the structurally complex caprazamycin scaffold is not trivial. The stereocontrolled construction of the seven-membered diazepanone core moiety is particularly challenging. So far, two main strategies to build up the diazepanone system (via reductive amination or Mitsunobu reaction) have been established, but they require different non-proteinogenic amino acid building blocks to be connected with the nucleoside moiety. Previously, these amino acid structures were obtained from different starting materials with no overlap of the according synthetic routes. In this work, we describe an efficient unified synthetic access to densely functionalized amino acid building blocks for both approaches towards the diazepanone core. This will enable the preparation of caprazamycin analogues with high modularity and variability.

Introduction

Bacterial resistances against established antibiotics are on the rise and represent a serious threat to human health.[1,2] It is therefore crucial to develop new antibacterial agents. Ideally, such compounds should display novel or clinically unexploited modes of action in order to avoid cross resistance to exisiting antimicrobial drugs.

Nucleoside antibiotics are such a class of potential antibacterial drug candidates.[3] They are naturally occurring uridine derivatives inhibiting the bacterial membrane enzyme MraY (translocase I), which catalyzes a key step in the early intracellular stages of cell wall (i.e., peptidoglycan) formation.[4] Thus, such MraY inhibitors fulfill the paradigm to address a clinically unexploited bacterial target.[5]

Nucleoside antibiotics have been grouped into several sub-classes, e.g., muraymycins, caprazamycins, liposidomycins, mureidomycins, pacidamycins, sansanmycins, capuramycins, and tunicamycins.[3] Using these natural product scaffolds for antibacterial drug development is facilitated by recently reported X-ray crystal structures of MraY[6] as well as efficient methods to overexpress the enzyme[7] and assay its activity (and therefore inhibition) in vitro.[8] Structure-activity relationship (SAR) studies have been reported for many of the aforementioned sub-classes of nucleoside antibiotics, among them the muraymycins[9] and caprazamycins.[10] In the case of caprazamycins, this has furnished the structurally simplified anti-tuberculotic drug candidate CPZEN-45.[11] However, the pronounced structural complexity of nucleoside antibiotics represents a significant hurdle in such investigations as the total synthesis of corresponding analogues is not trivial.

Caprazamycins are a highly promising sub-class of nucleoside antibiotics with respect to their activity against *M. tuberculosis*. Synthetic access to the caprazamycin scaffold (e.g., natural products caprazamycin A **1** and caprazamycin B **2**, Scheme 1) is very challenging though. Both for the synthesis of the parent natural products and of caprazamycin analogues, the target structures are usually traced back to a protected version **3** of the nucleoside-peptide core structure (often referred to as 'caprazol'). The preparation of the caprazol unit involves two major tasks: (i) the synthesis of the uridine-derived, 5'-*O*-aminoribosylated nucleosyl amino acid and (ii) the construction of the substituted diazepanone ring. Several researchers have developed approaches to overcome these hurdles. Ichikawa and Matsuda have reported a synthesis of the caprazol unit in which the diazepanone was formed by reductive amination.[12] Takemoto has achieved the first total synthesis of caprazamycin A **1** utilizing a Mitsunobu reaction for diazepanone ring closure.[13] Watanabe and Shibasaki have developed a total synthesis of caprazamycin B **2** which involved a reductive amination protocol for construction of the diazepanone.[14] Other noteworthy contributions include Sarabia's synthesis of a 6'-epimer of the caprazol unit via a Rh(II)-catalyzed carbene insertion key step[15] and Miyaoka's preparation of a caprazol 5'-epimer by intramolecular nucleophilic epoxide opening.[16]

Taken together, the most promising strategies for the construction of the substituted diazepanone ring system appear to be intramolecular reductive amination or Mitsunobu-type nucleophilic displacement. Thus, corresponding precursors of key intermediate **3** would be either aldehyde **4** or primary alcohol **5** (Scheme 1). For their syntheses, non-proteinogenic amino acid building blocks **6** and **7**, respectively, are required, with the olefin in **6** serving as a 'masking' unit for the reactive aldehyde moiety. Overall, the aforementioned literature on caprazamycin syntheses[12-16] strongly suggest that even subtle structural changes significantly influence the outcome of the diazepanone-forming reactions. For instance, when Sarabia aimed for a 6'-epimer of the caprazol core structure, ring closure of the diazepanone by nucleophilic epoxide opening or by Mitsunobu reaction failed.[15] On the other hand, Mitsunobu-type

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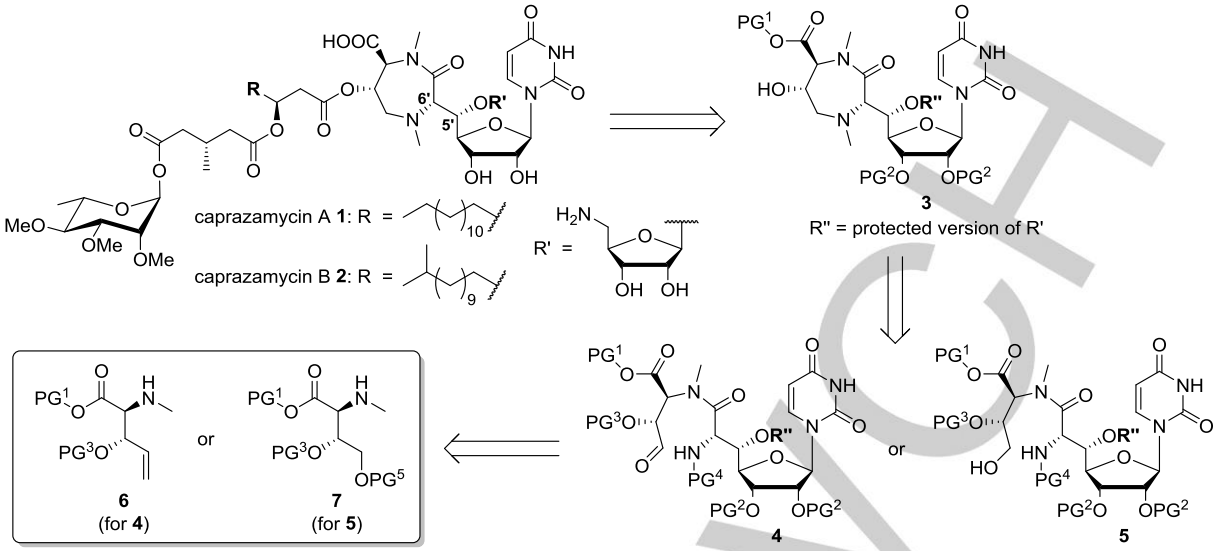


Scheme 1. Selected examples **1** and **2** of naturally occurring caprazamycin nucleoside antibiotics as well as their retrosynthesis leading to non-proteinogenic amino acid building blocks **6** and **7** (boxed) as principle target structures of this study. PG^1-PG^5 = protecting groups.

diazepanone formation was successfully employed in Takemoto's total synthesis of caprazamycin A1 **1**.[13] It should be noted that the substrates for the Mitsunobu transformation in both aforementioned cases differed not only in the stereochemistry at C-6', but also in their protecting group and subsitution patterns. In stark contrast to Sarabia's results, Miyaoka's synthesis of a caprazol 5'-epimer successfully proceeded via intramolecular nucleophilic epoxide opening.[16] Again, the ring closure precursors in both cases differed in more than just their stereochemical configurations.

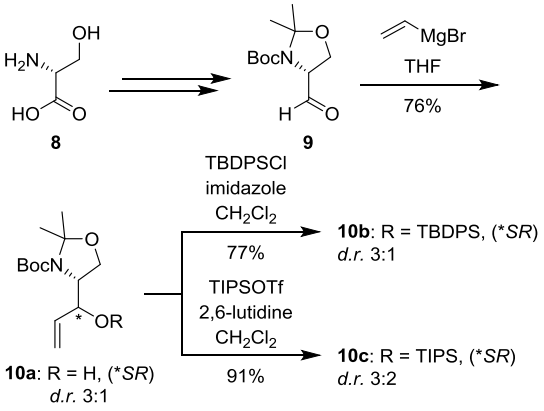
This review of the available literature on caprazamycin syntheses demonstrates that detailed SAR studies on caprazamycins and their analogues require strategic flexibility in the synthetic routes to diverse target structures. Hence, different amino acid precursors of types **6** or **7** should ideally be available from a small set of shared precursors, thus enabling a rapid switching between different syntheses of **3** (Scheme 1). However, browsing available syntheses of caprazamycins and their analogues[12-16] reveals that amino acid building blocks of types **6** or **7** were obtained via totally different routes and from different precursors. Ichikawa and Matsuda prepared an amino acid of type **6** or a reduced variant thereof starting from a derivative of the (*R*)-configured Garner aldehyde[17] and therefore, ultimately, from D-serine.[10c,12,18] In contrast, Takemoto obtained a building block of type **7** from L-diethyl tartrate.[13] Watanabe and Shibasaki chose a different route towards an analogue of **6** as they employed a catalytic enantioselective nitroaldol reaction.[14b] Thus, they constructed the stereocenters in **6** not via an ex-chiral pool-type strategy, but by stereoselective catalysis. In his comparative synthetic studies towards 6'-*epi*-caprazol,[15] Sarabia used analogues of **6** and **7** obtained from L-methionine[19] and via Sharpless aminohydroxylation,[20] respectively. In the synthesis of 5'-*epi*-caprazol,[16] Miyaoka required a γ-amino analogue of **7**, which was prepared starting from a derivative of the (*R*)-Garner aldehyde and therefore ultimately from D-serine.[21] Overall, these synthetic routes towards building blocks **6** and **7** are very diverse and show little to no overlap.

In this work, we have therefore aimed to develop a unified synthesis of densely functionalized, non-proteinogenic amino acids of both principle types **6** and **7**. Our goals were as follows: (i) both amino acid structures should be accessible from one shared precursor or a small set of precursors, respectively; (ii) the diversification towards **6** or **7** should occur at a rather late stage; (iii) different protecting group patterns should be accessible; (iv) the unified route should also enable the synthesis of stereoisomers of **6** and **7**, respectively. Taken together, these considerations were envisioned to furnish a small set of amino acid building blocks for a maximum of strategic and structural flexibility in the future preparation of caprazamycins and their analogues.

Results and Discussion

In order to develop the desired unified synthetic route, we decided to transform D-serine **8** into the (*R*)-configured Garner aldehyde **9**, according to established protocols (Scheme 2).[17] Chiral aldehyde **9** appeared to be an ideal candidate for the envisioned shared precursor en route to **6** and **7** for the following reasons: (i) it had already been proven useful in the works of Ichikawa and Matsuda[12] as well as Miyaoka[16] (vide supra); (ii) switching from D-serine to L-serine as starting material would readily enable the synthesis of enantiomeric target structures, thus ultimately providing access to stereochemically altered caprazamycin analogues; (iii) addition reactions to the Garner aldehyde can differ in diastereoselectivities,[22] which might furnish either *syn*- or *anti*-configured products, finally providing

α,β-*syn* or α,β-*anti* β-hydroxy-α-amino acids. In this context, it should be noted that α,β-*anti*-configured building blocks of types **6** and **7** lead to caprazamycins with native stereochemistry (see Scheme 1), while an α,β-*syn*-configuration would furnish epimeric caprazamycin analogues.

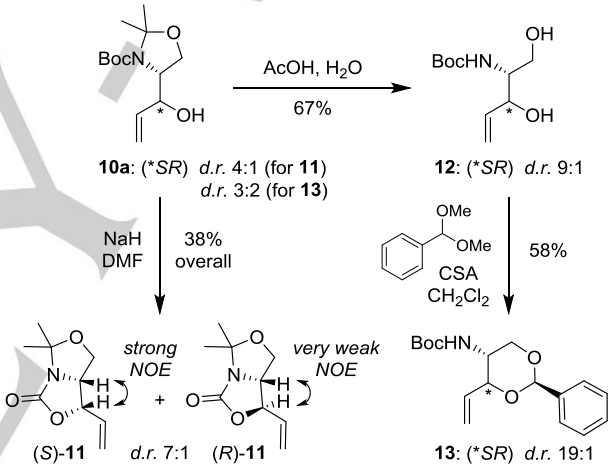


Scheme 2. Synthesis of differently protected amino alcohols **10a**-**c** as shared set of precursors.

The addition of vinyl magnesium bromide to **9** gave allylic alcohol **10a**[10c,12,18] in 76% yield in a non-stereocontrolled manner (Scheme 2). The further synthetic processing of **10a** required protection of the hydroxy group. Hence, **10a** was silylated to give TPDPS derivative **10b** in 77% yield and TIPS-protected congener **10c** in 91% yield, respectively. We prepared both *O*-protected derivatives because of the different stabilities of the silyl ether moieties and in order to pave the way for target structures with different protecting group patterns. Allylic alcohols **10a**-**c** already contained the vicinal amino alcohol motif found in **6** and **7** and can therefore be considered to be the envisioned small set of shared precursors for both target structures.

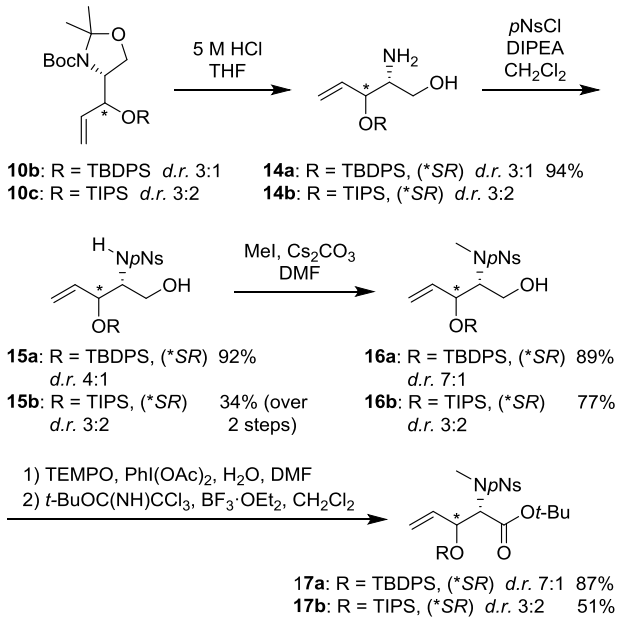
The diastereoselectivity of the Grignard addition to **9** was rather low, with **10a** being isolated as a diastereomeric mixture (*d.r.* 3:1, Scheme 2). In principle, this would provide the desired flexibility to prepare all possible stereoisomers of the target structures after separation of the diastereomeric mixtures. However, the separation of the obtained epimeric mixture of **10a** was tedious, and consequently, it was envisioned to separate the diastereomers at later stages of the synthetic routes.

Based on precedent,[22] it was postulated that the major diastereomer of the epimeric mixture of **10a** would be the *anti*-configured (**S*) Felkin-Anh product, which would correspond to the *anti*-stereochemistry in target structures **6** and **7**. In order to ensure that this proposed assignment was correct, we transformed the diastereomeric mixture of **10a** into cyclic analogues. This was expected to enable the elucidation of relative configurations based on nuclear Overhauser enhancement (NOE) NMR experiments or ^{1}H NMR coupling constants. Therefore, **10a** (a diastereomerically enriched fraction with *d.r.* 4:1) was converted into bicyclic carbamates **11** in 38% overall yield (*d.r.* 7:1), as a result of spontaneous ring closure after deprotonation of the alcohol with sodium hydride (Scheme 3). Using this diastereomeric mixture of **11**, the *cis* and *trans* configurations of the oxazolidinone moieties in (*S*)-**11** and (*R*)-**11**, respectively, were proven by 1D NOE ^{1}H NMR studies. The two protons attached to the oxazolidinone ring in the minor *trans* isomer (*R*)-**11** showed a very weak NOE, whereas *cis*-configured (*S*)-**11** as the major component gave a strong NOE. In addition, **10a** (a fraction with *d.r.* 3:2) was acidically deprotected to afford diol **12** in 67% yield (*d.r.* 9:1). Subsequent acetal formation then furnished 1,3-dioxane **13** in 58% yield (*d.r.* 19:1). The six-membered ring in **13** was ideally suited to assign relative configurations based on ^{1}H NMR coupling constants. Rigorous NMR analysis of **13** revealed the major diastereomer to be (*S*)-configured at the stereocenter in question. Taken together, it was therefore unambiguously proven that, as anticipated, the major diastereomer formed in the Grignard addition step was the *anti*-configured (**S*) Felkin-Anh product.



Scheme 3. Synthesis of bicyclic carbamates **11** and 1,3-dioxane **13** for the NMR-based stereochemical elucidation of **10a**. CSA = camphorsulfonic acid.

The synthetic route was continued with silylated Grignard addition products **10b** and **10c**. Acidic cleavage of the isopropylidene acetal in TBDPS-protected **10b** gave amino alcohol **14a** in 94% yield without significant change of diastereomeric purity (*d.r.* 3:1, Scheme 4). This was followed by *N*-nosyl protection with *para*-nitrobenzenesulfonyl chloride (product **15a**) in 92% yield, with slight enrichment of the major (**S*)-isomer after purification (*d.r.* 4:1). Remarkably, this procedure was not fully applicable for the TIPS-protected congener **10c**. The corresponding intermediate **14b** was instable and had to be protected immediately (without purification) with the *p*Ns group. Consequently, a yield of only 34% over two steps was obtained for TIPS-protected **15b**. We also explored other commonly used methods for cleavage of the acetonide unit in **10c**, such as acetyl chloride or TFA, but none of them led to improved yields.

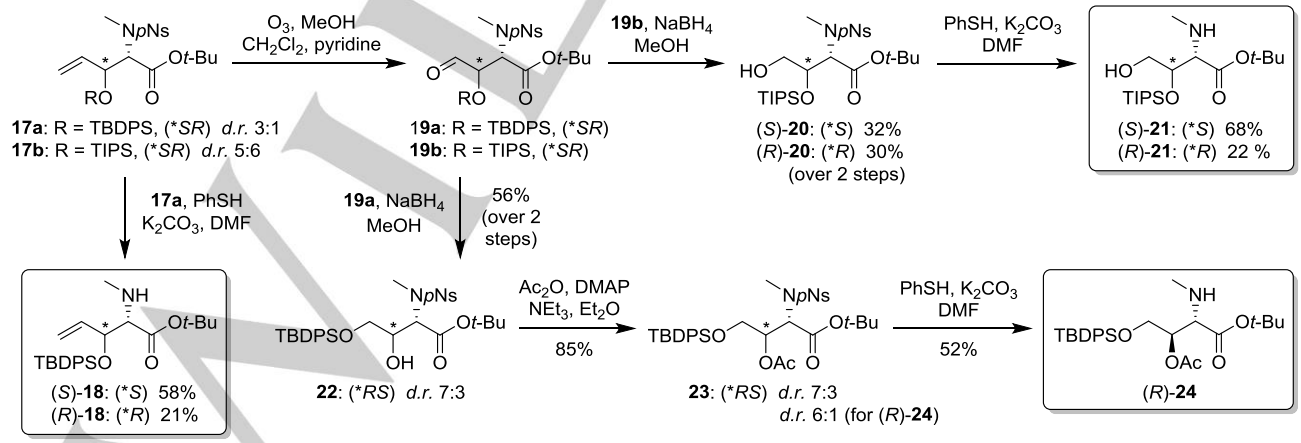


Scheme 4. Synthesis of protected amino acids **17a**,**b** as shared precursors of the target structures. *p*Ns = *para*-nitrobenzenesulfonyl.

The subsequent *N*-methylation step turned out to be challenging. Initial attempts using the conditions reported by Ichikawa and Matsuda (methyl iodide, sodium hydride, DMF)[10c] were unsuccessful. We initially explored several variations of the protecting group pattern, including *N*-trichloroethoxycarbonyl (Troc) in combination with *O*-dimethoxytrityl (DMTr), as well as different methylating reagents (i.e., dimethyl sulfate), but no reaction was observed. This was not overcome when the protecting group pattern was further changed to *N*-Cbz and *O*-TBDMS (reactions not shown). However, the nosyl derivatives **15a** and **15b** were sufficiently reactive when methyl iodide was applied in the presence of cesium carbonate, thus furnishing **16a** in 89% yield and **16b** in 77% yield (Scheme 4). Under these conditions, no protection of the primary hydroxy group was needed. Finally, a two-step protocol of oxidation (using TEMPO and bis-(acetoxy)-iodobenzene) with subsequent *tert*-butyl ester formation using a trichloroacetimidate afforded amino acids **17a** and **17b** in yields of 87% and 51%, respectively, over both steps of this sequence.

Protected amino acids **17a** and **17b** were then utilized as shared precursors for the synthesis of five different target amino acid building blocks. First, amino deprotection of **17a** (a fraction with *d.r.* 3:1) was performed with thiophenol in the presence of potassium carbonate (Scheme 5). For the resultant product, diasteromers could be separated by column chromatography, thus affording (*S*)-**18** and (*R*)-**18** in diastereomerically pure form and in yields of 58% and 21%, respectively. These two pure stereoisomers of **18** represented the first target structures as they were representatives of amino acids of type **6** (see Scheme 1). Second, both silylated precursors **17a** (a fraction with *d.r.* 3:1) and **17b** (a fraction with *d.r.* 5:6) were subjected to ozonolysis to cleave the olefin moieties. Resultant crude aldehydes **19a** and **19b** (each as epimeric mixtures) were directly converted in the next step. In the case of TIPS-protected **19b**, reduction of the aldehyde gave the corresponding primary alcohol. At this stage, diastereomers could be separated by column chromatography to furnish (*S*)-**20** and (*R*)-**20** in diastereomerically pure form and in yields of 32% and 30%, respectively, over two steps. Amino deprotection under the aforementioned conditions then gave amino acid building blocks (*S*)-**21** and (*R*)-**21** in yields of 68% and 22%, respectively (Scheme 5). These two pure stereoisomers of **21** represented another stereoisomeric couple of target structures as they were representatives of amino acids of type **7** (see Scheme 1).

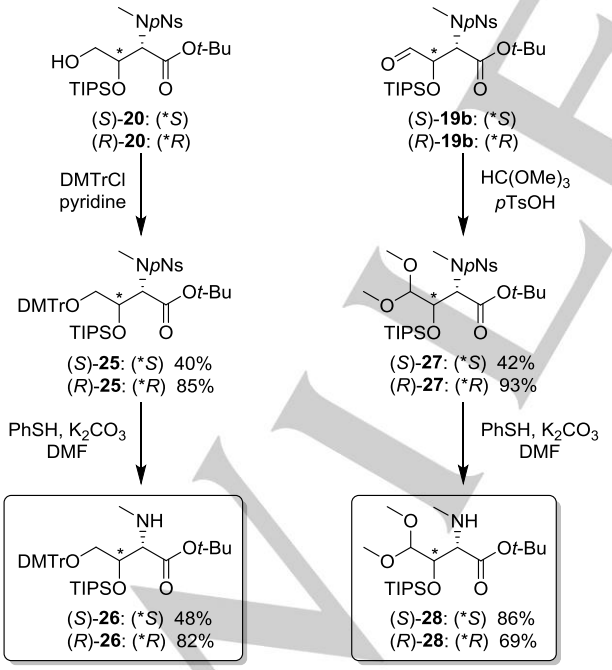
Remarkably, when a similar sequence was attempted with TBDPS-protected congener **19a**, the reduction step led to a migration of the TBDPS group onto the primary alcohol, thus affording **22** in 56% yield over two steps (*d.r.* 7:3, Scheme 5). We initially tried to reprotect the secondary alcohol with different silyl protecting groups which was unsuccessful, probably due to



Scheme 5. Synthesis of amino acid target structures **18**, **21** and (*R*)-**24** (boxed).

steric hindrance. However, acetylation of the hydroxy group was feasible and gave **23** in 85% yield (*d.r.* 7:3). When a fraction of this material (with *d.r.* 6:1) was subjected to amino deprotection, only one stereoisomer (*R*)-**24** was isolated in 52% yield. With respect to its amount, this diastereomer had to be equivalent to the major component of the precursor mixtures, i.e., it had to be a derivative of the *anti*-configured Grignard addition product. Due to altered priorities, this relative configuration corresponded to a formal (3*R*)-stereochemistry in derivative **24**. Amino acid **24** also represented a target structure as it was another representative of amino acids of type **7** (see Scheme 1).

Building blocks **21** were not protected at the primary alcohol functionality, assuming that subsequent peptide coupling reactions for caprazamycin syntheses would proceed selectively at the secondary amine. However, it was envisioned that the synthetic route shown in Scheme 5 would enable the facile introduction of an additional protecting group for the primary alcohol. This was demonstrated by DMTr protection of the hydroxy functionality. Starting from synthetic intermediates (*S*)-**20** and (*R*)-**20**, DMTr protection afforded (*S*)-**25** and (*R*)-**25** in diastereomerically pure form and in yields of 40% and 85%, respectively (Scheme 6). Subsequent amino deprotection gave two pure stereoisomers (*S*)-**26** (48% yield) and (*R*)-**26** (82% yield) as additional target structures representing amino acids of type **7** (see Scheme 1). When either diasteromer of **26** is employed for the synthesis of the diazepanone caprazamycin core, very mild acidic conditions are anticipated to selectively cleave the DMTr group, thus liberating the primary alcohol for Mitsunobu-type ring closure.



Scheme 6. Synthesis of amino acid target structures **26** and **28** (boxed). DMTr = 4,4'-dimethoxytrityl.

We have also considered alternative options for the 'masking' of the aldehyde moiety when reductive amination strategies are employed for diazepanone formation. In amino acid building blocks of type **6**, the aldehyde unit is masked as an olefin and therefore needs to be formed oxidatively, e.g., by bis-hydroxylation/periodate cleavage sequences.[12] However, such oxidative transformations might cause severe side reactions when applied to the densely functionalized caprazamycin scaffold. Therefore, alternative options for formation of the aldehyde moiety in caprazamycin syntheses are desirable. We managed to separate the diastereomeric mixture of TIPS-protected aldehyde **19b** (which had just been used as a crude synthetic intermediate before, see Scheme 5) by column chromatography (not shown). Resultant isomers (*S*)-**19b** and (*R*)-**19b** were then transformed in dimethyl acetal-forming reactions, furnishing (*S*)-**27** and (*R*)-**27** in diastereomerically pure form and in yields of 42% and 93%, respectively (Scheme 6). The moderate yield of isomer (*S*)-**27** resulted from an obvious side reaction that was not observed for (*R*)-**27**, i.e., unwanted cleavage of the *tert*-butyl ester and subsequent ring closure of the acid with the aldehyde (not shown). Finally, amino deprotection gave (*S*)-**28** and (*R*)-**28** in diastereomerically pure form and in yields of 86% and 69%, respectively, as additional target structures. When **28** is employed for the synthesis of the diazepanone caprazamycin core, very mild acidic conditions are anticipated to selectively cleave the dimethyl acetal moiety, thus liberating the aldehyde for subsequent ring closure by reductive amination. Hence, amino acid building blocks **28** can be classified as novel functional equivalents to amino acids of type **6** (see Scheme 1).

Conclusions

In summary, we have accomplished a unified synthesis of five different densely functionalized amino acid target compounds (see boxed structures in Schemes 5 and 6). Starting from D-serine **8** and via the (*R*)-Garner aldehyde **9**, amino alcohols **10a**-**c** were synthesized as a small set of shared precursors. These were then transformed into two amino acid precursors **17a** and **17b**. Further conversions of these key intermediates afforded the following target compounds: (i) **18** and **28** as representatives or functional analogues, respectively, of amino acid building blocks of type **6**; (ii) **21**, (*R*)-**24** and **26** as representatives of amino acid building blocks of type **7** (also see Scheme 1). With the exception of (*R*)-**24**, all of these amino acid target structures were obtained both with *anti*-configuration of the amino alcohol motif (equivalent to native caprazamycin structures) and as *syn*-configured congeners (equivalent to epimeric caprazamycin analogues), each in diastereomerically pure form. Stereochemical purity was efficiently achieved by chromatographic separations at late stages of the synthetic routes.

Overall, the reported unified synthetic strategy fulfilled the outlined goals (vide supra): (i) both amino acid structures of types **6** and **7** were accessible from one shared precursor (**8**/**9**) or a small set of precursors (**10a**-**c**/**17a**,**b**), respectively; (ii) the

diversification towards **6** or **7** occured at a rather late stage, i.e., after the synthesis of **17a**,**b**; (iii) similar target structures with different protecting group patterns were prepared; (iv) the unified route also enabled the synthesis of stereoisomers of **6** and **7**, respectively. It should be noted that, when L-serine is employed as a general starting material, all enantiomers of the target structures are in principle accessible as well. Therefore, the reported route provides facile access to all stereochemical variations of the corresponding structural motif in caprazamycins.

The different protecting group patterns of the target compounds and the two different approaches of 'masking' the reactive aldehyde (olefin vs. dimethyl acetal) will provide maximum flexibility in the non-trivial construction of the caprazamycin diazepanone core. In combination with the strong potential for stereochemical variations, the reported set of target amino acids (accessed via a unified route) therefore represents a highly useful 'toolbox' for the future synthesis of caprazamycins and their analogues for more detailed SAR studies. It should be noted that β-hydroxy-α-amino acids are ubiquitous structural motifs that are frequently found in many peptidic natural products. Therefore, our reported 'toolbox' might also be very versatile for the total synthesis of other peptide-derived target structures.

Experimental Section

General Methods: Chemicals were purchased from standard suppliers and used without further purification. Ozone was generated using a Fischer ozone generator model 502. Reactions involving oxygen and/or moisture sensitive reagents were carried out under an atmosphere of nitrogen using anhydrous solvents. The glass equipment used for these reactions was dried by heating prior to use. Anhydrous solvents were obtained in the following manner: CH_2Cl_2 and DMF were purchased in HPLC quality, dried with a solvent purification system (MBRAUN MB SPS 800) and stored over activated molecular sieves (4 Å). Pyridine was dried over CaH_2 and distilled. MeOH was of absolute quality, degassed and stored over activated molecular sieves (3 Å). Solvents for reactions without inert conditions, extractions, and chromatography were of technical quality and distilled prior to their use. All other solvents were of p.a. quality, and distilled water was used throughout. Column chromatography was carried out on silica gel 60 (0.040-0.063 mm, 230-400 mesh ASTM, VWR) under flash conditions. TLC was performed on aluminium plates precoated with silica gel 60 F_{254} (VWR). Visualization of the spots was carried out using UV light (254 nm) where appropriate and/or staining under heating ($KMnO_4$ staining solution: 1 g $KMnO_4$, 6 g K_2CO_3 and 1.5 mL 5% $NaOH_{aq}$ (w/v), all dissolved in 100 mL H_2O; ninhydrin staining solution: 0.3 g ninhydrin, 3 mL AcOH, all dissolved in 100 mL 1-butanol, H_2SO_4 staining solution: 4 g vanillin, 25 mL conc. H_2SO_4, 80 mL AcOH, all dissolved in 680 mL MeOH). Preparative TLC was performed on a Chromatotron (Harrison Research, Model 7924T-01, T-Squared Technology) using glass plates coated with 1 mm or 2 mm layers of silica gel containing a fluorescent indicator (VWR 60 PF_{254}). 500 MHz-^{1}H NMR and 126 MHz-^{13}C NMR spectra were recorded on Bruker AVANCE-500 spectrometers. All ^{13}C NMR spectra are ^{1}H-decoupled. All spectra were recorded at room temperature except where indicated otherwise and were referenced internally to solvent reference frequencies. Chemical shifts (δ) are quoted in ppm. Coupling constants (*J*) are reported in Hz to the nearest 0.1 Hz. The assignment of signals was carried out using ^{1}H,^{1}H-COSY and HSQC spectra obtained on the spectrometers mentioned above. In the case of diastereomeric mixtures, the minor component is labeled with an asterisk. Low resolution ESI mass spectrometry was performed on a Thermo Scientific Spectra System with a Finnigan ion-trap mass spectrometer MSQ. High resolution (HR) ESI mass spectrometry was carried out on a Bruker time-of-flight (TOF) maXis. Optical rotations were recorded on a Krüss Optronic Germany polarimeter with a Na source using a 5 cm cell. Infrared spectroscopy (IR) was performed on a Bruker Vertex 70 spectrometer equipped with an integrated ATR unit (PlatinumATR™). Wavenumbers (ν) are quoted in cm^{-1}. UV spectroscopy was carried out on an Agilent Cary 100 spectrophotometer. Wavelengths of maximum absorption (λ_{max}) are reported in nm.

General procedure (GP) for cleavage of the *p*Ns protecting group: A solution of the protected amine and K_2CO_3 (3.0 eq) in dry DMF was stirred at rt for 5 min. Thiophenol (1.2 eq) was added and the solution was stirred at rt. After complete conversion, sat. $NaHCO_3$ solution was added and the mixture was extracted with EtOAc (3 x). The combined organics were washed with water (2 x) and brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The resultant crude product was purified by column chromatography.

(*N*-Boc-(4*R*,1'*SR*)-4-(1'-(*tert*-butyldiphenylsilyloxy)-2'-propenyl)-2,2-dimethyl-1,3-oxazolidine (10b): To a solution of **10a**[10c,12,18] (686 mg, 2.67 mmol, *d.r.* 3:1) in dry DMF (10 mL), imidazole (725 mg, 10.7 mmol) followed 15 min later by TBDPS chloride (2.10 mL, 2.20 g, 8.00 mmol) were added and the mixture was stirred at rt for 4 h. Water (30 mL) and EtOAc (30 mL) were added. The organic layer was washed with water (2 x 30 mL) and brine (90 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resultant crude product was purified by column chromatography (petroleum ether-EtOAc, 15:1) to give **10b** as a brownish oil (1.01 g, 77%, *d.r.* 3:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.06-1.11 (m, 9H, $SiC(CH_3)_3$, $SiC(CH_3)_3$*), 1.40-1.56 (m, 15H, $C(CH_3)_2$, $C(CH_3)_3$, $C(CH_3)_2$*, $C(CH_3)_3$*), 3.87-4.21 (m, 3H, H-4, H-4*, H-5, H-5*), 4.24-4.41 (m, 0.75H, H-1'), 4.61-4.71 (m, 0.25H, H-1'*), 4.66 (dd, *J* = 17.4, 8.4 Hz, 0.75H, H-3'$_a$), 4.78 (dd, *J* = 19.0, 8.4 Hz, 0.75H, H-3'$_b$), 4.92-5.13 (m, 0.5H, H-3'*), 5.63-5.81 (m, 0.75H, H-2'), 8.81-5.94 (m, 0.25H, H-2'*), 7.32-7.49 (m, 6H, Ph), 7.62-7.74 (m, 4H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 19.42 ($SiC(CH_3)_3$), 23.15, 24.81 ($C(CH_3)_2$), ($C(CH_3)_2$*), 27.00, 27.10 ($SiC(CH_3)_3$, $SiC(CH_3)_3$*), 28.32, 28.39 ($C(CH_3)_3$, $C(CH_3)_3$*), 60.52 (C-5*), 61.89 (C-5), 63.42 (C-4*), 64.59 (C-4), 73.61 (C-1'*), 76.19 (C-1'), 79.69 ($C(CH_3)_3$), 79.95 ($C(CH_3)_3$*), 93.76 ($C(CH_3)_2$), 94.27 ($C(CH_3)_2$*), 116.65 (C-3'), 117.30 (C-3'*), 127.36, 127.43, 127.59, 129.45, 129.55, 133.86, 135.58, 135.81 (Ph), 136.24 (C-2'*), 138.22 (C-2'), 152.14, 152.82 (NHC=O, NHC=O*) ppm. MS (ESI): *m/z* = 518.1 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{29}H_{41}NO_4Si$ $[M+H]^+$ 496.2878; found 496.2896. TLC (petroleum ether-EtOAc, 5:1): R_f = 0.65.

(*N*-Boc-(4*R*,1'*SR*)-4-(1'-(triisopropylsilyloxy)-2'-propenyl)-2,2-dimethyl-1,3-oxazolidine (10c): To a solution of **10a** (3.23 g, 12.6 mmol, *d.r.* 3:2) in dry CH_2Cl_2 (10 mL), 2,6-lutidine (1.81 mL, 1.67 g, 16.3 mmol) and TIPS triflate (4.40 mL, 5.00 g, 16.3 mmol) were added at 0 °C and the mixture was stirred at 0 °C for 80 min. HCl (1 M, 75 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were washed with brine (100 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resultant crude product was purified by column chromatography (petroleum ether-EtOAc, 50:1→1:1) to give **10c** (4.70 g, 91%, *d.r.* 3:2) as a colorless oil. ^{1}H NMR (500 MHz, $[D_6]$DMSO, 100 °C): δ = 0.92-1.11 (m, 21H, 3 x $CH(CH_3)_2$), 1.38-1.52 (m, 15H, $C(CH_3)_3$, $C(CH_3)_2$), 3.74-3.80 (m, 0.4H, H-4*), 3.87-4.07 (m, 2.6H, H-4, H-5, H-5*), 4.47-4.54 (m, 0.4H, H-1'*), 4.69-4.77 (m, 0.6H, H-1'), 5.09-5.22 (m, 2H, H-3', H-3'*), 5.77-5.89 (m, 1H, H-2', H-2'*) ppm. ^{13}C NMR (126 MHz, $[D_6]$DMSO, 100 °C): δ = 12.40, 12.78 ($C(CH_3)_2$), 18.25, 28.55 ($C(CH_3)_2$), 28.66 ($C(CH_3)_3$), 61.27 (C-4), 62.53 (C-5), 63.01 (C-4*), 63.91 (C-5*), 72.27 (C-1'), 74.42 (C-1'*),

79.73, 79.92 (C(CH$_3$)$_3$, C(CH$_3$)$_3$*), 94.06 (C(CH$_3$)$_2$), 97.16 (C(CH$_3$)$_2$*), 116.52 (C-3'), 116.93 (C-3'*), 137.70 (C-2'), 140.10 (C-2'*) ppm. MS (ESI): *m/z* = 436.2 [M+Na]$^+$. HRMS (ESI): calcd. for $C_{22}H_{43}NO_4Si$ [M+H]$^+$ 414.3034; found 414.3029. TLC (petroleum ether-EtOAc, 7:3): R_f = 0.64.

(7a*R*)-5,5-Dimethyl-(1*SR*)-vinyldihydro-1*H*,3*H*,5*H*-oxazolo[3,4-c]oxazol-3-one (11): To a solution of **10a**[10c,12,18] (100 mg, 0.389 mmol, *d.r.* 4:1) in dry DMF (5 mL), NaH (60% dispersion in mineral oil, 19.0 mg, 0.467 mmol) was added at 0 °C and the mixture was stirred at 0 °C for 10 h and at rt for 13 h. Water (10 mL) was added and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organics were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resultant crude product was purified by column chromatography (petroleum ether-EtOAc, 6:1) to give **11** as a colorless oil (27 mg, 38%, *d.r.* 7:1). ^{1}H NMR (500 MHz, C_6D_6): δ = 1.32 (s, 0.4H, C(CH$_3$)$_2$*), 1.37 (s, 2.6H, C(CH$_3$)$_2$), 1.86 (s, 2.6H, C(CH$_3$)$_2$), 1.88 (s, 0.4H, C(CH$_3$)$_2$*), 3.13-3.19 (m, 0.1H, H-7$_a$*), 3.37 (d, *J* = 7.4, 1.8 H, H-7), 3.48-3.53 (m, 0.2H, H-7a*, H-7$_b$*), 3.61 (dd, *J* = 16.1, 8.1 Hz, 0.9H, H-7$_a$), 4.10-4.14 (m, 0.1H, H-1*), 4.40-4.43 (m, 0.9H, H-1), 4.96-5.01 (m, 1H, H-2'$_a$, H-2'$_a$*), 5.14 (dt, *J* = 17.1, 1.1 Hz, 0.1H, H-2'$_b$*), 5.20-5.32 (m, 1.8H, H-1', H-2'$_b$), 5.53 (ddd, *J* = 17.1, 10.5, 6.6 Hz, 0.1H, H-1'*) ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 23.43(C(CH$_3$)$_2$), 23.47 (C(CH$_3$)$_2$*), 27.41(C(CH$_3$)$_2$*), 27.86 (C(CH$_3$)$_2$), 60.97 (C-7a), 63.63 (C-7a*), 64.00 (C-7), 67.4 (C-7*), 74.17 (C-1), 78.21 (C-1*), 94.77 (C-5), 94.80 (C-5*), 118.06 (C-2'*), 118.33 (C-2'), 131.34 (C-1'), 134.86 (C-1'*), 156.26 (C=O) ppm. MS (ESI): *m/z* = 184.1 [M+H]$^+$. HRMS (ESI): calcd. for $C_9H_{13}NO_3$ [M+H]$^+$ 183.0968; found 183.0968. TLC (petroleum ether-EtOAc, 3:2): R_f = 0.36.

***N*-Boc-(2*R*,3*SR*)-2-amino-pent-4-en-1,3-diol (12):** A solution of **10a** (105 mg, 0.408 mmol, *d.r.* 3:2) in acetic acid (3 mL) and water (0.5 mL) was stirred at rt for 1.5 d. The solvent was evaporated under reduced pressure and the resultant crude product was purified by column chromatography (petroleum ether-EtOAc, 2:1) to give **12** as a brownish oil (59 mg, 67%, *d.r.* 9:1). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 100 °C): δ = 1.37 (s, 9H, C(CH$_3$)$_3$*, C(CH$_3$)$_3$), 3.34-3.52 (m, 3H, H-1*, H-1, OH, OH*), 3.89-3.98 (m, 0.9H, H-3), 4.11-4.19 (m, 0.1H, H-3*), 4.36-4.48 (m, 0.9H, OH), 4.54-4.60 (m, 0.1H, OH*), 4.74-4.81 (m, 0.1H, H-2*), 4.85-4.93 (m, 0.9H, H-2), 5.00-5.08 (m, 1H, H-5$_a$*, H-5$_a$), 5.12-5.24 (m, 1H, H-5$_b$*, H-5$_b$), 5.76-5.90 (m, 1H, H-4*, H-4), 6.01 (d, *J* = 7.5 Hz, 0.1H, NH*), 6.27 (d, *J* = 8.4 Hz, 0.9H, NH). TLC (petroleum ether-EtOAc, 1:2): R_f = 0.18.

***N*-Boc-(2*R*,4*RS*,5*R*)-amino-2-phenyl-4-vinyl-1,3-dioxane (13):** A solution of **12** (50 mg, 0.23 mmol, *d.r.* 9:1), camphorsulfonic acid (5.3 mg, 23 μmol) and benzaldehyde dimethyl acetal (69 μL, 70 mg, 0.46 mmol) in CH_2Cl_2 (4 mL) was stirred at rt for 5.5 h. After $NaHCO_3$ (40 mg) was added to the solution, stirring was continued for 1 h. The solution was filtered and the solvent was evaporated under reduced pressure. The resultant crude product was purified by column chromatography (petroleum ether-EtOAc, 5:1) to give **13** as a brownish oil (134 mg, 58%, *d.r.* 19:1). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 100 °C): δ = 1.41 (s, 9H, C(CH$_3$)$_3$), 3.49 (ddd, *J* = 10.8, 9.8, 5.2 Hz, 1H, H-5), 3.66 (dd, *J* = 10.8, 10.8 Hz, 1H, H-6$_a$), 4.09 (dd, *J* = 10.8, 5.2 Hz, 1H, H-6$_e$), 4.20 (dd, *J* = 9.8, 5.9 Hz, 1H, H-4), 5.21 (dt, *J* = 10.8, 1.3 Hz, 1H, H-2'$_a$), 5.36 (dt, *J* = 17.4, 1.3 Hz, 1H, H-2'$_b$), 5.53 (s, 1H, H-2), 5.90 (ddd, *J* = 17.4, 10.8, 5.9 Hz, 1H, H-1'), 6.49 (d, *J* = 7.9 Hz, 1H, NH), 7.32-7.53 (m, 5H, Ph). ^{13}C NMR (126 MHz, [D$_6$]DMSO, 100 °C): δ = 28.70 (C(CH$_3$)$_3$), 48.65 (C-5), 69.56 (C-6), 78.79 (C(CH$_3$)$_3$), 80.55 (C-4), 100.59 (C-2), 117.45 (C-2'), 126.62, 128.34 (C-2'', C-3'', C-5'', C-6''), 129.01 (C-4''), 135.89 (C-1'), 138.81 (C-1''), 155.53 (C=O) ppm. MS (ESI): *m/z* = 328.1 [M+Na]$^+$. HRMS (ESI): calcd. for $C_{17}H_{23}NO_4$ [M+H]$^+$ 306.1700; found 306.1701. TLC (petroleum ether-EtOAc, 3:1): R_f = 0.45.

(2*R*,3*SR*)-2-Amino-3-((*tert*-butyldiphenylsilyl)oxy)pent-4-en-1-ol (14a): HCl (5 M, 1.57 mL, 7.87 mmol) was added to a solution of **10b** (975 mg, 1.97 mmol, *d.r.* 3:1) in THF (5 mL), and the mixture was stirred under reflux for 3 h. CH_2Cl_2 (10 mL) and MeOH (10 mL) were added and the aqueous layer was brought to pH 2 by addition of 5% NaOH. After extraction with EtOAc (3 x 20 mL), the combined organics were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The resultant crude product was purified by column chromatography (CH_2Cl_2-MeOH, 99:1) to give **14a** as a brownish oil (660 mg, 94%, *d.r.* 3:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94 (s, 9H, C(CH$_3$)$_3$, C(CH$_3$)$_3$*), 2.59-2.87 (m, 3H, H-2, NH$_2$, NH$_2$*), 3.22-3.61 (m, 3H, H-1, OH, OH*), 3.97-4.06 (m, 1H, H-3, H-3*), 4.75-4.98 (m, 2H, H-5, H-5*), 5.56-5.71 (m, 1H, H-4, H-4*), 7.19-7.33 (m, 6H, Ph, Ph*), 7.46-7.55 (m, 4H, Ph, Ph*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 19.35 (C(CH$_3$)$_3$, C(CH$_3$)$_3$*), 27.03 (C(CH$_3$)$_3$, C(CH$_3$)$_3$*), 57.44 (C-2*), 57.54 (C-2), 62.42 (C-1), 62.73 (C-1*), 76.31 (C-3, C-3*), 117.83 (C-5*), 118.19 (C-5), 127.47, 127.72, 129.74, 129.91, 133.36, 133.42, 135.84, 135.88 (Ph), 136.34 (C-4), 136.97 (C-4*) ppm. MS (ESI): *m/z* = 356.1 [M+H]$^+$. HRMS (ESI): calcd. for $C_{21}H_{29}NO_2Si$ [M+Na]$^+$ 378.1860; found 378.1846. TLC (CH_2Cl_2-MeOH, 5:1): R_f = 0.31.

(2*R*,3*SR*)-2-Amino-3-((triisopropylsilyloxy)-pent-4-en-1-ol (14b): HCl (5 M, 2.70 mL, 13.5 mmol) was added to a solution of **10c** (1.40 g, 3.38 mmol, *d.r.* 3:2) in THF (25 mL), and the mixture was stirred under reflux for 4.5 h. The solution was cooled to rt and the solvent was evaporated under reduced pressure. The resultant crude **14b** (990 mg) was used without further purification. With respect to the limited stability of the crude product, it was prepared freshly and directly used in the subsequent reaction. ^{1}H NMR (500 MHz, C_6D_6): δ = 1.11-1.23 (m, 21H, CH(CH$_3$)$_2$, CH(CH$_3$)$_2$*), 2.85 (ddd, *J* = 9.7, 7.3, 5.1 Hz, 0.85H, H-2), 2.94 (ddd, *J* = 9.5, 7.1, 4.7 Hz, 0.15H, H-2*), 3.55 (dd, *J* = 9.7, 7.3 Hz, 0.85H, H-1$_a$), 3.61 (dd, *J* = 10.5, 7.1 Hz, 0.15H, H-1*$_a$), 3.70-3.77 (m, 1H, H-1$_b$, H-1*$_b$), 4.20-4.27 (m, 1H, H-3, H-3*), 5.04-5.21 (m, 2H, H-5, H-5*), 5.71-5.86 (m, 1H, H-4, H-4*) ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 11.35 (CH(CH$_3$)$_2$*), 11.41 (CH(CH$_3$)$_2$), 16.92 (CH(CH$_3$)$_2$), 16.95 (CH(CH$_3$)$_2$*), 56.79 (C-2), 56.95 (C-2*), 61.87 (C-1*), 62.13 (C-1), 75.23 (C-3*), 75.40 (C-3), 114.99 (C-5), 115.34 (C-5*), 137.12 (C-4*), 137.84 (C-4) ppm.

***N*-((2*R*,3*SR*)-3-((*tert*-butyldiphenylsilyl)oxy)-1-hydroxypent-4-en-2-yl)-4'-nitrobenzenesulfonamide (15a):** To a solution of **14a** (1.75 g, 4.91 mmol, *d.r.* 3:1) in CH_2Cl_2 (25 mL) at 0 °C, DIPEA (1.09 mL, 825 mg, 6.38 mmol) and after 10 min *p*NsCl (1.14 g, 5.16 mmol) were added. The mixture was stirred at 0 °C for 1 h and was then quenched by the addition of HCl (1 M, 20 mL). The organic layer was washed with HCl (1 M, 2 x 20 mL) and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give **15a** (2.44 g, 92%, *d.r.* 4:1). ^{1}H NMR (500 MHz, C_6D_6): δ = 1.18 (s, 8.1H, C(CH$_3$)$_3$), 1.20 (s, 0.9H, C(CH$_3$)$_3$*), 3.36-3.45 (m, 1.9H, H-2, H-2*, H-1$_a$), 3.56 (dd, *J* = 10.8, 5.2 Hz, 0.1H, H-1*$_a$), 3.63 (dd, *J* = 11.2, 5.6 Hz, 0.1H, H-1*$_b$), 3.72-3.78 (m, 0.9H, H-1$_b$), 4.39-4.43 (m, 0.9H, H-3), 4.45-4.48 (m, 0.1H, H-3*), 4.78 (dt, *J* = 10.5, 1.3 Hz, 0.9H, H-5$_a$), 4.82 (dt, *J* = 10.3, 1.4 Hz, 0.1H, H-5*$_a$), 4.87 (dt, *J* = 17.2, 1.3 Hz, 0.9H, H-5$_b$), 4.94 (dt, *J* = 17.2, 1.3 Hz, 0.1H, H-5*$_b$), 5.14 (d, *J* = 7.9 Hz, 0.9H, NH), 5.24 (d, *J* = 8.5 Hz, 0.1H, NH*), 5.55 (ddd, *J* = 17.2, 10.3, 6.9 Hz, 0.9H, H-4), 5.69 (ddd, *J* = 17.2, 10.3, 6.7 Hz, 0.1H, H-4*), 7.29-7.36 (m, 6H, Ph), 7.52-7.81 (m, 8H, Ph) ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 19.36 (C(CH$_3$)$_3$), 27.02 (C(CH$_3$)$_3$), 58.95 (C-2*), 60.04 (C-2), 60.77 (C-1*), 61.49 (C-1), 74.24 (C-3*), 75.83 (C-3), 117.42 (C-5*), 118.07 (C-5), 123.86, 127.82, 128.03, 128.18, 130.20, 130.35, 133.10, 133.11, 136.08, 136.12 (Ph), 136.25 (C-4*), 136.53 (C-4), 146.56, 149.66 (Ph) ppm. MS (ESI): *m/z* = 563.1 [M+Na]$^+$. HRMS (ESI): calcd. for $C_{27}H_{32}N_2O_6SSi$ [M+H]$^+$ 541.1823; found 541.1794. TLC (petroleum ether-EtOAc, 7:3): R_f = 0.37.

***N*-((2*R*,3*SR*)-3-(triisopropylsilyloxy)-1-hydroxypent-4-en-2-yl)-4'-nitrobenzenesulfonamide (15b): 15b** was prepared in the same way as **15a**, using **14b** (990 mg, 3.38 mmol, *d.r.* 3:2), CH_2Cl_2 (25 mL), DIPEA (1.30 mL, 981 mg, 7.60 mmol) and *p*NsCl (768 mg, 3.50 mmol). Column chromatography (CH_2Cl_2) gave **15b** (468 mg, 34 % over 2 steps from **10c**, *d.r.* 3:2). ^{1}H NMR (500 MHz, C_6D_6): δ = 0.94-1.08 (m, 21H, $CH(CH_3)_2$, $CH(CH_3)_2$*), 1.27-1.32 (m, 1H, OH, OH*), 3.16-3.23 (m, 0.25H, H-2*), 3.30-3.37 (m, 0.75H, H-2), 3.38-3.48 (m, 1.5H, H-1), 3.62-3.70 (m, 0.5H, H-1*), 4.41-4.45 (m, 0.75H, H-3), 4.48-4.52 (m, 0.25H, H-3*), 4.78 (dt, *J* = 10.4, 1.4 Hz, 0.75H, H-5$_a$), 4.86 (dt, *J* = 10.6, 1.4 Hz, 0.25H, H-5*$_a$), 5.01-5.06 (m, 1.75H, H-5$_b$, H-5*$_b$, NH), 5.23 (d, *J* = 7.1 Hz, 0.25H, NH*), 5.43-5.58 (m, 1H, H-4, H-4*), 7.50-7.56 (m, 4H, Ph) ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 12.41 ($CH(CH_3)_2$), 12.54 ($CH(CH_3)_2$*), 17.99 ($CH(CH_3)_2$), 18.10 ($CH(CH_3)_2$*), 59.47 (C-2), 59.80 (C-2*), 60.88 (C-1), 61.36 (C-1*), 74.06 (C-3), 76.22 (C-3*), 117.12 (C-5), 117.56 (C-5*), 123.92 (C-2', C-3', C-5', C-6', C-2'*, C-3'*, C-5'*, C-6'*), 137.25 (C-4), 137.56 (C-4*), 146.41 (C-1'), 149.79 (C-4', C-4'*) ppm. MS (ESI): *m/z* = 481.1 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{20}H_{34}N_2O_6SSi$ $[M+H]^+$ 459.1980; found 459.1976. TLC (CH_2Cl_2-MeOH, 95:5): R_f = 0.49.

***N*-Methyl-((2*R*,3*SR*)-3-((*tert*-butyldiphenylsilyl)oxy)-1-hydroxypent-4-en-2-yl)-4'-nitrobenzenesulfonamide (16a):** A solution of **15a** (980 mg, 1.81 mmol, *d.r.* 6:1) in DMF (16 mL) was added dropwise to a solution of Cs_2CO_3 (709 mg, 2.17 mmol) in DMF (2 mL) at 0 °C. After 5 min of stirring, a solution of methyl iodide (507 μL, 1.16 g, 8.14 mmol) in DMF (2 mL) was added and the mixture was stirred at 0 °C for 30 min and at rt for 16 h. The reaction was quenched wirth sat. NH_4Cl solution. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The resultant crude product was purified by column chromatography (petroleum ether-EtOAc, 5:1) to give **16a** as a colorless oil (893 mg, 89%, *d.r.* 7:1). ^{1}H NMR (500 MHz, C_6D_6): δ = 1.24 (s, 6.75H, $C(CH_3)_3$), 1.26 (s, 2.25H, $C(CH_3)_3$*), 2.60 (s, 2.25H, NCH_3), 2.82 (s, 0.75H, NCH_3*), 3.40 (dd, *J* = 11.1, 9.4 Hz, 0.25H, H-1*$_a$), 3.55-3.63 (m, 1H, H-1$_a$, H-1*$_b$), 3.79 (dd, *J* = 11.4, 3.7 Hz, 0.75H, H-1$_b$), 4.03 (dt, *J* = 9.1, 4.9 Hz, 0.25H, H-2*), 4.24 (ddd, *J* = 8.5, 6.9, 4.1 Hz, 0.75H, H-2), 4.34 (dd, *J* = 8.5, 6.9 Hz, 0.75H, H-3), 4.46-4.50 (m, 0.25H, H-3*), 4.65-4.75 (m, 1.5H, H-5), 4.83-4.91 (m, 0.5H, H-5*), 5.71-5.84 (m, 1H, H-4, H-4*), 7.30-7.39 (m, 6H, Ph), 7.59-7.63 (m, 2H, Ph), 7.77-7.90 (m, 6H, Ph) ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 19.40 ($C(CH_3)_3$, $C(CH_3)_3$*), 27.13 ($C(CH_3)_3$, $C(CH_3)_3$*), 30.16 (NCH_3), 30.64 (NCH_3*), 58.92 (C-1*), 59.78 (C-1), 63.10 (C-2*), 63.97 (C-2), 75.88 (C-3*), 76.11 (C-3), 117.76 (C-5*), 117.90 (C-5), 123.56, 123.60, 127.80, 127.93, 127.99, 128.18, 128.38, 128.53, 130.05, 130.16, 130.20, 133.40, 133.49, 133.60, 136.14, 136.27, 136.30, 136.35 (Ph), 136.94 (C-4*), 137.95 (C-4), 145.24, 145.58, 149.54 (Ph) ppm. MS (ESI): *m/z* = 577.1 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{28}H_{34}N_2O_6SSi$ $[M+H]^+$ 555.1980; found 555.2010. TLC (petroleum ether-EtOAc, 7:3): R_f = 0.39.

***N*-Methyl-((2*R*,3*SR*)-3-((triisopropylsilyloxy)-1-hydroxy-pent-4-en-2-yl)-4'-nitrobenzolsulfonamide (16b): 16b** was prepared in the same way as **16a**, using **15b** (1.10 g, 2.40 mmol, *d.r.* 3:2), Cs_2CO_3 (938 mg, 2.88 mmol), methyl iodide (672 μL, 1.53 g, 10.8 mmol) and DMF (40 mL). Column chromatography (petroleum ether-EtOAc, 5:1) gave **16b** (873 mg, 77%, *d.r.* 3:2). ^{1}H NMR (500 MHz, C_6D_6): δ = 0.60 (t, *J* = 4.7 Hz, 0.7H, OH), 0.67 (t, *J* = 5.2 Hz, 0.3H, OH*), 0.99-1.13 (m, 21H, $CH(CH_3)_2$), 2.65 (s, 3H, NCH_3, NCH_3*), 3.25 (ddd, *J* = 11.4, 9.4, 4.7 Hz, 0.7H, H-1$_a$), 3.49 (ddd, *J* = 11.6, 6.4, 5.2 Hz, 0.3H, H-1*$_a$), 3.54-3.61 (m, 1H, H-1$_b$, H-1*$_b$), 3.94 (ddd, *J* = 8.7, 6.4, 4.7 Hz, 0.3H, H-2*), 4.01 (ddd, *J* = 9.4, 4.7, 4.2 Hz, 0.7H, H-2), 4.37 (dd, *J* = 8.7, 6.4 Hz, 0.3H, H-3*), 4.45-4.48 (m, 0.7H, H-3), 4.85-4.89 (m, 0.3H, H-5*$_a$), 4.91 (ddd, *J* = 10.4, 1.6, 0.9 Hz, 0.7H, H-5$_a$), 5.03 (ddd, *J* = 17.3, 1.3, 0.9 Hz, 0.3H, H-5*$_b$), 5.12 (dt, *J* = 17.3, 1.6 Hz, 0.7H, H-5$_b$), 5.65 (ddd, *J* = 17.3, 10.4, 7.3 Hz, 0.7H, H-4), 5.74 (ddd, *J* = 17.3, 10.3, 8.3 Hz, 0.3H, H-4*), 7.52 (ddd, *J* = 8.8, 2.2, 2.0 Hz, 0.3H, H-3'*, H-5'*), 7.59 (ddd, *J* = 9.1, 2.2, 2.2 Hz, 0.7H, H-3', H-5'), 7.63-7.68 (m, 2H, H-2', H-2'*, H-6', H-6'*) ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 12.50 ($CH(CH_3)_2$), 12.75 ($CH(CH_3)_2$*), 18.15 ($CH(CH_3)_2$), 18.18 ($CH(CH_3)_2$*), 30.43 (NCH_3*), 30.62 (NCH_3), 58.64 (C-1), 59.50 (C-1*), 63.45 (C-2), 64.28 (C-2*), 76.00 (C-3), 76.75 (C-3*), 117.31 (C-5, C-5*), 123.92 (C-2', C-2'*, C-6', C-6'*), 128.37, 128.49 (C-3', C-3'*, C-5', C-5'*), 137.80 (C-4), 139.15 (C-4*), 145.09 (C-1'), 145.61 (C-1'*), 149.57 (C-4'*), 149.64 (C-4') ppm. MS (ESI): *m/z* = 495.1 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{21}H_{36}N_2O_6SSi$ $[M+H]^+$ 473.2136; found 473.2130. TLC (petroleum ether-EtOAc, 3:1): R_f = 0.45.

***tert*–Butyl-(2*S*,3*SR*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-((*N*-methyl-4-nitrophenyl)sulfonamido)pent-4-enoate (17a):** A solution of **15a** (865 mg, 1.56 mmol, *d.r.* 7:1), TEMPO (73.0 mg, 0.469 mmol) and bis-(acetoxy)-iodobenzene (1.11 g, 3.44 mmol) in MeCN (5 mL) and water (5 mL) was stirred at rt for 5 h. It was then extracted with Et_2O (20 mL). The organic layer was washed with sat. $NaHCO_3$ solution and the aqueous layer was acidified with HCl (1 M) and extracted with EtOAc. The combined organics were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The resultant crude carboxylic acid (1.04 g) was used in the next reaction without purification. To a solution of the crude carboxylic acid (790 mg) in CH_2Cl_2 (18 mL), *tert*-butyl trichloroacetimidate (3.04 g, 13.9 mmol) and boron trifluoride etherate (51 μL, 59 mg, 0.42 mmol) were added at 0 °C. The mixture was stirred at rt for 2 h, and then a mixture of EtOAc and sat. $NaHCO_3$ solution (1:1, 80 mL) was added. The organic layer was washed with sat. $NaHCO_3$ solution (2 x 40 mL) and brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The resultant crude product was purified by column chromatography (petroleum ether-EtOAc, 6:1) to give **17a** as a colorless oil (758 mg, 87%, *d.r.* 7:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.99 (s, 9H, $C(CH_3)_3$), 1.20 (s, 0.9H, $C(CH_3)_3$*), 1.27 (s, 8.1H; $C(CH_3)_3$), 2.78 (s, 2.7H, NCH_3), 3.13 (s, 0.3H, NCH_3*), 4.46 (dd, *J* = 8.9, 6.9 Hz, 0.9H, H-3), 4.50 (d, *J* = 4.9 Hz, 0.1H, H-2*), 4.60 (d, *J* = 6.9 Hz, 0.9H, H-2), 4.61- 4.66 (m, 1H, H-3*, H-5$_a$), 5.68-5.73 (m, 0.1H, H-5*$_a$), 5.85-5.88 (m, 0.9H, H-5$_b$), 4.92-4.95 (m, 0.1H, H-5*$_b$), 5.74-5.87 (m, 1H, H-4, H-4*), 7.29-7.45 (m, 6H, Si-Ph), 7.56-7.72 (m, 4H, Si-Ph), 7.90-7.99 (m. 2H, H-3', H-3'*, H-5', H-5'*), 8.25-8.32 (m, 2H, H-2', H-2'*, H-6', H-6'*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 19.25 ($SiC(CH_3)_3$), 26.93 ($C(CH_3)_3$), 27.80 ($C(CH_3)_3$), 31.61 (NCH_3), 64.48 (C-2), 75.11 (C-3), 82.54 ($C(CH_3)_3$), 118.95 (C-5), 123.99, 127.28, 127.45, 128.61, 129.63, 129.76, 132.79, 133.36, 136.59 (Ph), 136.01 (C-4), 145.26 (C-1'), 149.81 (C-4'), 166.95 (C-1) ppm. MS (ESI): *m/z* = 647.2 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{32}H_{40}N_2O_7SSi$ $[M+H]^+$ 647.2218; found 647.2221. TLC (petroleum ether-EtOAc, 4:1): R_f = 0.46.

***tert*–Butyl-(2*S*,3*SR*)-3-((triisopropylsilyloxy)-2-((*N*-methyl-4-nitrophenyl)sulfonamido)pent-4-enoate (17b): 17b** was prepared in the same way as **17a**, using **16b** (1.11 g, 2.35 mmol, *d.r.* 3:2), TEMPO (110 mg, 0.704 mmol), bis-(acetoxy)-iodobenzene (1.66 g, 5.17 mmol), MeCN (20 mL) and H_2O (20 mL). The mixture was stirred for 2 h. The obtained crude carboxylic acid (1.40 g) was used in the next reaction without purification. The next reaction was carried out using carboxylic acid (790 mg, 2.24 mmol), *tert*-butyl trichloroacetimidate (2.80 mL, 3.43 g, 15.7 mmol), boron trifluoride etherate (83 μL, 95 mg, 0.67 mmol) and CH_2Cl_2 (25 mL). The mixture was stirred for 2 h. Column chromatography (petroleum ether-EtOAc, 20:1→10:1) gave **17b** as a brownish oil (620 mg, 51%, *d.r.* 3:2). ^{1}H NMR (500 MHz, C_6D_6): δ = 1.02-1.14 (m, 30H, 3 x $CH(CH_3)_2$, 3 x $CH(CH_3)_2$*, $C(CH_3)_3$, $C(CH_3)_3$*), 2.73 (s, 0.6H, NCH_3*), 3.13 (s, 2.4H, NCH_3), 4.67 (d, *J* = 4.2 Hz, 0.8H, H-2), 4.70-4.73 (m, 0.4H, H-2*, H-3*), 4.91 (dd, *J* = 8.1, 4.2 Hz, 0.8H, H-3), 4.93-4.99 (m, 1H, H-5$_a$, H-5*$_a$), 5.01-5.06 (m, 0.8H, H-5$_b$), 5.06-5.11 (m, 0.2H, H-5*$_b$), 5.94 (ddd, *J* = 17.2, 10.2, 8.1 Hz, 0.8H, H-4), 5.98-6.05 (m, 0.2H, H-4*), 7.50-7.56 (m, 2H, H-3', H-3'*, H-5', H-5'*), 7.63-7.70 (m, 2H, H-2', H-2'*, H-6', H-6'*) ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 12.70 ($CH(CH_3)_2$), 12.78

(CH(CH$_3$)$_2$*), 17.82 (CH(CH$_3$)$_2$*), 18.18 (CH(CH$_3$)$_2$), 27.52 (C(CH$_3$)$_3$*), 27.56 (C(CH$_3$)$_3$), 31.32 (NCH$_3$*), 33.26 (NCH$_3$), 64.85 (C-2*), 65.48 (C-2), 74.94 (C-3*), 76.25 (C-3), 81.87 (C(CH$_3$)$_3$*), 82.12 (C(CH$_3$)$_3$), 118.03 (C-5), 118.37 (C-5*), 123.75 (C-2', C-2'*, C-6', C-6'*), 128.48, 128.50 (C-3', C-3'*, C-5', C-5'*), 137.95 (C-4), 138.42 (C-4*), 145.05 (C-1'), 145.45 (C-1'*), 149.76 (C-4'*, C-4'), 167.22 (C-1), 167.30 (C-1*) ppm. MS (ESI): *m/z* = 565.2 [M+Na]$^+$. HRMS (ESI): calcd. for $C_{25}H_{42}N_2O_7SSi$ [M+Na]$^+$ 565.2374; found 565.2383. TLC (petroleum ether-EtOAc, 3:1): R_f = 0.59.

***tert*–Butyl-(2*S*,3*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-(methylamino)pent-4-enoate [(*S*)-18] and *tert*–butyl-(2*S*,3*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-(methylamino)pent-4-enoate [(*R*)-18]:** (*S*)-**18** and (*R*)-**18** were prepared according to the GP, using **17a** (1.21 g, 1.94 mmol, *d.r.* 3:1), K_2CO_3 (803 mg, 5.81 mmol), thiophenol (239 µL, 256 mg, 2.33 mmol) and DMF (25 mL). The mixture was stirred at rt for 4 h. Column chromatography (CH_2Cl_2→CH_2Cl_2-EtOAc, 100:1) gave (*S*)-**18** as a colorless oil (491 mg, 58%) and (*R*)-**18** as a colorless oil (179 mg, 21%). (*S*)-**18**: $[\alpha]_D^{20}$ = +12.4 (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, C_6D_6): δ = 1.22 (s, 9H, SiC(CH$_3$)$_3$), 1.35 (s, 9H, C(CH$_3$)$_3$), 2.31 (s, 3H, NCH$_3$), 3.19 (d, *J* = 3.4 Hz, 1H, H-2), 4.68 (dddd, *J* = 7.2, 3.4, 1.3, 1.2 Hz, 1H, H-3), 4.90 (ddd, *J* = 10.2, 1.6, 1.2 Hz, 1H, H-5$_a$), 4.95 (ddd, *J* = 17.3, 1.6, 1.3 Hz, 1H, H-5$_b$), 6.04 (ddd, *J* = 17.3, 10.2, 7.2 Hz, 1H, H-4), 7.21-7.25 (m, 6H, Ph), 7.83-7.93 (m, 4H, Ph) ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 19.74 (SiC(CH$_3$)$_3$), 27.32 (SiC(CH$_3$)$_3$), 28.20 (C(CH$_3$)$_3$), 35.24 (NCH$_3$), 69.81 (C-2), 77.62 (C-3), 80.54 (C(CH$_3$)$_3$), 116.53 (C-5), 129.95, 130.01, 134.18, 134.43, 136.48, 136.58 (Ph), 137.94 (C-4), 172.22 (C-1) ppm. IR (ATR): ν = 2964, 2932, 2857, 1730, 1152, 1111, 1076, 700 cm^{-1}. UV (CH_2Cl_2): λ_{max} = 265 nm. MS (ESI): *m/z* = 462.1 [M+Na]$^+$. HRMS (ESI): calcd. for $C_{26}H_{37}NO_3Si$ [M+H]$^+$ 440.2615; found 440.2612. TLC (CH_2Cl_2-MeOH, 92:8): R_f = 0.25. (*R*)-**18**: $[\alpha]_D^{20}$ = +40.6 (c = 1.3, CH_2Cl_2). ^{1}H NMR (500 MHz, C_6D_6): δ = 1.21 (s, 9H, SiC(CH$_3$)$_3$), 1.44 (s, 9H, C(CH$_3$)$_3$), 2.21 (s, 3H, NCH$_3$), 3.27 (d, *J* = 4.5 Hz, 1H, H-2), 4.55 (dd, *J* = 7.9, 4.5 Hz, 1H, H-3), 4.83-4.88 (m, 2H, H-5), 6.22 (ddd, *J* = 16.4, 10.1, 8.1 Hz, 1H, H-4), 7.18-7.24 (m, 6H, Ph), 7.78-7.89 (m, 4H, Ph) ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 19.70 (SiC(CH$_3$)$_3$), 27.33 (SiC(CH$_3$)$_3$), 28.30 (C(CH$_3$)$_3$), 34.81 (NCH$_3$), 69.15 (C-2), 77.38 (C-3), 80.65 (C(CH$_3$)$_3$), 117.12 (C-5), 129.94, 130.01, 134.32, 134.33, 136.46, 136.51 (Ph), 137.86 (C-4), 172.42 (C-1) ppm. IR (ATR): ν = 2965, 2932, 2857, 1725, 1151, 1107, 1070, 700 cm^{-1}. UV (CH_2Cl_2): λ_{max} = 265 nm. MS (ESI): *m/z* = 462.1 [M+Na]$^+$. HRMS (ESI): calcd. for $C_{26}H_{37}NO_3Si$ [M+H]$^+$ 440.2615; found 440.2645. TLC (CH_2Cl_2-MeOH, 92:8): R_f = 0.33.

***tert*-Butyl-(2*S*,3*S*)-3-((triisopropylsilyloxy)-2-((*N*-methyl-4'-nitrophenyl)sulfonamido)-4-oxobutanoate [(*S*)-19b] and *tert*-butyl-(2*S*,3*R*)-3-((triisopropylsilyloxy)-2-((*N*-methyl-4'-nitrophenyl)sulfonamido)-4-oxobutanoate [(*R*)-19b]:** A solution of **17b** (670 mg, 1.23 mmol, *d.r.* 5:6) in MeOH (8 mL), CH_2Cl_2 (1 mL) and pyridine (0.4 mL) was cooled to -78 °C, and ozone was bubbled through this solution at -78 °C for 20 min. After the addition of dimethyl sulfide (465 µL, 547 mg, 12.3 mmol), the reaction was stirred and allowed to warm to rt overnight. The solvent was evaporated under reduced pressure, and the resultant crude product was purified by column chromatography (petroleum ether-EtOAc, 20:1) to give (*S*)-**19b** as a colorless oil (218 mg, 32%) and (*R*)-**19b** as a colorless oil (257 mg, 38%). (*S*)-**19b**: $[\alpha]_D^{20}$ = -159.0 (c = 0.7, MeOH).^{1}H NMR (500 MHz, C_6D_6): δ = 1.00-1.07 (m, 30H, 3 x CH(CH$_3$)$_2$, C(CH$_3$)$_3$), 2.99 (s, 3H, NCH$_3$), 4.84 (dd, *J* = 3.4, 1.0 Hz, 1H, H-3), 4.99 (d, *J* = 3.4 Hz, 1H, H-2), 7.44-7.49 (m, 2H, H-3', H-5'), 7.63-7.68 (m, 2H, H-2', H-6'), 9.55 (d, *J* = 1.0 Hz, 1H, H-4) ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 12.74 (CH(CH$_3$)$_2$), 17.87 (CH(CH$_3$)$_2$), 27.42 (C(CH$_3$)$_3$), 33.53 (NCH$_3$), 62.37 (C-2), 79.55 (C-3), 83.11 (C(CH$_3$)$_3$), 123.82 (C-2', C-6'), 128.51 (C-3', C-5'), 144.30 (C-1'), 149.92 (C-4'), 166.25 (C-1), 199.34 (C-4) ppm. IR (ATR): ν = 3408, 2931, 2867, 1737, 1605, 1532, 1349, 1138 cm^{-1}. UV (MeOH): λ_{max} = 277 nm. MS (ESI): *m/z* = 567.2 [M+Na]$^+$. HRMS (ESI): calcd. for $C_{25}H_{40}N_2O_8Si$ [M+Na]$^+$ 567.2167; found 567.2165. TLC (petroleum ether-EtOAc, 4:1): R_f = 0.52. (*R*)-**19b**: $[\alpha]_D^{20}$ = +25.8 (c = 0.4, MeOH). ^{1}H NMR (500 MHz, C_6D_6): δ = 0.91-1.04 (m, 30H, 3 x CH(CH$_3$)$_2$, C(CH$_3$)$_3$), 2.90 (s, 3H, NCH$_3$), 4.66 (dd, *J* = 3.9, 1.0 Hz, 1H, H-3), 5.29 (d, *J* = 3.9 Hz, 1H, H-2), 7.45-7.48 (m, 2H, H-3', H-5'), 7.62-7.65 (m, 2H, H-2', H-6'), 9.74 (d, *J* = 1.0 Hz, 1H, H-4) ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 12.76 (CH(CH$_3$)$_2$), 17.86 (CH(CH$_3$)$_2$), 27.35 (C(CH$_3$)$_3$), 33.26 (NCH$_3$), 63.71 (C-2), 80.22 (C-3), 83.16 (C(CH$_3$)$_3$), 123.86 (C-2', C-6'), 128.46 (C-3', C-5'), 144.41 (C-1'), 149.91 (C-4'), 165.72 (C-1), 200.54 (C-4) ppm. IR (ATR): ν = 3423, 2929, 2866, 1597, 1392, 1350, 1137 cm^{-1}. UV (MeOH): λ_{max} = 272 nm. MS (ESI): *m/z* = 567.2 [M+Na]$^+$. HRMS (ESI): calcd. for $C_{25}H_{40}N_2O_8Si$ [M+Na]$^+$ 567.2167; found 567.2161. TLC (petroleum ether-EtOAc, 4:1): R_f = 0.57.

***tert*-Butyl-(2*S*,3*S*)-3-((triisopropylsilyloxy)-4-hydroxy-2-(*N*-methyl-4'-nitrophenyl)sulfonamido)butanoate [(*S*)-20] and *tert*-butyl-(2*S*,3*R*)-3-((triisopropylsilyloxy)-4-hydroxy-2-(*N*-methyl-4'-nitrophenyl)sulfonamido)butanoate [(*R*)-20]:** A solution of **17b** (127 mg, 0.234 mmol, *d.r.* 5:6) in MeOH (4 mL), CH_2Cl_2 (0.5 mL) and pyridine (75 µL) was cooled to -78 °C, and ozone was bubbled through this solution at -78 °C for 20 min. After the addition of dimethyl sulfide (106 µL, 90.7 mg, 2.34 mmol), the reaction was stirred and allowed to warm to rt overnight. The solvent was evaporated under reduced pressure, and the resultant crude aldehyde **19b** was dissolved in MeOH (3 mL). Sodium borohydride (88 mg, 2.3 mmol) was added at 0 °C and the mixture was stirred for 4.5 h. The reaction was quenched by addition of sat. NH_4Cl solution (10 mL), and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organics were washed with water (2 x 25 mL) and brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The resultant crude product was purified by column chromatography (petroleum ether-EtOAc, 20:1→10:1) to give (*S*)-**20** as a yellowish oil (41 mg, 32%) and (*R*)-**20** as a yellowish oil (39 mg, 30%). (*S*)-**20**: ^{1}H NMR (500 MHz, C_6D_6): δ = 1.02 (s, 9H, C(CH$_3$)$_3$), 1.06-1.16 (m, 21H, CH(CH$_3$)$_2$), 2.20-2.27 (m, 1H, OH), 2.74 (s, 3H, NCH$_3$), 3.63-3.70 (m, 1H, H-4$_a$), 3.71-3.78 (m, 1H, H-4$_b$), 4.22 (ddd, *J* = 7.7, 4.7, 3.3 Hz, 1H, H-3), 4.79 (d, *J* = 7.7 Hz, 1H, H-2), 7.45-7.50 (m, 2H, H-3', H-5'), 7.64-7.68 (m, 2H, H-2', H-6') ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 13.28 (CH(CH$_3$)$_2$), 18.34 (CH(CH$_3$)$_2$), 27.62 (C(CH$_3$)$_3$), 31.75 (NCH$_3$), 61.51 (C-2), 63.26 (C-4), 73.14 (C-3), 82.05 (C(CH$_3$)$_3$), 124.02 (C-2', C-6'), 128.83 (C-3', C-5'), 144.71 (C-1'), 150.05 (C-4'), 167.43 (C-1) ppm. MS (ESI): *m/z* = 569.2 [M+Na]$^+$. HRMS (ESI): calcd. for $C_{24}H_{42}N_2O_8Si$ [M+H]$^+$ 547.2504; found 547.2503. TLC (petroleum ether-EtOAc, 4:1): R_f = 0.53. (*R*)-**20**: ^{1}H NMR (500 MHz, C_6D_6): δ = 0.93-1.03 (m, 30H, CH(CH$_3$)$_2$, C(CH$_3$)$_3$), 2.97-3.04 (m, 1H, OH), 3.16 (s, 3H, NCH$_3$), 3.70-3.77 (m, 1H, H-4$_a$), 3.77-3.85 (m, 1H, H-4$_b$), 4.71-4.78 (m, 2H, H-2, H-3), 7.36-7.41 (m, 2H, H-3', H-5'), 7.65-7.70 (m, 2H, H-2', H-6') ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 12.93 (CH(CH$_3$)$_2$), 18.34 (CH(CH$_3$)$_2$), 27.56 (C(CH$_3$)$_3$), 34.58 (NCH$_3$), 61.43 (C-2), 63.01 (C-4), 75.39 (C-3), 82.43 (C(CH$_3$)$_3$), 124.01 (C-2', C-6'), 128.63 (C-3', C-5'), 144.25 (C-1'), 150.09 (C-4'), 167.73 (C-1) ppm. MS (ESI): *m/z* = 569.2 [M+Na]$^+$. HRMS (ESI): calcd. for $C_{24}H_{42}N_2O_8Si$ [M+H]$^+$ 547.2504; found 547.2501. TLC (petroleum ether-EtOAc, 4:1): R_f = 0.46.

***tert*-Butyl-(2*S*,3*S*)-3-((triisopropylsilyloxy)-4-hydroxy-2-(methylamino)butanoate [(*S*)-21]:** (*S*)-**21** was prepared according to the GP, using (*S*)-**20** (56 mg, 0.10 mmol), K_2CO_3 (42 mg, 0.31 mmol), thiophenol (13 µL, 14 mg, 0.12 mmol) and DMF (3 mL). The mixture was stirred at rt for 5 h. Column chromatography (petroleum ether-EtOAc, 9:1→5:1) gave (*S*)-**21** as a yellowish oil (25 mg, 68%). $[\alpha]_D^{20}$ = +39.1 (c = 0.5, CH_2Cl_2). ^{1}H NMR (500 MHz, C_6D_6): δ = 1.04-1.15 (m, 21H, CH(CH$_3$)$_2$), 1.37 (s, 9H, C(CH$_3$)$_3$), 2.20 (s, 3H, NCH$_3$), 3.31 (d, *J* = 5.2 Hz, 1H, H-2), 3.83 (dd, *J* = 10.5, 7.4 Hz, 1H, H-4$_a$), 3.91 (dd, *J* = 10.5, 4.2 Hz, 1H, H-4$_b$), 4.28 (ddd, *J* = 7.4, 5.2, 4.2 Hz, 1H, H-3) ppm. ^{13}C NMR

(126 MHz, C_6D_6): δ = 13.05 (CH(CH_3)$_2$), 18.36 (CH(CH_3)$_2$), 28.09 (C(CH_3)$_3$), 35.29 (NCH_3), 66.07 (C-4), 69.44 (C-2), 74.27 (C-3), 81.11 (C(CH$_3$)$_3$), 171.82 (C-1) ppm. IR (ATR): ν = 2925, 2864, 1736, 1465, 1368, 1257, 1158, 681 cm^{-1}. MS (ESI): *m*/*z* = 362.2 [M+Na]$^+$. HRMS (ESI): calcd. for $C_{18}H_{39}NO_4Si$ [M+H]$^+$ 362.2721; found 362.2722. TLC (petroleum ether-EtOAc, 4:1): R_f = 0.12.

***tert*-Butyl-(2*S*,3*R*)-3-((triisopropylsilyloxy)-4-hydroxy-2-(methylamino)butanoate [(*R*)-21]:** (*R*)-**21** was prepared according to the GP, using (*R*)-**20** (243 mg, 0.444 mmol), K_2CO_3 (184 mg, 1.33 mmol), thiophenol (59 μL, 64 mg, 0.58 mmol) and DMF (5 mL). The mixture was stirred at rt for 5 h. Column chromatography (petroleum ether-EtOAc, 8:1→6:1) gave (*R*)-**21** as a yellowish oil (36 mg, 22%). $[\alpha]_D^{20}$ = +16.0 (c = 0.5, CH_2Cl_2). ^{1}H NMR (500 MHz, C_6D_6): δ = 1.01-1.20 (m, 21H, CH(CH_3)$_2$), 1.37 (s, 9H, C(CH_3)$_3$), 2.10 (s, 3H, NCH_3), 3.11 (d, *J* = 2.0 Hz, 1H, H-2), 3.79 (dd, *J* = 12.0, 2.2 Hz, 1H, H-4$_a$), 3.92 (dd, *J* = 12.0, 4.1 Hz, 1H, H-4$_b$), 4.21 (ddd, *J* = 4.1, 2.2, 2.0 Hz, 1H, H-3) ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 13.04 (CH(CH_3)$_2$), 18.32 (CH(CH_3)$_2$), 27.98 (C(CH_3)$_3$), 34.54 (NCH_3), 67.77 (C-4), 68.62 (C-2), 72.75 (C-3), 80.89 (C(CH$_3$)$_3$), 171.07 (C-1) ppm. IR (ATR): ν = 2942, 2866, 1729, 1391, 1155, 1113, 919, 680 cm^{-1}. MS (ESI): *m*/*z* = 362.2 [M+Na]$^+$. HRMS (ESI): calcd. for $C_{18}H_{39}NO_4Si$ [M+H]$^+$ 362.2721; found 362.2719. TLC (petroleum ether-EtOAc, 4:1): R_f = 0.11.

***tert*-Butyl-(2*S*,3*RS*)-4-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxy-2-((*N*-methyl-4'-nitrophenyl)sulfonamido)butanoate (22):** A solution of **17a** (1.10 g, 1.76 mmol, *d.r.* 3:1) in MeOH (16 mL), CH_2Cl_2 (2 mL) and pyridine (0.57 mL) was cooled to -78 °C, and ozone was bubbled through this solution at -78 °C for 20 min. After the addition of dimethyl sulfide (785 μL, 666 mg, 17.6 mmol), the reaction was stirred and allowed to warm to rt overnight. The solvent was evaporated under reduced pressure, and the resultant crude **19a** (1.10 g) was used in the next reaction without purification. Crude **19a** (505 mg, *d.r.* 3:1) was dissolved in MeOH (20 mL) and cooled to 0 °C. Sodium borohydride (304 mg, 8.06 mmol) was added to the solution and the mixture was stirred at 0 °C for 30 min and at rt for 6.5 h. The reaction was quenched by addition of sat. NH_4Cl solution (60 mL), and the aqueous layer was extracted with Et_2O (3 x 60 mL). The combined organics were washed with H_2O (2 x 100 mL) and brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The resultant crude product was purified by column chromatography (petroleum ether-EtOAc, 12:1→6:1) to give **22** as a colorless oil (220 mg, 39%, *d.r.* 7:3). ^{1}H NMR (500 MHz, C_6D_6): δ = 1.08 (s, 6.3H, C(CH_3)$_3$), 1.10 (s, 2.7H, C(CH_3)$_3$*), 1.15 (s, 2.7H, C(CH_3)$_3$*), 1.16 (s, 6.3H, C(CH_3)$_3$), 2.20 (d, *J* = 5.5 Hz, 0.3H, OH*), 2.48 (d, *J* = 5.9 Hz, 0.7H, OH), 2.80 (s, 2.1H, NCH_3), 2.92 (s, 0.9H, NCH_3*), 3.71-3.78 (m, 1.4H, H-4), 3.83-3.87 (m, 0.6H, H-4*), 3.91-3.97 (m, 0.7H, H-3), 4.17-4.23 (m, 0.3H, H-3*), 4.87 (d, *J* = 6.3 Hz, 0.3H, H-2*), 4.91 (d, *J* = 5.5 Hz, 0.7H, H-2), 7.20-7.29 (m, 6H, Si-Ph), 7.48-7.55 (m, 2H, H-3', H-5'), 7.57-7.62 (m, 2H, H-2', H-6'), 7.70-7.79 (m, 4H, Si-Ph) ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 19.32 (SiC(CH$_3$)$_3$), 26.87 (C(CH_3)$_3$), 27.47 (C(CH_3)$_3$), 31.79 (NCH_3), 60.53 (C-2), 65.01 (C-4), 72.70 (C-3), 82.29 (C(CH$_3$)$_3$), 123.07, 123.83, 128.41, 130.15, 130.21, 133.16, 135.85, 144.83, 149.76 (Ph), 167.94 (C-1) ppm. MS (ESI): *m*/*z* = 651.2 [M+Na]$^+$. HRMS (ESI): calcd. for $C_{31}H_{40}N_2O_8SSi$ [M+H]$^+$ 651.2167; found 651.2171. TLC (CH_2Cl_2): R_f = 0.66.

***tert*-Butyl-(2*S*,3*RS*)-3-acetoxy-4-((*tert*-butyldiphenylsilyl)oxy)-2-((*N*-methyl-4'-nitrophenyl)sulfonamido)butanoate (23):** NEt_3 (180 μL, 132 mg, 1.30 mmol), DMAP (15.9 mg, 0.130 mmol) and acetic anhydride (123 μL, 133 mg, 1.30 mmol) were added to a solution of **22** (410 mg, 0.652 mmol, *d.r.* 7:3) in Et_2O (10 mL) at 0 °C. After stirring at rt for 18 h, HCl (1 M, 40 mL) was added. The organic layer was washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative TLC (Chromatotron) to give **23** as a yellowish oil (370 mg, 85%, *d.r.* 7:3). ^{1}H NMR (500 MHz, C_6D_6): δ = 1.06 (s, 6.3H, C(CH_3)$_3$), 1.07 (s, 2.7H, C(CH_3)$_3$*), 1.21 (s, 6.3H, C(CH_3)$_3$), 1.22 (s, 2.7H, C(CH_3)$_3$*), 1.69 (s, 2.1H, C=OCH_3), 1.70 (s, 0.9H, C=OCH_3*), 2.63 (s, 2.1H, NCH_3), 2.78 (s, 0.9H, NCH_3*), 3.84-3.96 (m, 2H, H-4, H-4*), 5.20 (d, *J* = 7.0 Hz, 0.7H, H-2), 5.31 (d, *J* = 7.6 Hz, 0.3H, H-2*), 5.55 (ddd, *J* = 7.0, 5.4, 2.2 Hz, 0.7H, H-3), 5.76 (ddd, *J* = 7.6, 4.8, 2.6 Hz, 0.3H, H-3*), 7.18-7.32 (m, 6H, Si-Ph), 7.46-7.50 (m, 1.5H, H-3', H-5'), 7.54-7.59 (m, 2H, H-2', H-6', H-3'*, H-5'*), 7.59-7.63 (m, 0.6H, H-2'*, H-6'*), 7.76-7.89 (m, 4H, Si-Ph) ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 19.33 (SiC(CH$_3$)$_3$), 20.33 (C=OCH_3), 26.82 (C(CH_3)$_3$), 27.35 (C(CH_3)$_3$), 31.22 (NCH_3), 59.18 (C-2), 62.83 (C-4), 72.19 (C-3), 82.29 (C(CH$_3$)$_3$), 123.83, 128.58, 130.13, 130.16, 133.22, 135.82, 135.95, 144.48, 149.76 (Ph), 166.62, 168.86 (C-1, C=OCH$_3$) ppm. MS (ESI): *m*/*z* = 693.3 [M+Na]$^+$. HRMS (ESI): calcd. for $C_{33}H_{42}N_2O_9SSi$ [M+Na]$^+$ 693.2272; found 693.2275. TLC (CH_2Cl_2): R_f = 0.81.

***tert*-Butyl-(2*S*,3*R*)-3-acetoxy-4-((*tert*-butyldiphenylsilyl)oxy)-2-(methylamino)butanoate [(*R*)-24]:** (*R*)-**24** was prepared according to the GP, using **23** (42 mg, 0.10 mmol, *d.r.* 6:1), K_2CO_3 (22 mg, 0.19 mmol), thiophenol (8.0 μL, 8.3 mg, 75 μmol) and DMF (1 mL). The mixture was stirred at rt for 4 h. Column chromatography (petroleum ether-EtOAc, 9:1→7:1) gave (*R*)-**24** as a yellowish oil (16 mg, 52%).^{1}H NMR (500 MHz, C_6D_6): δ = 1.16 (s, 9H, SiC(CH_3)$_3$), 1.33 (s, 9H, C(CH_3)$_3$), 1.78 (s, 3H, C=OCH_3), 2.20 (s, 3H, NCH_3), 3.44 (d, *J* = 7.4 Hz, 1H, H-2), 4.03-4.05 (m, 2H, H-4), 5.38 (ddd, *J* = 7.4, 5.1, 4.4 Hz, 1H, H-3), 7.18-7.24 (m, 6H, Si-Ph), 7.76-7.83 (m, 4H, Si-Ph) ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 19.37 (SiC(CH$_3$)$_3$), 20.56 (C=OCH_3), 26.84 (C(CH_3)$_3$), 27.85 (C(CH_3)$_3$), 34.65 (NCH_3), 63.63 (C-4), 64.27 (C-2), 74.86 (C-3), 80.69 (C(CH$_3$)$_3$), 129.84, 133.76, 135.90 (Ph), 169.21 (C=OCH$_3$), 171.51 (C-1) ppm. MS (ESI): *m*/*z* = 486.2 [M+H]$^+$. TLC (petroleum ether-EtOAc, 4:1): R_f = 0.50.

***tert*-Butyl-(2*S*,3*S*)-4-(4'',4'''-dimethoxytrityloxy)-3-((triisopropylsilyloxy)-2-(*N*-methyl-4'-nitrophenyl)sulfonamido)-butanoate [(*S*)-25]:** A solution of (*S*)-**20** (34 mg, 62 μmol) and DMTr chloride (30 mg, 87 μmol) in dry pyridine (1 mL) was stirred at rt for 4 d. The solvent was evaporated under reduced pressure, and the resultant crude product was purified by column chromatography (petroleum ether-CH_2Cl_2, 1:1 + 1% pyridine) to give (*S*)-**25** as a yellowish foam (21 mg, 40%). $[\alpha]_D^{20}$ = -9.5 (c = 0.7, CH_2Cl_2).^{1}H NMR (500 MHz, C_6D_6): δ = 0.77-0.87 (m, 3H, CH(CH_3)$_2$), 0.89-0.99 (m, 18H, CH(CH$_3$)$_2$), 1.17 (s, 9H, C(CH_3)$_3$), 3.18 (s, 3H, NCH_3), 3.31 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 3.56 (dd, *J* = 9.4, 4.5 Hz, 1H, H-4$_a$), 3.85 (dd, *J* = 9.4, 9.4 Hz, 1H, H-4$_b$), 4.84 (ddd, *J* = 9.4, 4.5, 2.8 Hz, 1H, H-3), 5.56 (d, *J* = 2.8 Hz, 1H, H-2), 6.81-6.88 (m, 4H, H-3'', H-3''', H-5'', H-5'''), 7.03-7.08 (m, 1H, H-4''''), 7.23-7.28 (m, 2H, H-3'''', H-5''''), 7.62-7.71 (m, 8H, H-2', H-3', H-5'. H-6', H-2'', H-2''', H-6'', H-6'''), 7.80-7.84 (m, 2H, H-2'''', H-6'''') ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 12.57 (CH(CH_3)$_2$), 18.23, 18.29 (CH(CH_3)$_2$), 27.69 (C(CH_3)$_3$), 33.83 (NCH_3), 54.61 (OCH_3), 62.10 (C-2), 64.13 (C-4), 74.55 (C-3), 82.31 (C(CH$_3$)$_3$), 88.10 (CPh$_3$), 113.51, 113.59 (C-3'', C-5'', C-3''', C-5'''), 123.71 (C-3', C-5'), 127.03 (C-4''''), 128.19 (C-3'''', C-5''''), 128.75, 129.05 (C-2'', C-6'', C-2'''; C-2''', C-6''''; C-6''''), 130.62, 130.83 (C-2', C-6'), 136.26, 136.46 (C-1'', C-1'''), 144.78 (C-1'), 145.66 (C-1''''), 149.79 (C-4'), 159.14, 159.19 (C-4', C-4''), 168.76 (C-1) ppm. MS (ESI): *m*/*z* = 871.4 [M+Na]$^+$.TLC (CH_2Cl_2): R_f = 0.69.

***tert*-Butyl-(2*S*,3*R*)-4-(4'',4'''-dimethoxytrityloxy)-3-((triisopropylsilyloxy)-2-(*N*-methyl-4'-nitrophenyl)sulfonamido)-butanoate [(*R*)-25]:** A solution of (*R*)-**20** (67 mg, 0.12 mmol) and DMTr chloride (58 mg, 0.17 mmol) in dry pyridine (3 mL) was stirred at rt for 4.5 d. The solvent was evaporated under reduced pressure, and the resultant crude product was purified by column chromatography (petroleum ether-EtOAc, 20:1 + 0.5% pyridine) to give (*R*)-**25** as a yellowish foam (88 mg, 85%). ^{1}H NMR (500 MHz, C_6D_6): δ = 0.78-0.87

(m, 3H, C<u>H</u>(CH$_3$)$_2$), 0.90-0.94 (m, 18H, CH(C<u>H</u>$_3$)$_2$), 1.11 (s, 9H, C(CH$_3$)$_3$), 3.21 (s, 3H, NCH$_3$), 3.27 (s, 6H, OCH$_3$), 3.45 (dd, *J* = 9.0, 5.0 Hz, 1H, H-4$_a$), 3.79 (dd, *J* = 9.6, 9.0 Hz, 1H, H-4$_b$), 4.48 (ddd, *J* = 9.6, 5.0, 1.5 Hz, 1H, H-3), 5.62 (d, *J* = 1.5 Hz, 1H, H-2), 6.81-6.85 (m, 4H, H-3'', H-3''', H-5'', H-5'''), 7.05-7.10 (m, 1H, H-4''''), 7.21-7.27 (m, 2H, H-3'''', H-5''''), 7.54-7.74 (m, 10H, H-2', H-3', H-5'. H-6', H-2'', H-2''', H-6'', H-6''', H-2'''', H-6'''') ppm. ^{13}C NMR (126 MHz, C$_6$D$_6$): δ = 13.15 (<u>C</u>H(CH$_3$)$_2$), 18.33, 18.34 (CH(<u>C</u>H$_3$)$_2$), 27.91 (C(<u>C</u>H$_3$)$_3$), 33.12 (NCH$_3$), 54.80 (OCH$_3$), 62.47 (C-2), 65.25 (C-4), 76.43 (C-3), 81.97 (<u>C</u>(CH$_3$)$_3$), 87.56 (CPh$_3$), 113.66 (C-3'', C-5'', C-3''', C-5'''), 124.02 (C-3', C-5'), 125.69 (C-4''''), 127.31 (C-3'''', C-5''''), 128.55, 128.76, 129.32 (C-2'', C-6'', C-2'''; C-2''', C-6''''; C-6''''), 130.68 (C-2', C-6'), 136.24, 136.40 (C-1'', C-1'''), 145.19, 145.28 (C-1', C-1''''), 149.94 (C-4'), 159.37, 159.39 (C-4', C-4''), 167.37 (C-1). MS (ESI): *m*/*z* = 871.4 [M+Na]$^+$. TLC (CH$_2$Cl$_2$-MeOH, 99:0.1): R_f = 0.81.

***tert*-Butyl-(2*S*,3*S*)-4-(4',4''-dimethoxytrityloxy)-3-((triisopropylsilyloxy)-2-(methylamino)butanoate [(*S*)-26]:** (*S*)-**26** was prepared according to the GP, using (*S*)-**25** (16 mg, 19 μmol), K_2CO_3 (7.8 mg, 56 μmol), thiophenol (2.3 μL, 2.5 mg, 23 μmol) and DMF (1 mL). The mixture was stirred at rt for 15 h. Column chromatography (petroleum ether-CH_2Cl_2, 1:2 + 0.5% pyridine) gave (*S*)-**26** as a yellowish foam (6.0 mg, 48 %). $[\alpha]_D^{20}$ = +7.1 (c = 0.7, CH_2Cl_2).^{1}H NMR (500 MHz, C_6D_6): δ = 0.87-1.11 (m, 21H, CH(CH$_3$)$_2$), 1.45 (s, 9H, C(CH$_3$)$_3$), 2.54 (s, 3H, NCH$_3$), 3.27-3.31 (m, 7H, H-4$_a$, OCH$_3$), 3.85-3.87 (m, 1H, H-2), 4.00 (dd, *J* = 8.9, 8.6 Hz, 1H, H-4$_b$), 4.60-4.66 (m, 1H, H-3), 6.70-6.81 (m, 4H, H-3', H-3'', H-5', H-5''), 7.02-7.09 (m, 1H, H-4'''), 7.17-7.22 (m, 2H, H-3''', H-5'''), 7.52-7.58 (m, 4H, H-2', H-2'', H-6', H-6''), 7.69-7.74 (m, 2H, H-2''', H-6''') ppm. MS (ESI): *m*/*z* = 686.4 [M+Na]$^+$.

***tert*-Butyl-(2*S*,3*R*)-4-(4',4''-dimethoxytrityloxy)-3-((triisopropylsilyloxy)-2-(methylamino)butanoate [(*R*)-26]:** (*R*)-**26** was prepared according to the GP, using (*R*)-**25** (88 mg, 0.10 mmol), K_2CO_3 (43 mg, 0.31 mmol), thiophenol (13 μL, 14 mg, 0.12 mmol) and DMF (1 mL). The mixture was stirred at rt for 15 h. Column chromatography (petroleum ether-CH_2Cl_2, 1:2 + 0.5% pyridine) gave (*R*)-**26** as a yellowish foam (56 mg, 82%). $[\alpha]_D^{20}$ = +7.1 (c = 0.7, CH_2Cl_2).^{1}H NMR (500 MHz, C_6D_6): δ = 1.02-1.15 (m, 21H, CH(CH$_3$)$_2$), 1.38 (s, 9H, C(CH$_3$)$_3$), 2.45 (s, 3H, NCH$_3$), 3.30 (s, 6H, OCH$_3$), 3.50 (dd, *J* = 9.1, 5.3 Hz, 1H, H-4), 3.70 (d, *J* = 2.2 Hz, 1H, H-2), 3.76 (dd, *J* = 9.1, 7.9 Hz, 1H, H-4), 4.56 (ddd, *J* = 7.9, 5.3, 2.2 Hz, 1H, H-3), 6.75-6.80 (m, 4H, H-3', H-3'', H-5', H-5''), 7.03-7.09 (m, 1H, H-4'''), 7.17-7.22 (m, 2H, H-3''', H-5'''), 7.53-7.58 (m, 4H, H-2', H-2'', H-6', H-6''), 7.69-7.73 (m, 2H, H-2''', H-6''') ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 12.91 (<u>C</u>H(CH$_3$)$_2$), 18.30 (CH(<u>C</u>H$_3$)$_2$), 28.18 (C(<u>C</u>H$_3$)$_3$), 35.68 (NCH$_3$), 54.60 (OCH$_3$), 65.60 (C-4), 67.44 (C-2), 75.79 (C-3), 80.43 (<u>C</u>(CH$_3$)$_3$), 87.07 (CPh$_3$), 113.34 (C-3', C-5', C-3'', C-5''), 126.86 (C-4''''), 127.37 (C-3''', C-5'''), 128.76 (C-2''', C-6'''), 130.60, 130.66 (C-2'; C-2'', C-6'; C-6''), 136.60, 136.74 (C-1', C-1''), 145.80 (C-1'''), 159.02, 159.05 (C-4', C-4''), 171.25 (C-1) ppm. IR (ATR): ν = 3397, 2931, 2866, 2364, 1606, 1509, 1318, 1251, 1132 cm^{-1}. UV (MeOH): λ_{max} = 233 nm. MS (ESI): *m*/*z* = 686.4 [M+Na]$^+$. HRMS (ESI): calcd. for $C_{39}H_{57}NO_6Si$ [M+H]$^+$ 664.4028; found 664.4027. TLC (CH_2Cl_2-MeOH, 96:4): R_f = 0.63.

***tert*-Butyl-(2*S*,3*S*)-4,4-dimethoxy-3-(triisopropylsilyl-oxy)-2-((*N*-methyl-4'-nitrophenyl)sulfonamido)-butanoate [(*S*)-27]:** A solution of (*S*)-**19b** (230 mg, 0.422 mmol) and *para*-toluenesulfonic acid (8.0 mg, 42 μmol) in trimethyl orthoformate (5 mL) was stirred at rt for 13 h. EtOAc (50 mL) and sat. $NaHCO_3$ solution (50 mL) were added. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The resultant crude product was purified by column chromatography (petroleum ether-EtOAc, 25:1→20:1) to give (*S*)-**27** as a colorless oil (106 mg, 42%). $[\alpha]_D^{20}$ = -28.8 (c = 1.2, MeOH).^{1}H NMR (500 MHz, C_6D_6): δ = 1.10 (s, 9H, C(CH$_3$)$_3$), 1.12-1.16 (m, 18H, CH(C<u>H</u>$_3$)$_2$), 1.16-1.24 (m, 3H, C<u>H</u>(CH$_3$)$_2$), 3.09 (s, 3H, OCH$_3$), 3.25 (s, 3H, NCH$_3$), 3.46 (s, 3H, OCH$_3$), 4.35 (d, *J* = 7.4 Hz, 1H, H-4), 4.68 (dd, *J* = 7.4, 2.8 Hz, 1H, H-3), 5.18 (d, *J* = 2.8 Hz, 1H, H-2), 7.60-7.64 (m, 2H, H-3', H-5'), 7.69-7.73 (m, 2H, H-2', H-6') ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 13.82 (<u>C</u>H(CH$_3$)$_2$), 18.99, 19.07 (CH(<u>C</u>H$_3$)$_2$), 28.09 (C(<u>C</u>H$_3$)$_3$), 34.43 (NCH$_3$), 56.78, 57.26 (OCH$_3$), 62.33 (C-2), 75.95 (C-3), 82.90 (<u>C</u>(CH$_3$)$_3$), 106.44 (C-4), 124.09 (C-2', C-6'), 129.47 (C-3', C-5'), 145.14 (C-1'), 150.31 (C-4'), 168.80 (C-1) ppm. IR (ATR): ν = 2932, 2858, 1731, 1154, 1112, 1075, 702, 508 cm^{-1}. UV (MeOH): λ_{max} = 277 nm. MS (ESI): *m*/*z* = 613.2 [M+Na]$^+$. HRMS (ESI): calcd. for $C_{26}H_{46}N_2O_9SSi$ [M+H]$^+$ 613.2585; found 613.2581. TLC (petroleum ether-EtOAc, 4:1): R_f = 0.48.

***tert*-Butyl-(2*S*,3*R*)-4,4-dimethoxy-3-(triisopropylsilyl-oxy)-2-((*N*-methyl-4'-nitrophenyl)sulfonamido)-butanoate [(*R*)-27]:** (*R*)-**27** was prepared in the same way as isomer (*S*)-**27,** using (*R*)-**19b** (233 mg, 0.428 mmol), *para*-toluenesulfonic acid (8.1 mg, 43 μmol) and trimethyl orthoformate (5 mL). The reaction mixture was stirred at rt for 16 h. Column chromatography (petroleum ether-EtOAc, 25:1→20:1) gave (*R*)-**27** as a colorless oil (235 mg, 93%). $[\alpha]_D^{20}$ = +38.2(c = 1.1, CH_2Cl_2).^{1}H NMR (500 MHz, C_6D_6): δ = 1.12-1.16 (m, 30H, C<u>H</u>(C<u>H</u>$_3$)$_2$, (CH$_3$)$_3$), 3.08 (s, 3H, OCH$_3$), 3.10 (s, 3H, NCH$_3$), 3.26 (s, 3H, OCH$_3$), 4.36 (dd, *J* = 6.9, 2.7 Hz, 1H, H-3), 4.68 (d, *J* = 6.9 Hz, 1H, H-4), 5.24 (d, *J* = 2.7 Hz, 1H, H-2), 7.58-7.62 (m, 2H, H-3', H-5'), 7.66-7.70 (m, 2H, H-2', H-6') ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 13.61 (<u>C</u>H(CH$_3$)$_2$), 18.46, 18.53 (CH(<u>C</u>H$_3$)$_2$), 27.61 (C(<u>C</u>H$_3$)$_3$), 32.78 (NCH$_3$), 52.95, 54.73 (OCH$_3$), 61.86 (C-2), 76.64 (C-3), 81.91 (<u>C</u>(CH$_3$)$_3$), 104.78 (C-4), 123.75 (C-2', C-6'), 128.25, 128.63 (C-3', C-5'), 144.72 (C-1'), 149.81 (C-4'), 166.95 (C-1) ppm. IR (ATR): ν = 2933, 2864, 1731, 1533, 1350, 1152, 1112, 739 cm^{-1}. UV (MeOH): λ_{max} = 276 nm. MS (ESI): *m*/*z* = 613.2 [M+Na]$^+$. HRMS (ESI): calcd. for $C_{26}H_{46}N_2O_9SSi$ [M+H]$^+$ 613.2585; found 613.2578. TLC (petroleum ether-EtOAc, 4:1): R_f = 0.45.

***tert*-Butyl-(2*S*,3*S*)-4,4-dimethoxy-3-(triisopropylsilyl-oxy)-2-(*N*-methylamino)-butanoate [(*S*)-28]:** (*S*)-**28** was prepared according to the GP, using (*S*)-**27** (98 mg, 0.17 mmol), K_2CO_3 (69 mg, 0.50 mmol), thiophenol (20 μL, 22 mg, 0.20 mmol) and DMF (1 mL). The mixture was stirred at rt for 19 h. Column chromatography (CH_2Cl_2) gave (*S*)-**28** as a colorless oil (58 mg, 86%). $[\alpha]_D^{20}$ = 9.0 (c = 0.7, CH_2Cl_2). ^{1}H NMR (500 MHz, C_6D_6): δ = 1.15-1.29 (m, 21H, C<u>H</u>(C<u>H</u>$_3$)$_2$, 1.40 (s, 9H, (CH$_3$)$_3$), 2.39 (s, 3H, NCH$_3$), 3.15 (s, 3H, OCH$_3$), 3.26 (s, 3H, OCH$_3$), 3.46 (d, *J* = 1.8 Hz, 1H, H-2), 4.37 (dd, *J* = 7.2, 1.8 Hz, 1H, H-3), 4.63 (d, *J* = 7.2 Hz, 1H, H-4) ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 13.45 (<u>C</u>H(CH$_3$)$_2$), 18.58 (CH(<u>C</u>H$_3$)$_2$), 28.05 (C(<u>C</u>H$_3$)$_3$), 34.84 (NCH$_3$), 54.62, 54.95 (OCH$_3$), 65.33 (C-2), 75.23 (C-3), 80.50 (<u>C</u>(CH$_3$)$_3$), 106.03 (C-4), 172.40 (C-1) ppm. IR (ATR): ν = 2940, 2867, 1737, 1459, 1144, 1105, 1069, 677 cm^{-1}. MS (ESI): *m*/*z* = 406.2 [M+H]$^+$. HRMS (ESI): calcd. for $C_{20}H_{43}NO_5Si$ [M+H]$^+$ 406.2983; found 406.2978. TLC (petroleum ether-EtOAc, 4:1): R_f = 0.44.

***tert*-Butyl-(2*S*,3*R*)-4,4-dimethoxy-3-(triisopropylsilyl-oxy)-2-(*N*-methylamino)-butanoate [(*R*)-28]:** (*R*)-**28** was prepared according to the GP, using (*R*)-**27** (19 mg, 32 μmol), K_2CO_3 (13 mg, 97 μmol), thiophenol (4.0 μL, 4.2 mg, 39 μmol) and DMF (1 mL). The mixture was stirred at rt for 7 h. Column chromatography (petroleum ether-EtOAc, 22:1→9:1) gave (*R*)-**28** as a colorless oil (9.0 mg, 69%). $[\alpha]_D^{20}$ = -15.0 (c = 0.4, CH_2Cl_2). ^{1}H NMR (500 MHz, C_6D_6): δ = 1.22-1.24 (m, 21H, C<u>H</u>(C<u>H</u>$_3$)$_2$, 1.43 (s, 9H, (CH$_3$)$_3$), 2.47 (s, 3H, NCH$_3$), 3.22 (s, 3H, OCH$_3$), 3.30 (s, 3H, OCH$_3$), 3.45 (d, *J* = 2.0 Hz, 1H, H-2), 4.40 (dd, *J* = 7.3, 2.0 Hz, 1H, H-3), 4.57 (d, *J* = 7.3 Hz, 1H, H-4) ppm. ^{13}C NMR (126 MHz, C_6D_6): δ = 13.07 (<u>C</u>H(CH$_3$)$_2$), 18.37 (CH(<u>C</u>H$_3$)$_2$), 28.02 (C(<u>C</u>H$_3$)$_3$), 36.46 (NCH$_3$), 55.42, 55.83 (OCH$_3$), 67.30 (C-2), 76.80 (C-3), 80.31 (<u>C</u>(CH$_3$)$_3$), 106.78 (C-4), 170.57 (C-1) ppm. IR (ATR): ν = 2941, 2798, 1734, 1464, 1391, 1148, 1108, 1069, 882, 702 cm^{-1}. UV (MeOH): λ_{max} = 237 nm. MS

(ESI): *m/z* = 406.2 $[M+H]^+$. HRMS (ESI): calcd. for $C_{20}H_{43}NO_5Si$ $[M+H]^+$ 406.2983; found 406.2981. TLC (petroleum ether-EtOAc, 4:1): R_f = 0.33.

Keywords: natural products • antibiotics • amino acids • modular synthesis • protecting groups

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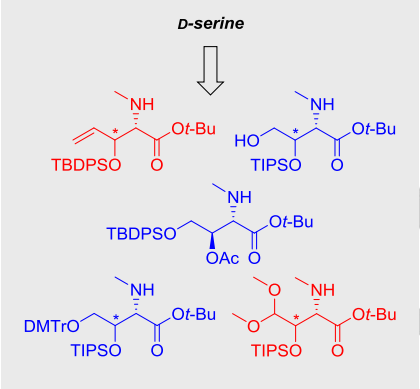
Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

The total synthesis of caprazamycin nucleoside antibiotics and their analogues is not trivial. For instance, it requires a densely functionalized amino acid building block to construct the diazepanone core motif. We now report a unified synthesis of five different amino acid building blocks of this type, thus providing a highly useful 'toolbox' for the synthesis of caprazamycins as well as other complex peptidic natural products.



Amino Acids

*Ruth Linder, Christian Ducho**

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Unified Synthesis of Densely Functionalized Amino Acid Building Blocks for the Preparation of Caprazamycin Nucleoside Antibiotics