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Synthesis and In Vitro Biological Properties of Novel Cationic Derivatives of Amphotericin B

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Abstract: Novel cationic amphotericin B derivatives as highly potent antifungal agents are reported. These semisynthetic derivatives of amphotericin B were elaborated through a series of modifications both on the nitrogen atom of the mycosamine and on the C-16 carboxylic acid moiety. The antifungal activity of the new conjugates was tested against *Saccharomyces cerevisiae* and also against nine different strains of *Candida albicans* and *Candida glabrata*, including an amphotericin resistant strain. High potency was observed in the case of polyamine derivatives bearing two 3-aminopropyl chains on the mycosamine. The evaluation of the biological properties also included the determination of the hemolytic activity of the compounds by measuring the EH_{50} values.

Keywords: amphotericin B · antifungal agents · bioorganic chemistry · natural products · total synthesis

Introduction

In recent decades, the incidence of nocosomial fungal infections clearly has risen to a point where some mycoses are real therapeutic challenges. In the case of blood infections caused by *Candida* species, the incidence has increased by almost 500% throughout the 1980s. This was mainly attributed to aggravating factors such as immunosuppressive therapy, an increasing number of AIDS patients and chemotherapy.[1]

Fungal species, typically *Candida* and *Aspergillus*, account for up to 25% of all hospital-acquired blood infections but the emergence of other fungal species is now changing the spectrum of disease.[2] Amphotericin B (AmB, **1**) is the most effective antifungal agent available for the treatment of systemic mycoses. With the broadest spectrum of activity, AmB is often referred to as the "golden standard" of antifungal agents.[3–5] However, some drawbacks are normally associated with treatment, especially severe side effects, which include nephrotoxicity. Furthermore, AmB is only available as a deoxycholate suspension (Fungizone) since the amphiphilic nature of this molecule makes it insoluble in water. Therefore this drug is poorly absorbed orally and intravenous administration is essential to ensure effectiveness. A great deal of effort has been devoted to reduce the toxicity of AmB and some improvement was achieved by modifying the formulations used to administer AmB, such as liposomal product AmBisome.[6–9] In this study, structural modifications of the molecule have been made in order to improve the therapeutic index. In addition, different strategies were tested to alter the physical, chemical and pharmacological properties of AmB.

To date the majority of the structure–activity relationship studies relied on chemical modification of natural AmB[10–15] To a lesser extent, genetic engineering has also been used to access other derivatives.[16–18] Previous studies revealed that the presence of a positively charged nitrogen atom on the mycosamine is essential for antifungal activity.[10] Furthermore, results indicate that the lack of a negative charge on the carboxylic acid reduces the hemotoxicity of the molecule. Even though biological activity is not always affected by synthetic alteration, it is clear that the overall charge of the molecule is crucial. Following these observations, the zwitterionic character of AmB appears as a decisive factor in the conformation and the aggregation state of the molecule which is ultimately reflected on the activity. Therefore the design of new derivatives should mainly focus on the ionizable groups of AmB. Since good biological activity is exhibited by compounds in which the nitrogen atom is positively charged at physiological pH, cationic derivatives of AmB are potentially highly active analogues. The presence of a net charge on the molecule should hinder self-associa-

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tion thus favoring the existence of monomeric AmB with reduced toxicity. At the same time, cationic AmB derivatives could increase hydrogen-binding ability essential according to the proposed ion channel model.[19] Moreover, the presence of polar functional groups may give rise to the formation of water soluble salts.

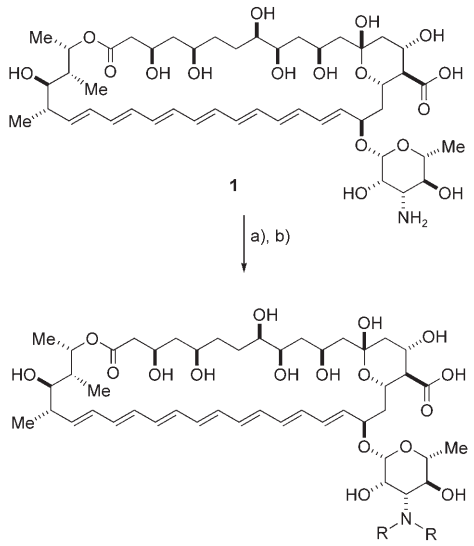
The natural polyamines putrescine, spermidine and spermine are found in living organisms where they interact with a wide variety of cellular targets. Even though these polycationic molecules have increased binding affinity for several biomolecules, their specific function is still obscure.[20] Since they are protonated at physiological pH, polyamines efficiently interact with negatively charged phospholipids in the biological membrane. In the case of yeast cells, exogenous polyamines are specifically internalized by a membrane uptake system.[21] Consequently, these strong interactions between polyamines and polar head-groups might influence not only the membrane functions but also various properties such as permeability.[22] Recently, polyamine conjugates and synthetic analogues were found to be involved in many biological processes just as the naturally occurring polyamines.[23] In fact, research on polyamine-based compounds is a very active field especially for pharmaceutical oriented applications.[24,25] Since the membrane is suggested to be to be the primary target of AmB, polyamine conjugates of AmB have the potential of displaying increased potency. Herein, we report novel cationic derivatives of AmB as highly potent antifungal agents. Some of the semi-synthetic derivatives were elaborated by anchoring a polyamine moiety to the mycosamine of AmB using a reductive alkylation reaction. Further chemical elaboration at the C-16 position was performed through various amide coupling reactions. The antifungal activity of the new derivatives was tested against *Saccharomyces cerevisiae* and several *Candida* strains. The hemolytic activity was ranked on the basis of measured EH_{50} value, which can be related to the toxicity of the new AmB derivatives.

Results and Discussion

Design and synthesis: In order to increase the biological activity of AmB, we mainly focused our research on modifying both the position and the number of amine functions on the mycosamine moiety. The rationale behind these structural alterations was that the primary amine group on AmB is believed to play an important role in membrane interactions.[26] This approach was also supported by the presence of a positive charge that modifies the conformation and the aggregation state of the molecule which are important factors for activity.[27,28]

In addition to primary amine functions, amino acid and polyamine structures also introduce basic functionalities protonated at physiological pH thereby giving access to cationic derivatives of AmB. In the same way, the guanidine group has the ability to promote hydrogen-bonding interactions even with the phosphate group present in lipid bilayers.[29] Even though the mycosamine has been previously modified, it was reported that *N*-alkylation of polyene macrolides is rather difficult.[30] However, from our previous work on AmB,[31] we have demonstrated that selective alkylation of the primary amine by reductive alkylation can be efficiently accomplished using unprotected AmB (**1**). We also employed this reductive alkylation approach for the synthesis of new conjugates of pimaricin and nystatin.[32]

Using this alkylation strategy, the synthesis of polyamines analogues of AmB was carried out. The mycosamine of AmB was reductively alkylated twice using a variety of aminoaldehydes and $NaBH_3CN$ as reducing agent (Scheme 1).

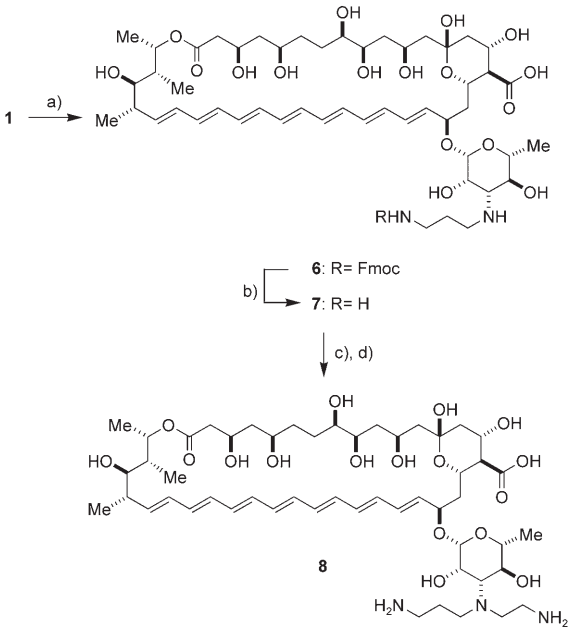


Scheme 1. a) $FmocNH(CH_2)_nCHO$ ($n=1$–3) or $FmocNH_2(CH_2)_4$-(NHFmoc)$CHCH_2CHO$, $NaBH_3CN$, DMF; b) piperidine, DMSO.

The reported yields (22–76%) are the combined yields for the double alkylation reaction and the removal of the 9-fluorenylmethoxycarbonyl (Fmoc) protecting groups on the amine functionalities. Various chain lengths between the nitrogen atoms were chosen in order to screen their effect on potency. Furthermore, compound **5** bearing four primary amine groups might eventually give some indications on the number of protonable nitrogen atoms optimal for good biological activity.

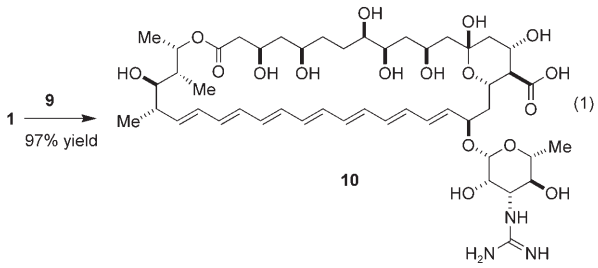
After the synthesis of symmetrically substituted polyamines derivatives of AmB, monoalkylation reaction was performed (Scheme 2) using reaction conditions previously described.[33]

The monoalkylated derivative **6** can be directly deprotected using piperidine to afford **7**. Alternately, **6** can be further alkylated using a different aldehyde moiety thus generating asymmetrically substituted mycosamine. The derivative **8** was isolated in 26% yield after a sequence of three steps from the native AmB.



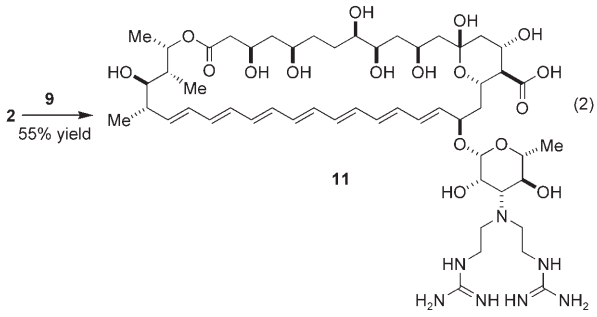
Scheme 2. a) $FmocNHCH_2CH_2CHO$, $NaBH_3CN$, DMF; b) piperidine, DMSO, 7%; c) $FmocNHCH_2CHO$, $NaBH_3CN$, DMF; d) piperidine, DMSO, 26%.

Nitrogen-based AmB derivatives were also elaborated by the introduction of guanidine functionality. The guanidine group can be directly attached to the mycosamine of AmB by using 1*H*-pyrazolecarboxamidine hydrochloride (**9**) as reagent [Eq. (1)]. [34] The derivative **10** was then isolated in 97% yield in only one step.



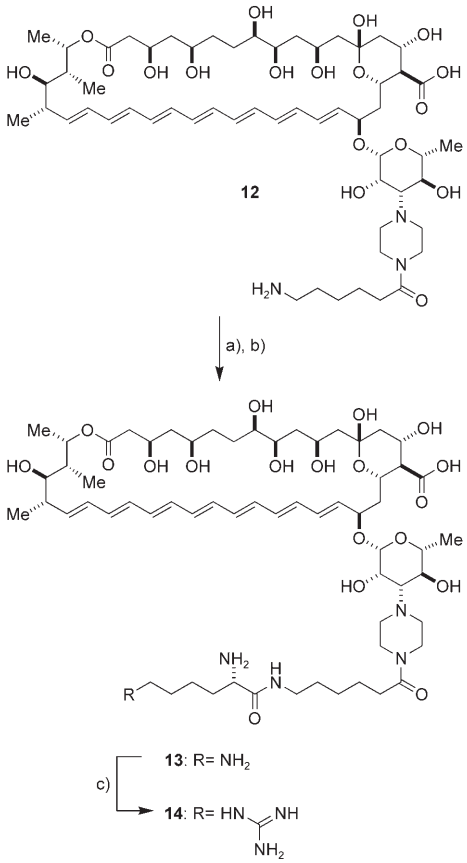
The introduction of the guanidine functionality is also possible on the side chains already attached to the mycosamine. The bisguanidine derivative **11** was synthesized by reacting the bis-2-aminoethyl derivative **2** with an excess of 1*H*-pyrazolecarboxamidine hydrochloride (**9**) [Eq. (2)]. Finally, **11** was isolated in 55% yield after a double guanidination reaction.

In addition to the polyamine structures, there are several accessible amino acids containing multiple amines that can be linked to the mycosamine. Although peptide coupling reaction could be used to link amino acids to the mycosamine, only very few examples are known. However, our group has previously reported the synthesis of a readily accessible piperazine linker as a synthetic anchor for the conjugation of



various biomolecules to AmB, such as fluorescein.[31] This linker has the advantage of being selectively attached through a double reductive alkylation reaction and at the same time preserving the basicity of the nitrogen on the mycosamine. After the assembly of the linker with AmB, the intermediate can be easily deprotected following a known procedure (Scheme 3).[35]

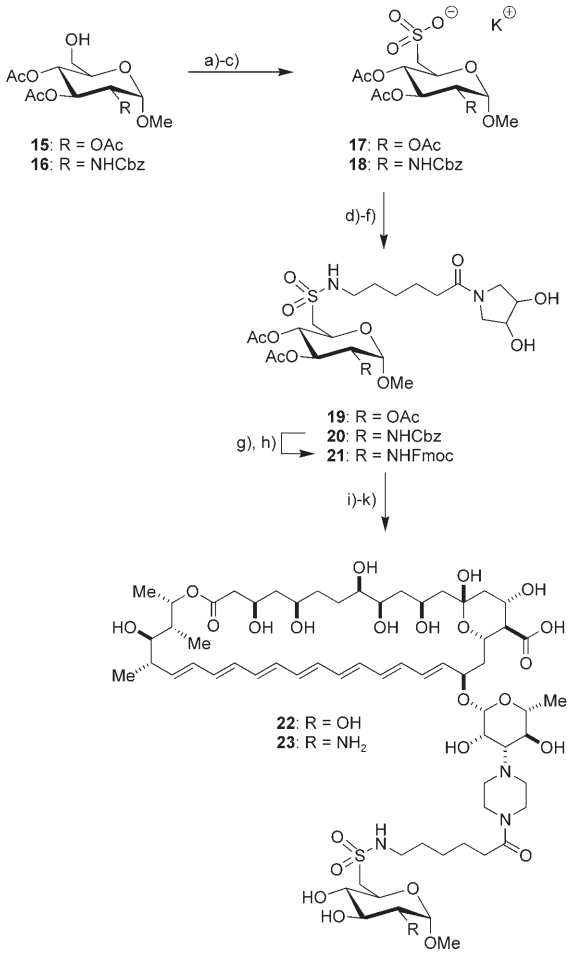
The 6-amino-1-hexanoyl-(piperazinyl)-AmB derivative **12** was then ready for an amide coupling reaction using *N*-protected lysine activated as the hydroxysuccinimide ester (Succ). After removal of the Fmoc group, the desired lysine derivative **13** was isolated in 28% yield. Subsequently, the arginine derivative **14** can be synthesized in one step in 20% yield using reagent **9**.



Scheme 3. a) $FmocNH(CH_2)_4CH(NHFmoc)CO_2Suc$, DIPEA, DMF; b) piperidine, DMSO, 28%; c) **9**, DIPEA, 20%.

Many of AmBs toxic side effects are a direct result of the high dosage that have to be administered to patients. Its low solubility is a major problem in the field. One of the possibilities to increase the solubility of a compound is to attach a carbohydrate.[36] A common, but limited method to attach carbohydrates to amines is via the Amadori rearrangement.[37–39] A glycoconjugation method, which is not only limited to the anomeric position and based on sulfonyl esters, was developed in our group.[40] It gives the possibility to introduce conjugation at any position at the sugar unit. In addition, it is possible to conjugate to a linker and vary the chain length of this linker, making it a versatile method. In this study, this strategy was used to link carbohydrates to the piperazine linker (Scheme 4). Glucose and glucosamine were both attached to the mycosamine to examine the cumulative effect of the carbohydrate and the influence of the extra amine of glucosamine on the activity of AmB.

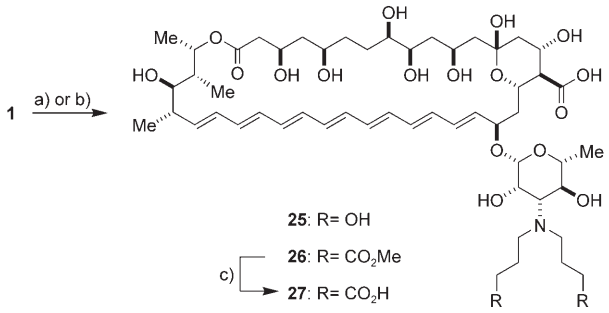
Methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (**15**) was prepared according to known literature procedures.[41–43]



Scheme 4. a) MsCl, Et_3N, CH_2Cl_2; b) KSAc, DMF; c) H_2O_2, KOAc, AcOH, 79% for **17**, 60% for **18** over three steps; d) SO_2Cl_2, PPh_3, CH_2Cl_2; e) Et_3N, **24**; f) K_2OsO_4, NMO, acetone/H_2O/*t*BuOH, 24% for **19**, 46% for **20** over three steps; g) H_2, Pd/C; h) FmocSuc, Na_2CO_3, H_2O/dioxane 26% over two steps; i) $NaIO_4$, SiO_2, H_2O/$CHCl_3$; j) AmB, $NaBH_3CN$, DMF; k) K_2CO_3, piperidine, H_2O/MeOH, 59% for **22**, 66% for **23** over three steps.

Employing similar standard methods methyl 3,4-di-*O*-acetyl-2-deoxy-α-D-glucopyranoside (**16**) was synthesized.[39,44–47] Both compounds were subjected to the same reaction conditions, which through displacement of the mesylate and oxidation of the corresponding sulfonyl acetate lead to compounds **17** and **18** in a yield of 79 and 60%, respectively, over three steps. Generation of the sulfonyl chloride under standard conditions,[48] followed by coupling to [6-(2,5-dihydro-1*H*-pyrrol-1-yl)-6-oxohexyl]amine (**24**)[31] and dihydroxylation of the pyrroline double bond afforded compounds **19** and **20** (24 and 46% yield) in three steps. Protection group exchange of **20** to **21** in 26% yield makes both compounds ready for oxidative cleavage to subject this to AmB in a double reductive alkylation reaction. **22** and **23** (47 and 39% yield) were isolated after a sequence of two sequential deprotection steps.

Cognizant of the fact that the overall charge of the molecule will be an important aspect of these new cationic derivatives of AmB, we also prepared other conjugates. In order to retain good hydrogen-bonding ability, we surveyed derivatives that contained alcohol and carbonyl functionality on the side chains (Scheme 5).



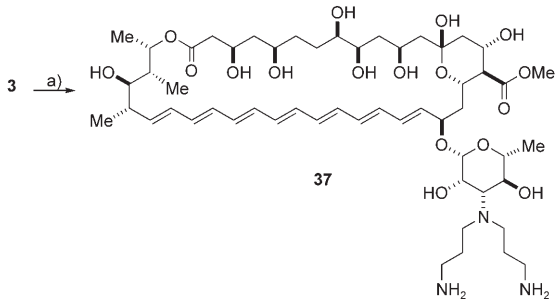
Scheme 5. a) i) $TBSOCH_2CH_2CHO$, $NaBH_3CN$, DMF, ii) HF/pyridine, 28% for **25**; b) $MeO_2CCH_2CH_2CHO$, $NaBH_3CN$, DMF, 45% for **26**; c) LiOH, THF/H_2O, 43%.

We first prepared diol derivative **25** using the corresponding protected aldehyde for the alkylation reaction followed by the deprotection of the silyl groups using HF/pyridine. The two steps sequence allowed the isolation of **25** in 28% yield. In the case of the diester **26**, the double alkylation was carried out using methyl-4-oxobutanoate, thus affording directly the desired compound in 45% yield. Finally, after the hydrolysis of the two esters on **26**, the diacid derivative **27** was isolated in 43% yield.

The incorporation of several basic amino groups, especially polyamine structures on the mycosamine is believed to enhance the potency of AmB. These structural modifications will most likely also have a positive influence on the solubility properties of the new derivatives. To achieve our goal of improving the pharmacological properties of AmB, we sought to address toxicity as manifest by hemolysis because this represents a serious issue. The hemolytic property of AmB is among one of the major problems associated with the clinical use of this antibiotic. However, substitution of

the carboxylic acid at C16 has been shown to reduce its hemotoxicity. Esterification reactions were reported early on for the introduction of various substituents at that position.[49] More recently, some polyene compounds underwent chemical modification or isolation from a recombinant strain of S*treptomyces diastaticus* var. 108 leading to partricin A,[50] CE-108 and rimocidin derivatives.[51] For AmB, amide derivatives were also generated in order to introduce diversity.[52–54] Although a variety of amide derivatives have been synthesized over the years, only limited improvement in therapeutic index has been noted. The majority of the compounds had lower antifungal activity over AmB and the enhancement is often attributed to greater water solubility or reduced toxicity. Unfortunately, no direct correlation can be draw between the structure of the amide moiety and the effect on the toxicity of the compound. For example, the relationship between self-association and the toxicity of some derivatives was studied because it was demonstrated for AmB that monomers and non-water-soluble aggregates are less toxic then water-soluble aggregates.[55] However, it was shown by UV spectroscopy that the toxicity was independent of the ratio monomer/aggregate in the case of amide derivatives of AmB.[56] Despite very little indication on the nature of the best side chain, amide derivatives were synthesized using peptide coupling reagents. And even if the effect on the toxicity seemed unpredictable, several amine structures were used in the reaction in order to generate analogues with very low hemotoxicity (Scheme 6).

The amide coupling reaction was performed on the polyamine derivative **28** where the mycosamine side chains were protected as Fmoc groups. Primary and secondary amines were used in the reaction in combination with (benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (PyBOP) and 1-hydroxybenzotriazole (HOBt). The low yields (7 to 49%) obtained over the two steps are mostly attributable to the partial deprotection of the Fmoc groups and difficulties in the purification of these compounds. Further optimization with respect to the protecting group should allow improvements in yields. For comparison purpose, the corresponding methyl ester derivative **37** was synthesized in 59% yield using trimethylsilyldiazomethane in methanol (Scheme 7).

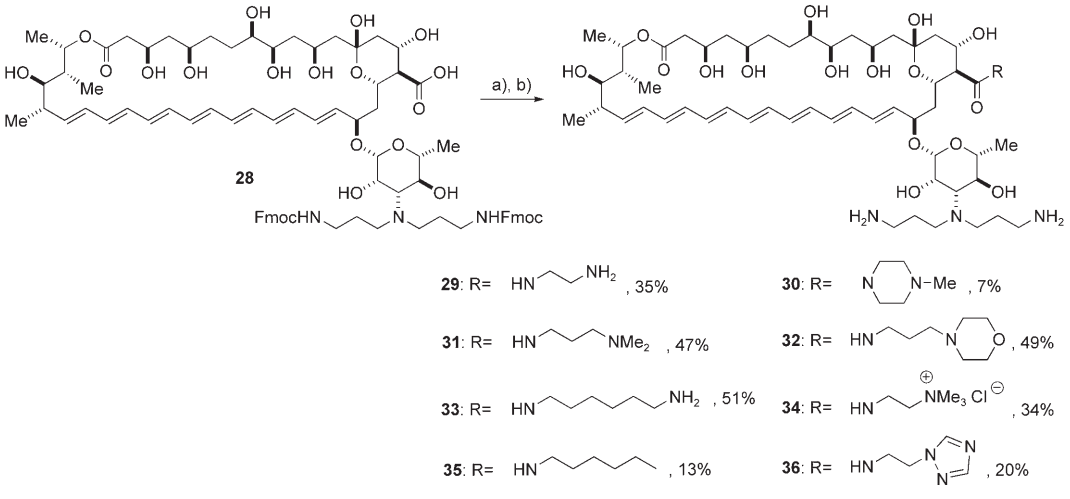


Scheme 7. a) $TMSCHN_2$, MeOH, 59%.

In this study, reductive alkylation was used in order to introduce several nitrogen-based functionalities specifically on the mycosamine of AmB. Further chemical elaboration at C_{16} was also possible using amide coupling reaction conditions. A series of new semi-synthetic derivatives of AmB are now accessible through these simple transformations.

Biological assays: The antifungal activity of the semi-synthetic derivatives of AmB was tested following the NCCLS protocol by measuring the minimal inhibitory concentrations (MICs) required to completely inhibit growth of yeast. This assay served as the basis for the comparison between the novel compounds and natural AmB.

First, the effect on the activity of the new derivatives as a result of the chemical modification on the mycosamine was evaluated. As shown in Table 1, the amino derivatives were assayed against *Saccharomyces cerevisiae* in order to compare their antifungal activity. We expected that the introduction of several basic amino groups on the mycosamine, especially polyamine derived structures, would improve the po-



Scheme 6. a) PyBOP, HOBt, DIPEA, RNH_2; b) piperidine, DMSO.

Table 1. Minimum inhibitory concentration for compounds bearing modified mycosamine.

Entry	Compound	MIC [μM][a]
1	**1**	0.30
2	**2**	0.25
3	**7**	0.10
4	**8**	0.090
5	**3**	0.020
6	**4**	>10
7	**28**	0.50
8	**5**	0.080
9	**10**	0.020
10	**11**	0.10
11	**25**	0.50
12	**26**	2.0
13	**27**	>10
14	**13**	0.10
15	**14**	0.10
16	**22**	2.0
17	**23**	0.30

[a] Assayed with *S. cerevisiae* wild type (BY4741) following the NCCLS protocol; see Experimental Section for details.

tency. Two aminoethylene side chains had no beneficial effect on the MIC value of compound **2** (entry 2). However, the presence of only one aminopropylene side chain (**7**) led to improved activity with a MIC value of 0.10 μM compared with 0.30 μM for AmB (entries 1 vs 3). A similar antifungal activity is obtained after the introduction of an aminoethylene group on the mycosamine in derivative **8** with a MIC value of 0.090 μM. Moreover, the bis-aminopropyl derivative **3** with a MIC value of 0.020 μM is 15 times more potent than the native drug.

In addition, the slightly decreased activity of **4** (entry 6) suggests that the length of the spacer between the amino groups is a very important factor for activity. Furthermore, the basicity of the amino groups placed on the side chains is crucial because masking of the primary amine as carbamate groups completely inhibits the activity (**28**, entry 7). However, the reduced potency of derivative **5** compared to **3** (entries 8 vs 5) gives some indications that a large number of primary amino groups are not necessary for optimal antifungal activity. The modification of the mycosamine by incorporation of a guanidine group considerably improved the potency of compound **10** (entry 9). But the substitution of the two amino groups by guanidines in compound **11** had only limited effect on the MIC value with a three-fold increase in antifungal activity (entry 10). Conjugates containing different functional groups that could also participate in hydrogen-bonding interactions were also surveyed. Diol derivative **25** showed no significant gain in activity (entry 11). In the case of the diester derivative **26**, the biological activity is diminished to a MIC value of 2.0 μM which was six times less then with natural AmB (entries 12 vs 1). In compound **27** the presence of negatively charge functional groups on the mycosamine was detrimental and the diacid derivative was completely inactive (entry 13). The screening of various amino derivatives of AmB was pursued through the incorporation of an amino acid moiety. Lysine and arginine were chosen because they include nitrogen-based functionalities. Derivatives **13** and **14** were tested and a MIC value of 0.10 μM was obtained in both cases revealing a three-fold increase in activity. Without a primary amine in carbohydrate derivative **22** a seven-fold loss in activity is found (entry 16). With the reintroduction of an amino group as a glucosamine moiety the original activity was restored for compound **23** (entry 17) with respect to natural AmB.

From the first screening on the mycosamine, we found that the introduction of bisaminopropylene moiety on the mycosamine of AmB improves significantly the antifungal activity. Although the incorporation of a guanidine on the mycosamine enhanced the potency, the observed effect was limited to AmB. The other polyene macrolides modified with the guanidine moiety did not benefit from this modification.[32] Since the bisaminopropylene motif on the mycosamine lead to superior results, its use was continued in the amide derivative in order to capitalize on the improved potency. Amide analogues **29–36** were first tested against *S. cerevisiae* to compare their activity with the reference compound **3** and natural AmB (Table 2). Most compounds exhibit similar antifungal activity to AmB where the MIC values ranged between 0.20 and 0.60 μM. However, the com-

Table 2. Minimum inhibitory concentration against various yeast strains.

Entry	Compound	*S. cerevisiae*	*C. albicans*						*C. glabrata*	
		BY4741 [μM]	CAF2-1 [μM]	DSY294 [μM]	DSY296 [μM]	DSY654 [μM]	DSY1751 [μM]	DSY1764 [μM]	DSY562 [μM]	DSY565 [μM]
1	**1**	0.30	0.30	0.40	0.40	0.50	0.30	50	0.50	0.50
2	**7**	0.10	0.10	0.10	0.20	0.25	0.10	2.0	0.10	0.20
3	**3**	0.020	0.10	0.20	0.10	0.10	0.10	1.0	0.20	0.20
4	**37**	0.10	0.50	0.25	0.10	0.25	0.50	3.0	0.25	0.25
5	**29**	0.040	2.0	1.0	0.75	2.0	2.0	3.0	0.50	0.50
6	**30**	0.20	0.30	0.30	0.30	0.40	0.40	0.50	0.30	0.20
7	**31**	0.40	0.50	0.50	0.30	0.50	1.0	1.0	0.30	0.30
8	**32**	0.40	0.25	0.25	0.50	0.25	1.0	0.50	0.50	0.25
9	**33**	0.060	0.30	0.30	0.10	0.20	0.50	1.5	0.080	0.070
10	**34**	0.60	1.4	1.0	1.0	1.5	1.5	4.0	0.70	1.0
11	**35**	0.60	0.50	0.50	0.50	1.0	1.5	1.0	0.40	1.0
12	**36**	0.040	0.040	0.040	0.020	0.060	0.080	1.0	0.040	0.040

parison of azole derivative **36** with AmB or even with the ester analogue **37** shows a clear improvement in the potency. Interestingly, derivatives **29** and **33** both containing a primary amine in the amide side chain were also much more active with MIC values of 0.040 and 0.060 μM.

Screening was pursued in order to explore further the scope of the antifungal activity. The novel derivatives were tested against several Candida strains which include wild type strain as well as different clinical isolates and mutant strains (Table 2). The majority of the derivatives were as potent as AmB against the wild type Candida strain (CAF2-1) with the exception of **29** and **34** where the MIC values were higher (1.4 and 2.0 μM, respectively). Against the *C. albicans* clinical isolates DSY294 and DSY296, the MIC values observed for the various amide analogues were in the same range as AmB (0.10–1.0 μM vs 0.40 μM). As with the wild type, the strains appear to be very sensitive to the azole derivative **36** with MIC values of 0.040 and 0.020 μM. Mutant strains DSY654 (Δ*cdr1*/*cdr2*) and DSY1751 (Δ*erg3*) were very sensitive to only a few compounds (**3**, **7** and **36**) while most amide derivatives exhibit limited antifungal activity (0.20–2.0 μM) when compared to AmB. The compounds were next screened against an AmB-resistant strain (DSY1764, Δ*erg3*/*erg11*). AmB has a MIC value of 50 μM against this strain, and it is well worth noting that such high MIC value can be categorized as resistant strain. In the assay, all the compounds (**3**, **7** and **29--37**) displayed a dramatic increase in activity over AmB with MIC values ranging between 0.50 and 4.0 μM. In some cases (**30** and **32**), this represented a 100-fold increase, which is the highest increase in potency observed in this study. Finally, antifungal tests were carried out using clinical isolated *Candida glabrata* strains (DSY562 and DSY565). With the exception of **34** and **35**, the antifungal activity of the derivatives was generally superior to AmB. This was especially true in the case of azole **36** which was at least 10 times more active than AmB (0.040 vs 0.50 μM). Overall, the derivative **36** displays the best improvement in antifungal activity to AmB. Throughout the various yeast strains tested, this conjugate was typically 10 times more active and even more so with the resistant strain.

The question of the toxicity of the novel AmB derivatives had to be addressed in order to complete this comparative study. All the amide and ester derivatives were tested in a hemolysis assay in order to evaluate their toxicity toward human erythrocytes. The EH_{50} value which is the concentration of an agent that causes 50% hemoglobin release can be measured and compared to natural AmB (Table 3. As expected, AmB and derivative **3** displayed the highest toxicity since the free carboxylic acid was unmodified (entries 1 and 2). The methyl ester derivative **37** was 5 times less toxic than AmB with an EH_{50} value of 50 μM, a result consistent with previous observations involving ester analogues. Significantly, compounds containing an amide functionality at C_{16} exhibited a very low toxicity with an EH_{50} values up to 200 μM in the case of compounds **30**, **31** and **32** (entries 5 to 7). The chemical structure of the side chain on the amide seems to play an important role in the resulting toxicity. For example, derivatives **29** and **33** both incorporate a primary amino group on the side chain but their corresponding toxicity is completely different. The length of the side chain appears to make a notable effect because **29** has an EH_{50} value of 30 μM while **33** is four times less toxic with an EH_{50} value of 120 μM (entries 3 and 8). Interestingly, derivative **36** was almost 20 times less toxic than AmB with an EH_{50} value of 75 μM, even more when the observed enhanced antifungal activity is also taken in to consideration.

Table 3. Hemotoxicity of semi-synthetic derivatives of AmB.

Entry	Compound	EH_{50} [μM]
1	**1**	4.0
2	**3**	10
3	**37**	50
4	**29**	30
5	**30**	200
6	**31**	200
7	**32**	200
8	**33**	120
9	**34**	100
10	**35**	150
11	**36**	75

The substitution patterns present on the mycosamine have a tremendous impact on the biological properties of the AmB derivatives. It appears that superior potency arises from the presence of a specific polyamine motif on the mycosamine, namely a bisaminopropylene pattern. The observed effect on the antifungal activity strongly depends on the mechanism operating in that case. Although the exact mechanism of action is still under debate, AmB is believed to interact with the yeast membrane and forms a channel, leading to K^+ efflux and ultimately to cell death. The transmembrane pore model is based on the formation a barrel-stave structure with up to eight molecules of AmB interdigitated with eight molecules of sterol.[57] However, several other mechanisms have been postulated for AmB and very few studies have been conducted on semi-synthetic derivatives of AmB.[58]

Taking into account the activity enhancement observed for polyamine derivative **3**, a different mechanistic hypothesis might be invoked in order to explain the improved antifungal properties. It is difficult to explain the superior antifungal activity of **3**, only with the increase solubility since highly soluble derivatives have been made and their potency was equivalent to the natural AmB.[13] Furthermore, the specificity of the bisaminopropylene motif cannot be explained solely by proton-donor properties or improved ion channel formation. Because the derivatives have similar structure to natural polyamines, these analogues might efficiently use the same transport system present in yeast cell. Moreover, internalization of AmB has been postulated as the origin of the toxicity towards mammalian cells. This polyamine motif on the mycosamine seems to confer internalization capacity to the derivatives. It was established that internalization of

AmB leads to a 10-fold increase in activity which is similar to the enhancement we observed in the case of derivative **3**.[59] Furthermore, cationic derivatives of AmB are used as tools to promote the internalization of oligonucleotides.[60–62] These similar cationic derivatives have the ability to transiently permeabilize the membrane thus allowing large molecules to penetrate inside the cell. Moreover, the fact that the polyamine analogues were highly active against the AmB resistant strain also tends to confirm that an alternative mechanism is operating in those cases. Finally, the superior activity displayed by derivative **36** could be attributed to the synergistic combination of the bisaminopropylene moiety on the mycosamine and the presence of a triazole motif on the side chain of the amide functionality. The antifungal properties of the triazole portion were predicted because azoles constitute a large, successful class of antifungal agents. Any biological activity derived from the triazole implies some degree of internalization since the molecular target of those compounds is the cytochrome P450.[63] Even though these new cationic derivatives might operate through discrete mechanisms, we speculate their behavior differs from unmodified AmB. Their cationic nature seems to confer to the compounds improved permeabilizing properties. It is still not clear, if the improvement is the result of internalization or those compounds are acting just as cationic surfactants similarly to cationic peptides.[64]

Conclusion

As a member of the polyene macrolide family, AmB is highly insoluble in water and also causes severe side effects. Many attempts to overcome those drawbacks were undertaken through the chemical modification of its structure. As previously mentioned, the chemical alteration of the carboxylate and the mycosamine moieties have been reported thus changing the zwitterionic character of AmB.

In this study, the biological properties of a series of cationic derivatives of AmB were investigated in order to improve the therapeutic index of the natural drug. Based on the comparison of several mycosamine analogues, we found that the incorporation of a specific polyamine motif resulted in a dramatic increase in antifungal activity. Derivative **3** was 15 times more active than AmB with a MIC value of 0.020 μM. Because the presence of a bisaminopropylene moiety led to an enhancement of activity, amide derivatives were synthesized in order to optimize the biological activity. Amide **36** bearing a triazole functionality displayed the best antifungal activity compare to all the compounds. The 10-fold increase in activity was observed not only with *S. cerevisiae* but also with several Candida strains including *C. albicans* and *C. glabrata*. Even against an AmB resistant strain, the various cationic derivatives were much more active then AmB. Finally, the replacement of the carboxylic acid for an amide group had a positive effect since the compounds were significantly less hemotoxic.

Experimental Section

Antifungal activity: The minimum inhibitory concentration (MIC) values were determined for the various strains (Table 4) using an assay inspired by the standard protocol approved by the National Committee of Clinical Laboratory Standards (NCCLS) but using YEPD liquid medium instead of the RPMI-1640 medium.[65] The strains were cultivated overnight in 5 mL YEPD liquid medium at 30 °C (37 °C for the strain DSY1764) with constant shaking. The saturated cultures were diluted to an OD_{600} of 0.1 (3×10^7 cells mL^{-1}). Using 24 wells plate, each well was prepared by adding 1% (12 μL) of DMSO solution of the tested compound with 1% (12 μL) yeast cells solution and completed with YEPD (1.176 mL). The plates were sealed with Parafilm and then incubated for 18 h at 30 °C (36 h at 37 °C for the strain DSY1764). The optical density was read at 600 nm using 1.5 mL cuvettes. The MIC value was defined as the drug concentration needed to inhibit growth, less than 5% compared to a drug-free culture.

Table 4. Yeast strains used in this study.

Strains	Genotype	Reference
BY4741	*MATα his3Δ1 leu2Δ0 lys2Δ0 ura3Δ0*	[66]
CAF2-1	*Δura3:imm434/URA3*	[67]
DSY294	azole-susceptible clinical strain	[68]
DSY296	azole-resistant clinical strain	[68]
DSY562	azole-susceptible clinical strain	[69]
DSY565	azole-resistant clinical strain	[69]
DSY654	*Δcdr1:hisG/Δcdr1:hisG Δcdr2:hisG-URA3-hisG/Δcdr2:hisG*	[70]
DSY1751	*Δerg3A:hisG/Δerg3B:hisG-URA3-hisG Δerg11:hisG/ERG11*	[71]
DSY1764	*Δerg3A:hisG/Δerg3B:hisG Δerg11:hisG/Δerg11:hisG-URA3-hisG*	[71]

Hemolytic activity: Human blood, anticoagulated with citrate or EDTA, was centrifuged (2000×g) at 4 °C for 10 min. The pellets were washed three times with PBS buffer (pH 7.2 with 2 g L^{-1} glucose) and then diluted to a concentration of 4% (4×10^8 cells mL^{-1}). All experiments were done in triplo and the total volume for the hemolysis tubes was 1.5 mL. The solutions were prepared by adding 1% (14 μL) of DMSO solution of the tested compound with 736 μL of PBS buffer and completed with 750 μL of 4% erythrocytes. After one hour incubation at 37 °C, the samples were centrifuged (1500×g) at 4 °C for 5 min and the absorbance of the supernatant was measured at 560 nm. The concentration that led to 50% hemolysis (EH_{50}) was intrapolated graphically. The value for the 100% hemolysis was obtained by the treatment with 100 μM of AmB.

Chemistry: All reactions were carried out in oven-dried glassware under an atmosphere of argon. Amphotericin B (AmB) was purchased from Apollo Scientifics (90% HPLC purity). All the other compounds were purchased from Fluka, Senn and Aldrich and used without further purification. Dimethylformamide was purified by distillation and methanol was distilled over magnesium oxide. Diisopropylethylamine and piperidine were distilled from KOH under nitrogen. The reactions were monitored by thin layer chromatography using Merck silica gel 60 FB254B plates and visualized using UV, aqueous ceric ammonium molybdate stain and 10% sulfuric acid in methanol. Flash chromatography was performed using E. Merck silica gel 60 (230–400 mesh). Analytical high-performance liquid chromatography (HLPC) was performed on a Merck Hitachi Chromatography System (Interface D-7000, UV detector L-7400, Pump L-7100, degasser). The flow rate was 1.0 mL min^{-1} and the detector wavelength was fixed at $\lambda = 405$ nm. Column: LiChrospher 100 RP-18 (5 μm) (LiChroCART (250×4 mm), (solvent A: MeOH, solvent B: 5 mM NH_4OAc). All chromatograms were taken at ambient temperature. The NMR spectra were recorded on Varian Gemini (300 MHz) and a Bruker DRX-500 spectrometer (500 MHz). Chemical shifts (δ) are reported in ppm with the tetramethylsilane resonance as the internal standard (δ 0.00) or the solvent signal for ^{1}H (δ 7.26 or 3.31) and ^{13}C (δ 77.0 or 49.0).

The data are reported as follows: (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, br = broad signal, coupling constant in Hz, integration). ^{13}C NMR spectra were recorded with complete proton decoupling. ^{1}H and ^{13}C NMR spectra are included in the Supporting Information. Mass spectrometric measurements were performed by the mass spectrometry service of the LOC at the ETHZ on a Ion Spec Ultima 4.7 spectrometer for MALDI-FT: *m*/*z*: using 2,5-dihydroxy benzoic acid as matrix (20 kV) and ESI-FT.

***N,N*-Di-(2-aminoethyl)-AmB (2)**: To a solution of *N*-(9-fluorenylmethoxycarbonyl)-2-aminoacetaldehyde[72] (290 mg, 1.03 mmol) and AmB (**1**) (320 mg, 0.340 mmol) in DMF (3.00 mL) was added $NaBH_3CN$ (65.0 mg, 1.03 mmol) followed by a drop of conc. HCl. After 16 h at room temperature, Amberlite IRA-743 (500 mg) was added and the mixture was stirred for an hour. After filtration, the solution was concentrated down and added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and purified by flash chromatography ($CHCl_3$/MeOH/H_2O 40:8:1). The isolated yellow solid was dissolved in DMSO (5.00 mL) and piperidine (0.200 mL, 2.10 mmol) was added. After 2 h at room temperature, the solution was added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2 × 100 mL) providing the desired compound **2** as a yellow solid (70 mg, 74 %). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 6.46–6.01 (m, 13H), 5.42 (dd, J = 15, 10 Hz, 1H), 5.23 (brs, 1H), 4.85–4.57 (m, 3H), 4.30–4.24 (m, 3H), 4.06–3.45 (m, 15H), 3.09 (m, 2H), 2.35–2.26 (m, 2H), 2.16 (d, J = 6 Hz, 1H), 1.82–1.18 (m, 21H), 1.11 (d, J = 6 Hz, 3H), 1.04 (d, J = 6 Hz, 3H), 0.92 ppm (d, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 176.8, 170.5, 136.6, 134.0, 133.6, 133.4, 133.1, 132.7, 132.4, 132.1, 131.8, 131.2, 128.2, 96.8, 77.2, 73.9, 73.5, 73.2, 72.1, 69.1, 68.7, 67.9, 66.1, 66.0, 51.4, 46.5, 44.7, 44.3, 42.5, 42.2, 41.9, 35.1, 30.6, 29.0, 28.3, 18.4, 18.2, 16.8, 12.0 ppm; MALDI-FT: *m*/*z*: calcd for $C_{51}H_{83}N_3O_{17}$: 1010.5801; found: 1010.5795 $[M+H]^+$.

***N,N*-Di-(3-aminopropyl)-AmB (3)**: Piperidine (0.100 mL, 1.06 mmol) was added to a solution of **28**[32] (200 mg, 0.135 mmol) in DMSO (3.00 mL). After 2 h at room temperature, the solution was added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2 × 100 mL) providing the desired compound **3** as a yellow solid (135 mg, 95 %). R_f = 0.10 ($CHCl_3$/MeOH/H_2O 10:6:1); ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 6.48–5.97 (m, 13H), 5.42 (dd, J = 15, 10 Hz, 1H), 5.23 (brs, 1H), 4.82–4.66 (m, 3H), 4.46–4.40 (m, 1H), 4.28–4.21 (m, 2H), 4.07–4.02 (m, 1H), 3.94–3.88 (m, 1H), 3.34 (brs, OH), 3.13–3.07 (m, 3H), 2.82–2.64 (m, 3H), 2.31–2.26 (m, 1H), 2.16 (d, J = 6 Hz, 1H), 1.83–1.24 (m, 18H), 1.18 (d, J = 6 Hz, 3H), 1.11 (d, J = 6 Hz, 3H), 1.04 (d, J = 6 Hz, 3H), 0.92 ppm (d, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 177.5, 170.4, 136.7, 134.0, 133.8, 133.7, 133.1, 132.4, 132.1, 131.9, 131.2, 128.1, 96.5, 77.2, 74.2, 73.9, 73.4, 70.7, 69.1, 68.7, 68.6, 67.8, 66.1, 65.6, 65.5, 65.4, 46.5, 44.7, 44.3, 42.5, 41.9, 38.6, 35.1, 29.0, 18.4, 18.2, 17.1, 16.9, 12.0 ppm; MALDI-FT: *m*/*z*: calcd for $C_{53}H_{87}N_3O_{17}$: 1038.6114; found: 1038.6108 $[M+H]^+$.

***N,N*-Di-(4-aminobutyl)-AmB (4)**: To a solution of 2,2,2-trifluoro-*N*-(4-oxobutyl)acetamide[73] (160 mg, 0.860 mmol) and AmB (**1**) (200 mg, 0.216 mmol) in DMF (2.00 mL) was added $NaBH_3CN$ (54.0 mg, 0.860 mmol) followed by a drop of conc. HCl. After 16 h at room temperature, Amberlite IRA-743 (500 mg) was added and the mixture was stirred for an hour. After filtration, the solution was concentrated and added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and purified by flash chromatography ($CHCl_3$/MeOH/H_2O 40:8:1). The isolated yellow solid was dissolved in THF (5.00 mL) and 1 M LiOH solution (2.00 mL, 2.00 mmol) was added at 0 °C. After 2 h, the solution was acidified dropwise to pH 4 with diluted HCl. The mixture was concentrated and added slowly to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2 × 100 mL) providing the desired compound **4** as a yellow solid (155 mg, 69 %). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 6.48–5.99 (m, 13H), 5.42 (dd, J = 15, 10 Hz, 1H), 5.23 (brs, 1H), 4.87–4.57 (m, 4H), 4.48–4.38 (m, 2H), 4.30–4.21 (m, 4H), 4.09–4.03 (m, 3H), 3.98–3.92 (m, 4H), 3.49 (brs, OH), 3.16–3.04 (m, 4H), 2.35–2.26 (m, 2H), 2.16 (d, J = 6 Hz, 1H), 1.85–1.19 (m, 23H), 1.11 (d, J = 6 Hz, 3H), 1.04 (d, J = 6 Hz, 3H), 0.92 pppm (d, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 177.4, 170.5, 136.7, 133.8, 133.6, 133.3, 133.1, 132.4, 132.1, 131.8, 131.2, 128.2, 98.4, 96.8, 96.7, 77.1, 76.6, 74.2, 73.9, 73.5, 70.3, 69.2, 68.7, 68.2, 67.8, 66.2, 65.5, 65.2, 46.5, 44.7, 44.2, 42.5, 42.4, 41.9, 35.1, 29.0, 18.4, 18.2, 16.7, 12.0 ppm; MALDI-FT: *m*/*z*: calcd for $C_{55}H_{91}N_3O_{17}$: 1066.3209; found: 1066.6421 $[M+H]^+$.

2,6-Bis-{amino-(9-fluorenylmethoxy-carbonyl)}hexanal: To a solution of 2,6-bis-{amino-(9-fluorenylmethoxycarbonyl)}-hexanol[74] (500 mg, 0.860 mmol) in CH_2Cl_2 (50.0 mL) was added Dess–Martin periodinane (730 mg, 1.72 mmol). After 2 h at room temperature, EtOAc (100 mL) was added to the reaction mixture which was then washed with a saturated aqueous solution $Na_2S_2O_5$ (2 × 100 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude aldehyde was purified by flash chromatography (EtOAc/hexane 1:1) providing the desired aldehyde as a white solid (300 mg, 60 %). R_f = 0.4 (EtOAc/hexane 1:1); ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.44 (s, 1H), 7.88 (d, J = 7 Hz, 4H), 7.74 (d, J = 8 Hz, 2H), 7.67 (d, J = 8 Hz, 2H), 7.41 (t, J = 7 Hz, 4H), 7.32 (t, J = 7 Hz, 4H), 4.36 (d, J = 7 Hz, 2H), 4.30 (d, J = 7 Hz, 2H), 4.26–4.18 (m, 2H), 3.87 (m, 1H), 2.97 (q, J = 6 Hz, 2H), 1.71 (brs, 1H), 1.47–1.25 ppm (m, 6H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 201.7, 156.4, 156.1, 144.0, 143.8, 140.8, 127.7, 127.6, 127.1, 125.2, 120.2, 65.6, 65.2, 59.7, 46.8, 29.1, 27.3, 22.5 ppm; MALDI-FT: *m*/*z*: calcd for $C_{36}H_{34}N_2O_5$: 597.2365; found: 597.2360 $[M+Na]^+$.

***N,N*-Di-(2,6-diaminohexyl)-AmB (5)**: To a solution of AmB (**1**) (92 mg, 0.100 mmol) and 2,6-bis-{amino-(9-fluorenylmethoxycarbonyl)}hexanal (290 mg, 0.500 mmol) in DMF (5.00 mL) was added $NaBH_3CN$ (31.0 mg, 0.500 mmol) followed by a drop of conc. HCl. After 16 h at room temperature, Amberlite IRA-743 (500 mg) was added and the mixture was stirred for an hour. After filtration, the solution was concentrated and added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and purified by flash chromatography ($CHCl_3$/MeOH/H_2O 40:8:1). The isolated yellow solid was dissolved in DMSO (2.00 mL) and piperidine (0.100 mL, 1.06 mmol) was added. After 2 h at room temperature, the solution was added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2 × 100 mL) providing the desired compound **5** as a yellow solid (10 mg, 22 %). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 6.40–5.86 (m, 13H), 5.47–5.41 (m, 1H), 5.36 (dd, J = 15, 10 Hz, 1H), 5.14 (brs, 1H), 4.75–4.60 (m, 3H), 4.46–4.44 (m, 1H), 4.27–4.12 (m, 3H), 4.00–3.96 (m, 1H), 3.32 (brs, OH), 3.06–3.01 (m, 3H), 2.87–2.80 (m, 3H), 2.60–2.50 (m, 1H), 2.24–2.18 (m, 1H), 2.09 (d, J = 6 Hz, 1H), 1.73–1.08 (m, 24H), 1.04 (d, J = 6 Hz, 3H), 0.96 (d, J = 6 Hz, 3H), 0.84 ppm (d, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 177.4, 170.5, 137.5, 135.2, 134.0, 133.8, 133.6, 133.2, 132.3, 132.1, 131.9, 131.2, 128.8, 96.7, 77.0, 74.2, 73.9, 73.5, 73.2, 70.9, 69.3, 69.1, 68.8, 68.5, 67.8, 66.5, 66.3, 66.1, 65.5, 65.4, 52.6, 40.4, 35.0, 33.2, 29.0, 22.8, 18.4, 18.1, 18.0, 17.0, 16.9, 12.0 ppm; MALDI-FT: *m*/*z*: calcd for $C_{59}H_{101}N_5O_{17}$: 1152.7271; found: 1152.7265 $[M+H]^+$.

***N*-(3-Aminopropyl)-AmB (7)**:[33] To AmB (**1**) (300 mg, 0.324 mmol) in DMF/MeOH (6:4, 30 mL) was added *N*-(9-fluorenyl-methoxycarbonyl)-3-aminopropanal[72] (96 mg, 0.324 mmol) and $NaBH_3CN$ (122 mg, 1.95 mmol). After 18 h the reaction mixture was added dropwise to diethyl ether (1 L). The yellow precipitate was filtered and washed with diethyl ether (2 × 10 mL) and purified by flash chromatography ($CHCl_3$/MeOH/H_2O 40:8:1) affording *N*-(9-fluorenylmethoxycarbonyl)-3-aminopropyl-AmB (**6**) (73.7 mg, 61.2 μmol). The resulting yellow solid was dissolved in DMSO (0.720 mL) and piperidine (72 μL) was added. After 1 h the reaction mixture was added dropwise to diethyl ether (100 mL). Filtration and washing (2 × 5 mL) afforded **7** (20 mg, 6.8 %) as an orange solid. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 6.46 (dd, J = 14, 11 Hz, 1H), 6.42–6.22 (m, 8H), 6.18 (s, 1H), 6.16 (d, J = 4 Hz, 1H), 6.12–6.06 (m, 1H), 6.05 (d, J = 10 Hz, 1H), 6.00 (dd, J = 15, 8 Hz, 1H), 5.74 (brs, 1H), 5.43 (dd, J = 15, 10 Hz, 1H), 5.38 (brs, 1H), 5.26–5.19 (m, 1H), 4.85–4.58 (m, 7H), 4.45 (s, 2H), 4.43–4.35 (m, 2H), 4.30–4.22 (m, 4H), 4.09–4.03 (m, 2H), 4.02–3.95 (m, 2H), 3.82 (s, 2H), 3.93–3.22 (m, 14H), 3.15 (dd, J = 9, 6 Hz, 1H), 3.13–3.05 (m, 3H), 3.03–2.91 (m, 3H), 2.89–2.71 (m, 4H), 2.38–2.32 (m, 1H), 2.32–2.20 (m, 2H), 2.16 (d, J = 6 Hz, 2H), 1.86–1.76 (m, 2H), 1.75–1.66 (m, 2H), 1.66–1.21 (m, 12H), 1.14 (d, J = 6 Hz, 3H), 1.11 (d, J = 6 Hz, 3H), 1.04 (d, J = 6 Hz, 3H), 0.92 ppm (d, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 177.0, 170.5, 137.0, 136.6, 133.8, 133.6, 133.4, 133.1, 132.8, 132.4, 132.1, 131.8, 131.7, 131.2, 127.9, 100.1, 96.8, 77.9, 77.1, 73.8, 73.5, 70.3, 69.1, 68.7, 67.8, 67.4, 66.1, 65.6,

62.4, 58.5, 46.5, 44.7, 44.6, 44.3, 42.4, 41.9, 37.8, 35.0, 29.0, 26.7, 18.4, 18.1, 17.0, 16.8, 12.0 ppm; MALDI-FT: *m/z*: calcd for $C_{50}H_{80}N_2O_{17}$: 981.5530; found: 981.5512 $[M+H]^+$.

***N*-(3-Aminopropyl)-*N*-(2-aminoethyl)-AmB (8)**: To a solution of *N*-(9-fluorenylmethoxycarbonyl)-3-aminopropanal[72] (0.320 mg, 1.08 mmol) in DMF (5.00 mL) and MeOH (3.00 mL) was added AmB (**1**) (1.00 g, 1.08 mmol). After 5 h, $NaBH_3CN$ (200 mg, 3.32 mmol) was added to the mixture. After 16 h at room temperature, Amberlite IRA-743 (2.00 g) was added and the mixture was stirred for an hour. After filtration, the solution was concentrated down and added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and purified by flash chromatography ($CHCl_3$/MeOH/H_2O 40:8:1) providing *N*-(9-fluorenylmethoxycarbonyl)-3-aminopropyl-AmB (**6**) as a yellow solid. To a solution of *N*-(9-fluorenylmethoxycarbonyl)-2-aminoacetaldehyde[75] (70 mg, 0.250 mmol) in DMF (3.00 mL) and MeOH (3.00 mL) was added to the previously isolated **6** (100 mg, 0.083 mmol). After 3 h, $NaBH_3CN$ (16.0 mg, 0.250 mmol) was added to the mixture. After 16 h at room temperature, Amberlite IRA-743 (500 mg) was added and the mixture was stirred for an hour. After filtration, the solution was concentrated and added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and purified by flash chromatography ($CHCl_3$/MeOH/H_2O 40:8:1). The isolated yellow solid was dissolved in DMSO (5.00 mL) and piperidine (0.200 mL, 2.10 mmol) was added. After 2 h at room temperature, the solution was added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2×100 mL) providing the desired compound **8** as a yellow solid (22.0 mg, 26%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 6.48–5.97 (m, 13H), 5.70–5.50 (m, 1H), 5.46–5.40 (m, 1H), 5.23 (brs, 1H), 4.91–4.54 (m, 5H), 4.45–4.18 (m, 6H), 4.07–3.77 (m, 6H), 3.60–3.36 (m, 7H), 3.23–3.01 (m, 5H), 2.94–2.74 (m, 5H), 2.35–2.22 (m, 2H), 2.16 (d, J=6 Hz, 1H), 1.81–1.14 (m, 22H), 1.11 (d, J=6 Hz, 3H), 1.04 (d, J=6 Hz, 3H), 0.91 ppm (d, J=7 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 177.5, 170.5, 136.7, 133.9, 133.6, 133.1, 132.4, 132.3, 132.1, 132.0, 131.8, 131.2, 128.5, 96.8, 77.1, 74.2, 73.9, 73.8, 73.5, 73.4, 70.4, 69.3, 69.1, 68.8, 68.7, 68.6, 67.9, 67.8, 66.1, 65.6, 46.5, 45.6, 44.7, 44.4, 44.3, 42.5, 42.4, 41.9, 35.1, 29.0, 25.1, 23.8, 18.4, 18.2, 16.9, 12.0 ppm; MALDI-FT: *m/z*: calcd for $C_{52}H_{85}N_3O_{17}$: 1024.5930; found: 1024.5950 $[M+H]^+$.

Guanidine-AmB (10): To a solution of AmB (**1**) (295 mg, 0.320 mmol) in DMF (3.00 mL) was added 1*H*-pyrazole-1-carboxamidine monohydrochloride (**9**) (50.0 mg, 0.340 mmol) and diisopropylethylamine (0.230 mL, 1.30 mmol). After 16 h at room temperature, the solution was concentrated down and added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2×100 mL) providing the desired compound **10** as a yellow solid (300 mg, 97%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 6.47–6.06 (m, 12H), 6.00 (dd, J=14, 8 Hz, 1H), 5.77 (brs, 1H), 5.44 (dd, J=15, 10 Hz, 1H), 5.22 (brs, 1H), 4.76–4.50 (m, 4H), 4.41–4.37 (m, 1H), 4.26 (brs, 1H), 4.19–4.15 (m, 1H), 4.07–4.04 (m, 1H), 4.01–3.96 (m, 1H), 3.53 (brs, OH), 3.24–3.21 (m, 1H), 3.17–3.14 (m, 1H), 3.11–3.08 (m, 2H), 2.79–2.77 (m, 1H), 2.31–2.26 (m, 1H),2.17 (d, J=6 Hz, 1H), 1.85–1.26 (m, 18H), 1.18 (d, J=6 Hz, 3H), 1.11 (d, J=6 Hz, 3H), 1.04 (d, J=6 Hz, 3H), 0.92 ppm (d, J=7 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 176.3, 170.5, 157.9, 136.7, 133.8, 133.6, 133.4, 133.1, 132.4, 132.1, 131.8, 131.2, 128.6, 97.0, 95.7, 77.1, 74.2, 73.9, 73.5, 72.7, 71.0, 70.1, 69.1, 68.8, 68.1, 67.7, 66.1, 65.4, 65.2, 56.1, 46.3, 44.7, 44.3, 42.3, 42.0, 40.4, 35.0, 29.0, 18.4, 17.9, 16.9, 12.0 ppm; MALDI-FT: *m/z*: calcd for $C_{48}H_{75}N_3O_{17}$: 966.5175; found: 966.5169 $[M+H]^+$.

***N*,*N*-Di-(2-ethylguanidine)-AmB (11)**: To a solution of *N*,*N*-di-(2-aminoethyl)-AmB (**2**) (100 mg, 0.100 mmol) in DMF (2.00 mL) was added **9** (36.0 mg, 0.250 mmol) and diisopropylethylamine (0.350 mL, 2.00 mmol). After 48 h at room temperature, the solution was concentrated down and added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2×100 mL) providing the desired compound **11** as a yellow solid (60.0 mg, 55%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.60 (brs, 1H), 7.42 (brs, 2H), 6.52–6.02 (m, 13H), 5.43 (dd, J=15, 10 Hz, 1H), 5.23 (brs, 1H), 4.80–4.72 (m, 3H), 4.64 (s, 1H), 4.45–4.22 (m, 3H), 4.08–3.98 (m, 2H), 3.53 (m, 18H, OH), 3.15–3.08 (m, 1H), 2.32–2.26 (m, 1H), 2.17 (d, J=6 Hz, 1H), 1.83–1.23 (m, 18H), 1.19 (d, J=6 Hz, 3H), 1.11 (d, J=6 Hz, 3H), 1.04 (d, J=6 Hz, 3H), 0.92 ppm (d, J=7 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 177.6, 170.5, 157.1, 142.1, 136.7, 133.8, 133.6, 133.4, 133.1, 132.4, 132.1, 131.8, 131.2, 128.5, 97.6, 96.9, 77.1, 74.1, 73.9, 73.5, 69.1, 68.7, 68.4, 67.9, 66.1, 65.5, 65.1, 64.8, 63.6, 50.0, 45.9, 44.7, 42.7, 41.9, 41.0, 40.4, 35.7, 30.7, 29.0, 24.9, 23.1, 18.6, 18.4, 18.3, 18.0, 16.8, 12.0 ppm; MALDI-FT: *m/z*: calcd for $C_{53}H_{88}N_7O_{17}$: 1094.6237; found: 1094.6231 $[M+H]^+$.

2,6-Diamino-*N*-[6-oxo-6-(piperazin-1-yl)-hexyl]-hexanamide-AmB (13): To a solution of 6-amino-1-hexanoyl-(piperazinyl)-AmB[31] (**12**) (110 mg, 0.100 mmol) in DMF (2.00 mL) was added 2,6-di-[*N*-(9-fluorenylmethoxycarbonyl)]-lysine hydroxysuccinimide ester[76] (380 mg, 0.500 mmol) and diisopropylethylamine (0.100 mL, 0.500 mmol). After 18 h at room temperature, the solution was concentrated down and added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and purified by flash chromatography ($CHCl_3$/MeOH/H_2O 40:8:1). The isolated yellow solid was dissolved in DMSO (3.00 mL) and piperidine (0.100 mL, 1.00 mmol) was added. After 2 h at room temperature, the solution was added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2×100 mL) providing the desired compound **13** as a yellow solid (10 mg, 27%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.78 (brs, 1H), 6.46–5.95 (m, 13H), 5.51 (dd, J=15, 10 Hz, 1H), 5.44 (dd, J=15, 10 Hz, 1H), 5.20 (brs, 1H), 5.13–5.11 (m, 1H), 4.79–4.70 (m, 3H), 4.48 (s, 1H), 4.29–4.14 (m, 4H), 4.06 (s, 2H), 3.90–3.79 (m, 2H), 3.38 (s, OH), 3.14–3.04 (m, 2H), 2.72–2.58 (m, 2H), 2.38–2.21 (m, 3H), 2.16 (d, J=6 Hz, 1H), 1.74–1.24 (m, 21H), 1.17 (d, J=6 Hz, 3H), 1.11 (d, J=6 Hz, 3H), 1.04 (d, J=6 Hz, 3H), 0.91 ppm (d, J=7 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 174.9, 173.8, 170.4, 170.2, 137.5, 136.6, 133.9, 133.7, 133.6, 133.5, 133.2, 132.7, 132.3, 132.0, 131.8, 131.4, 128.3, 96.7, 77.1, 73.8, 73.5, 72.2, 69.3, 69.2, 68.8, 67.7, 67.6, 67.5, 67.3, 66.2, 66.1, 65.9, 65.5, 64.8, 54.6, 44.6, 44.3, 42.3, 42.0, 41.9, 35.0, 34.9, 30.7, 28.9, 26.1, 26.0, 25.6, 24.5, 22.3, 18.4, 18.2, 17.1, 16.9, 12.1, 12.0 ppm; MALDI-FT: *m/z*: calcd for $C_{63}H_{103}N_5O_{19}$: 1256.7145; found: 1256.7140 $[M+Na]^+$.

2-Amino-6-guanidine-*N*-[6-oxo-6-(piperazin-1-yl)-hexyl]hexanamide-AmB (14): To a solution of **13** (50.0 mg, 0.0400 mmol) in DMF (2.00 mL) was added **9** (8.00 mg, 0.0500 mmol) and diisopropylethylamine (0.0170 mL, 0.100 mmol). After 18 h at room temperature, the solution was concentrated down and added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2×100 mL) providing the desired compound **14** as a yellow solid (10.0 mg, 20%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.60 (brs, 1H), 6.49–5.91 (m, 14H), 5.44 (dd, J=15, 10 Hz, 1H), 5.37 (brs, 1H), 5.21 (brs, 1H), 4.81–4.64 (m, 3H), 4.44–4.31 (m, 1H), 4.28–4.16 (m, 2H), 4.07–4.04 (m, 1H), 4.00–3.96 (m, 1H), 3.83–3.79 (m, 2H), 3.34 (s, OH), 3.09–3.06 (m, 2H), 2.32–2.24 (m, 3H), 2.16 (d, J=6 Hz, 1H), 1.85–1.22 (m, 18H), 1.17 (d, J=6 Hz, 3H), 1.11 (d, J=6 Hz, 3H), 1.04 (d, J=6 Hz, 3H), 0.91 ppm (d, J=7 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 174.7, 173.5, 170.5, 170.2, 157.1, 136.7, 136.1, 133.8, 133.6, 133.4, 133.1, 132.7, 132.4, 132.1, 131.8, 131.5, 131.1, 128.6, 96.9, 77.0, 74.4, 73.8, 73.6, 73.5, 69.2, 69.1, 68.7, 67.7, 67.4, 67.2, 66.1, 65.5, 65.4, 65.3, 64.9, 53.4, 46.1, 46.0, 44.7, 44.3, 43.6, 42.0, 35.0, 28.9, 28.5, 28.3, 25.1, 24.8, 24.5, 22.2, 22.0, 18.4, 18.1, 16.9, 13.8, 12.0 ppm; MALDI-FT: *m/z*: calcd for $C_{64}H_{105}N_7O_{19}$: 1298.7363; found: 1298.7358 $[M+Na]^+$.

Methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (15): The following compound was synthesized according to known procedures[41–43] starting from α-methyl D-glucopyranoside affording compound **15** as white solid in 55% yield over three steps. M.p. 109°C; R_f = 0.42 (hexane/EtOAc 4:5); $[\alpha]_D^{27}$ = +132.6° (*c* = 1.07, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.41 (dd, J=10, 10 Hz, 1H), 4.93 (dd, J=10, 10 Hz, 1H), 4.86 (d, J=4 Hz, 1H), 4.76 (dd, J=10, 4 Hz, 1H), 3.69 (ddd, J=10, 4, 2 Hz, 1H), 3.60 (dd, J=13, 2 Hz, 1H), 3.49 (dd, J=13, 4 Hz, 1H), 3.31 (s, 3H), 2.74 (brs, 1H), 1.96 (s, 3H), 1.94 (s, 3H), 1.91 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.1, 169.9, 169.8, 96.5, 70.7, 69.7, 69.2, 68.6, 68.5, 60.1, 55.1, 20.7, 20.4 ppm; IR (film): $\tilde{\nu}$=3512, 2941, 1750, 1432, 1370, 1224, 1168, 1128, 1038, 929, 772, 600, 488 cm^{-1}; MALDI-FT: *m/z*: calcd for $C_{13}H_{20}O_9$: 343.1000; found: 343.1006 $[M+Na]^+$; elemental analysis calcd (%) for $C_{13}H_{20}O_9$: C 48.75, H 6.29; found: C 48.75, H 6.20.

Methyl 3,4-di-*O*-acetyl-2-deoxy-2-[(benzyloxycarbonyl)amino]-α-D-glucopyranoside (16): The following compound was synthesized starting from

methyl 2-deoxy-2-[(benzyloxycarbonyl)amino]-α-D-glucopyranoside according to known procedures[39,44–47] affording compound **16** in 60% yield in three steps as white solid. M.p. 111–113°C; R_f = 0.26 (hexane/EtOAc 1:2); $[\alpha]_D^{24}$ = +101.2° (*c* = 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.29 (m, 5H), 5.26 (dd, *J* = 11, 9 Hz, 1H), 5.13 (d, *J* = 12 Hz, 1H), 5.07–4.96 (m, 3H), 4.76 (d, *J* = 4 Hz, 1H), 4.02 (ddd, *J* = 11, 10, 4 Hz, 1H), 3.76–3.70 (m, O*H*), 3.68 (dd, *J* = 8, 3 Hz, 1H), 3.58 (ddd, *J* = 13, 6, 4 Hz, 1H), 3.38 (s, 3H), 2.40 (dd, *J* = 8, 6 Hz, 1H), 2.05 (s, 3H), 1.90 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8, 170.3, 155.6, 136.1, 128.4, 128.1, 128.0, 98.5, 71.0, 69.7, 68.7, 66.9, 61.1, 55.5, 53.8, 20.8, 20.7 ppm; IR (film): $\tilde{\nu}$ = 3500, 3400, 3350, 2941, 1747, 1520, 1456, 1368, 1239, 1156, 1122, 1035 cm^{-1}; MALDI-FT: *m*/*z*: calcd for $C_{19}H_{25}NO_9$: 434.1422; found: 434.1415 $[M+Na]^+$; elemental analysis calcd (%) for $C_{19}H_{25}NO_9$: C 55.47, H 6.30, N 3.40; found: C 55.35, H 6.30, N 3.42.

Methyl 6-methylsulfonyl-2,3,4-tri-O-acetyl-α-D-glucopyranoside: To a solution of **15** (834 mg, 2.60 mmol) in CH_2Cl_2 (26 mL) was added pyridine (3.15 mL, 39.0 mmol) and methylsulfonyl chloride (503 μL, 6.50 mmol) and was stirred at 0°C for 1 h. After another 3 h stirring at room temperature the reaction mixture was concentrated to $^1/_3$ of the volume, saturated $NaHCO_3$ solution (10 mL) was added, and the water layer was extracted with EtOAc (4×20 mL). The combined organic layers were washed with saturated NaCl solution (20 mL) and dried over $MgSO_4$. The organic layer was concentrated and flash chromatography (hexane/EtOAc 1:1) afforded the desired mesylate (983 mg, 95%) as a white solid. M.p. 113°C; R_f = 0.26 (hexane/EtOAc 1:1); $[\alpha]_D^{25}$ = +129.3° (*c* = 0.91, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.47 (dd, *J* = 10, 10 Hz, 1H), 5.02 (dd, *J* = 10, 10 Hz, 1H), 4.95 (d, *J* = 4 Hz, 1H), 4.86 (dd, *J* = 10, 4 Hz, 1H), 4.27 (d, *J* = 4 Hz, 2H), 4.05 (ddd, *J* = 7, 4, 4 Hz, 1H), 3.41 (s, 3H), 3.05 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 2.00 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 169.8, 169.5, 96.7, 70.6, 69.8, 68.3, 67.0, 66.8, 55.7, 37.7, 20.8, 20.7 ppm; IR (film): $\tilde{\nu}$ = 2942, 1750, 1360, 1223, 1175, 1035, 969, 942, 829, 751 cm^{-1}; ESI-FT: *m*/*z*: calcd for $C_{14}H_{22}O_{11}S$: 421.0775; found: 421.0769 $[M+Na]^+$; elemental analysis calcd (%) for $C_{14}H_{22}O_{11}S$: C 42.21, H 5.57; found: C 42.02, H 5.61.

Methyl 6-acetylthio-2,3,4-tri-*O*-acetyl-α-D-glucopyranoside: To a solution of the mesylate (938 mg, 2.35 mmol) in ethanol was added potassium thioacetate. This was stirred for 3 h at reflux. After cooling to room temperature, water (75 mL) was added. The water layer was extracted with EtOAc (4×50 mL), the combined organic layers were washed with saturated NaCl solution (50 mL) and dried over $MgSO_4$. The organic layer was concentrated and flash chromatography (hexane/EtOAc 2:1) afforded the thioacetate (881 mg, 99%) as a green oil. R_f = 0.40 (hexane/EtOAc 1:1); $[\alpha]_D^{26}$ = +109.5° (*c* = 0.84, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.42 (dd, *J* = 10, 9 Hz, 1H), 4.94 (dd, *J* = 10, 10 Hz, 1H), 4.87 (d, *J* = 4 Hz, 1H), 4.83 (dd, *J* = 10, 4 Hz, 1H), 3.90 (ddd, *J* = 10, 7, 3 Hz, 1H), 3.38 (s, 3H), 3.19 (dd, *J* = 14, 3 Hz, 1H), 3.06 (dd, *J* = 14, 7 Hz, 1H), 2.33 (s, 3H), 2.05 (s, 3H), 1.98 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.4, 170.0, 169.9, 169.8, 96.5, 70.9, 70.8, 70.0, 68,2, 55.4, 30.5, 30.1, 20.8, 10.8 ppm; IR (film): $\tilde{\nu}$ = 2360, 2341, 1750, 1697, 1369, 1225, 1044, 668 cm^{-1}; ESI-FT: *m*/*z*: calcd for $C_{15}H_{22}O_9S$: 401.0877; found: 401.0871 $[M+Na]^+$; elemental analysis calcd (%) for $C_{15}H_{22}O_9S$ C 47.61, H 5.86; found: C 47.54, H 5.87.

Methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside-6-sulfate potassium salt (17): 30% H_2O_2 (2.16 mL, 19.1 mmol) and potassium acetate (187 mg, 1.91 mmol) were added to a solution of the thioacetate (602 mg, 1.59 mmol) in glacial acetic acid (8.00 mL). After 9 h at 50°C the reaction mixture was quenched by the addition of potassium sulfite (319 mg, 17.5 mmol). The reaction was concentrated and flash chromatography (CH_2Cl_2/MeOH 6:1) afforded the desired compound **17** (563 mg, 84% mmol) as a white solid. M.p. 122°C; R_f = 0.43 (CH_2Cl_2/MeOH 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.43 (dd, *J* = 10, 10 Hz, 1H), 5.01 (dd, *J* = 10, 9 Hz, 1H), 4.99 (s, 1H), 4.92 (dd, *J* = 10, 4 Hz, 1H), 4.38–4.20 (m, 1H), 3.44 (s, 3H), 3.32–3.08 (m, 2H), 2.07 (s, 3H), 2.05 (s, 3H), 1.99 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8, 170.3, 169.8, 96.5, 70.9, 70.6, 70.3, 65.7, 55.8, 50.8, 20.9, 20.8 ppm; IR (KBr): $\tilde{\nu}$ = 3487, 2950, 2849, 1752, 16.46, 1574, 1374, 1224, 1123, 1037, 931, 907, 882, 824, 792, 754, 631, 598, 567, 535, 489, 470 cm^{-1}; ESI-FT: *m*/*z*: calcd for $C_{13}H_{19}KO_{11}S$: 429.0438; found 429.0430 $[M+Na]^+$; elemental analysis calcd (%) for C 36.96, H 4.53; found: C 36.76, H 4.62.

Methyl 6-methylsulfonyl-3,4-di-*O*-acetyl-2-deoxy-2-[(benzyloxycarbonyl)-amino]-α-D-glucopyranoside: Triethylamine (6.20 mL, 44.7 mmol) and methylsulfonyl chloride (3.50 mL, 44.7 mmol) was added at room temperature to a solution of **16** (16.7 g, 40.6 mmol) in CH_2Cl_2 (400 mL). After stirring for 3 h the reaction volume was concentrated to half the volume. The concentrated reaction mixture was washed with water (2×200 mL). The combined organic layers were washed with saturated NaCl solution (400 mL), dried over $MgSO_4$ and concentrated. The isolated mesylate (19.9 g, quant.) was obtained as a white solid. The NMR showed that it was pure enough for the next reaction. An analytical sample was purified by flash chromatography (hexane/EtOAc 2:1). M.p. 113–114°C; R_f = 0.50 (hexane/EtOAc 1:2); $[\alpha]_D^{22}$ = +95.4° (*c* = 0.97, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 5H), 5.21 (dd, *J* = 11, 9 Hz, 1H), 5.12 (d, *J* = 12 Hz, 1H), 5.03 (d, *J* = 12 Hz, 1H), 5.03 (dd, *J* = 10, 9 Hz, 1H), 4.98 (br s, 1H), 4.76 (d, *J* = 4 Hz, 1H), 4.27 (d, *J* = 4 Hz, 2H), 4.05 (dd, *J* = 11, 4 Hz, 1H), 4.00 (dd, *J* = 4, 4 Hz, 1H), 3.41 (s, 3H), 3.05 (s, 3H), 2.04 (s, 3H), 1.90 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 169.3, 155.5, 128.4, 127.9, 128.1, 98.4, 71.0, 136.0, 68.1, 67.5, 67.0, 55.7, 53.6, 37.7, 20.6, 20.7 ppm; IR (film): $\tilde{\nu}$ = 3358, 2941, 1749, 1522, 1456, 1360, 1235, 1176, 1043, 1010, 944 cm^{-1}; MS MALDI-FT: *m*/*z*: calcd for $C_{20}H_{27}NO_{11}S$: 512.1197; found 512.1192 $[M+Na]^+$; elemental analysis calcd (%) for $C_{20}H_{27}NO_{11}S$: C 49.07, H 5.56, N 2.86; found: C 48.84, H 5.64, N 2.82.

Methyl 6-acetylthio-3,4-di-*O*-acetyl-2-deoxy-2-[(benzyloxycarbonyl)-amino]-α-D-glucopyranoside: Potassium thioacetate (13.9 g, 122 mmol) was added at room temperature to a solution of the mesylate (19.9 g, 40.6 mmol) in DMF. After stirring at 55°C for 18 h DMF was distilled off under high vacuum until a volume of 50 mL was obtained. To the mixture was added CH_2Cl_2 (500 mL) and this was washed with water (3×500 mL) and with saturated NaCl (400 mL) and dried over $MgSO_4$. The organic phase was concentrated and flash chromatography (hexanes/EtOAc 2:1) and recrystallization from ethanol afforded the thioacetate (14.5 g, 76%) as light orange needles. M.p. 97°C; R_f = 0.27 (hexane/EtOAc 1:1); $[\alpha]_D^{28}$ = +85.8° (*c* = 0.94, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5H), 5.15 (dd, *J* = 11, 9 Hz, 1H), 5.12 (d, *J* = 12 Hz, 1H), 5.03 (d, *J* = 12 Hz, 1H), 4.97 (br s, 1H), 4.96 (dd, *J* = 10, 9 Hz, 1H), 4.68 (d, *J* = 10 Hz, 1H), 4.00 (ddd, *J* = 10, 10, 4 Hz, 1H), 3.84 (ddd, *J* = 10, 8, 3 Hz, 1H), 3.37 (s, 3H), 3.21 (dd, *J* = 14, 3 Hz, 1H), 3.02 (dd, *J* = 14, 8 Hz, 1H), 2.34 (s, 3H), 2.07 (s, 3H), 1.89 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.3, 170.7, 169.5, 155.5, 136.0, 128.3, 128.0, 127.9, 98.2, 71.1, 70.7, 68.7, 66.9, 55.3, 53.7, 30.4, 30.2, 20.7, 20.6 ppm; IR (film): $\tilde{\nu}$ = 3343, 2950, 1748, 1697, 1519, 1366, 1238, 1119, 1044, 747, 699, 627 cm^{-1}; HRMS MALDI: *m*/*z*: calcd for $C_{21}H_{27}NO_9S$: 492.1299; found: 492.1299 $[M+Na]^+$; elemental analysis calcd (%) for $C_{21}H_{27}NO_9S$: C 53.72, H 5.80, N 2.98; found: C 53.72, H 5.79, N 3.09.

Methyl 3,4-di-*O*-acetyl-2-deoxy-2-[(benzyloxycarbonyl)amino]-α-D-glucopyranoside-6-sulfonate potassium salt (18): To a solution of the thioacetate (6.80 g, 14.5 mmol) in acetic acid (73.0 mL) was added potassium acetate (1.70 g, 17.4 mmol) and dropwise hydrogen peroxide (20.0 mL, 174 mmol) and the reaction mixture was stirred for 24 h at 40°C. Then potassium sulfite (30.0 g, 191 mmol) was added to quench the hydrogen peroxide. Filtration, concentration and flash chromatography afforded the desired compound (**18**) (5.90 g, 79%) as a white solid. M.p. 63–64°C; R_f = 0.26 (CH_2Cl_2/MeOH 5:1); ^{1}H NMR (300 MHz, CD_3OD): δ = 7.41–7.27 (m, 5H), 7.03 (d, *J* = 10 Hz, N*H*), 5.20 (dd, *J* = 11, 9 Hz, 1H), 5.13 (d, *J* = 13 Hz, 1H), 5.00 (d, *J* = 13 Hz, 1H), 4.81 (d, *J* = 10 Hz, 1H), 4.71 (d, *J* = 4 Hz, 1H), 4.31 (ddd, *J* = 10, 5, 5 Hz, 1H), 3.95 (ddd, *J* = 11, 10, 6 Hz, 1H), 3.49 (s, 3H), 2.97 (dd, *J* = 4, 4 Hz, 2H), 2.01 (s, 3H), 1.81 ppm (s, 3H); ^{13}C NMR (75 MHz, CD_3OD): δ = 172.0, 171.8, 158.4, 138.3, 129.5, 129.1, 128.8, 99.6, 73.1, 72.9, 67.6, 67.4, 56.3, 55.1, 53.6, 20.7, 20.6 ppm; IR (neat): $\tilde{\nu}$ = 3347, 2947, 2843, 1732, 1529, 1451, 1372, 1217, 1031, 929, 742, 697 cm^{-1}; MALDI-FT: *m*/*z*: calcd for $C_{19}H_{24}KNO_{11}S$: 536.0599; found: 536.0589 $[M+Na]^+$.

Methyl 6-(chlorosulfonyl)-2,3,4-tri-*O*-acetyl-α-D-glucopyranoside: Triphenyl phosphine (1.55 g, 5.92 mmol) and sulfuryl chloride (475 μL, 5.92 mmol) were added at 0°C to a solution of **17** (500 mg, 1.18 mmol) in

CH_2Cl_2 (12 mL). After 3.5 h at room temperature solvents were evaporated and purification over a short silica plug (hexane/EtOAc 1:1) afforded the sulfonyl chloride (175 mg, 43%) as a white solid. R_f = 0.54 (hexane/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.51 (dd, J=10, 9 Hz, 1H), 4.98 (d, J=4 Hz, 1H), 4.88 (dd, J=10, 10 Hz, 1H), 4.85 (dd, J=10, 5 Hz, 1H), 4.54 (ddd, J=10, 9, 2, 1H), 3.96 (dd, J=15, 10 Hz, 1H), 3.79 (dd, J=15, 2 Hz, 1H), 3.49 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.01 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 170.0, 169.7, 96.8, 70.7, 70.3, 69.4, 66.3, 64.7, 56.2, 20.6 ppm; ESI-FT: m/z: calcd for $C_{26}H_{28}O_6$: 425.0280; found: 425.0273 $[M+Na]^+$.

Methyl 6-((*N*-(6-(2,5-dihydro-1*H*-pyrrol-1-yl)-6-oxohexyl)sulfamoyl)-methyl-2,3,4-tri-*O*-acetyl-α-D-glucopyranoside: Triethylamine (200 μL, 1.43 mmol) and [6-(2,5-dihydro-1*H*-pyrrol-1-yl)-6-oxohexyl]amine (63.0 mg, 344 μmol) were added to a solution of the sulfonyl chloride (115 mg, 287 μmol) in CH_2Cl_2 (3.0 mL).[31] After stirring for 2.5 h at room temperature the solvent was evaporated and the crude was purified immediately by flash chromatography (hexane/EtOAc 1:1 → hexane/EtOAc 1:10), which afforded the desired compound (95.0 mg, 61%) as a colorless oil. R_f = 0.40 (CH_2Cl_2/MeOH 10:1); $[\alpha]_D^{24}$ = +73.0° (c = 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.85–5.72 (m, 2H), 5.43 (dd, J=10, 9 Hz, 1H), 4.94 (d, J=4 Hz, 1H), 4.91 (d, J=3 Hz, 1H), 4.82 (dd, J=10, 10 Hz, 1H), 4.79 (dd, J=10, 3 Hz, 1H), 4.33 (ddd, J=10, 10, 3 Hz, 1H), 4.18 (s, 4H), 3.46 (s, 3H), 3.21 (dd, J=15, 10 Hz, 2H), 3.14–3.03 (m, 2H), 2.24 (t, J=7 Hz, 2H), 2.03 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H), 1.70–1.51 (m, 4H), 1.45–1.33 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 170.0, 169.80, 169.7, 126.2, 124.7, 96.6, 71.0, 70.5, 69.4, 65.0, 56.0, 53.2, 52.7, 52.0, 43.0, 33.8, 29.6, 26.0, 23.6, 20.5 ppm; IR (film): $\tilde{\nu}$=2938, 2860, 1750, 1639, 1617, 1433, 1369, 1326, 1221, 1149, 1044, 771 cm^{-1}; MALDI-FT: m/z: calcd for $C_{23}H_{36}N_2O_{11}S$: 571.1932; found: 571.1923 $[M+Na]^+$.

Methyl 6-((*N*-(6-(3,4-dihydroxypyrrolidine-1-yl)-6-oxohexyl)sulfamoyl)-methyl-2,3,4-tri-O-acetyl-α-D-glucopyranoside (19): The above isolated oil (95.0 mg, 173 μmol) was dissolved in acetone/water/*tert*-butanol 15:6:2 (3.5 mL) and sequentially *N*-methyl morpholine oxide (47.0 mg, 346 μmol) and potassium osmate dihydrate (6.5 mg, 17 μmol) were added. After stirring at room temperature for 16 h the reaction mixture was quenched with sodium dithionite (30.0 mg, 173 μmol) and Florisil (30.0 mg) by stirring for an additional 30 min. The reaction mixture was filtrated and after concentration of the filtrate, the compound was purified by flash chromatography (CH_2Cl_2/MeOH 15:1). The desired product **19** (93.0 mg, 92%) was obtained as a colorless oil. R_f = 0.28 (CH_2Cl_2/MeOH 10:1); $[\alpha]_D^{25}$ = +56.1° (c = 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.43 (dd, J=10, 9 Hz, 1H), 5.18–5.10 (m, 1H), 4.93 (d, J=4 Hz, 1H), 4.85 (dd, J=10, 10 Hz, 1H), 4.81 (dd, J=10, 3 Hz, 1H), 4.35 (ddd, J=10, 10, 3 Hz, 1H), 4.31–4.20 (m, 2H), 3.73–3.66 (m, *N*H), 3.65–3.55 (m, 2H), 3.48 (s, 3H), 3.24 (dd, J=15, 10 Hz, 1H), 3.20–3.02 (m, 3H), 2.41 (t, J=4 Hz, 1H), 2.27–2.20 (m, 2H), 2.07 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H), 1.68–1.50 (m, 4H), 1.44–1.32 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 170.3, 169.9, 169.8, 96.7, 71.3, 71.0, 70.6, 69.8, 69.4, 65.0, 56.0, 55.2, 52.1, 51.0, 50.3, 46.2, 42.9, 33.6, 29.5, 25.9, 23.7, 20.6, 20.5 ppm; IR (film): $\tilde{\nu}$=3313, 2939, 1749, 1620, 1452, 1369, 1326, 1220, 1148, 1043, 772 cm^{-1}; MALDI-FT: m/z: calcd for $C_{23}H_{38}N_2O_{13}S$: 605.1987; found: 605.1978 $[M+Na]^+$.

Methyl 6-((*N*-(6-(2,5-dihydro-1*H*-pyrrol-1-yl)-6-oxohexyl)sulfamoyl)-methyl-3,4-di-*O*-acetyl-2-deoxy-2-[(benzyloxycarbonyl)amino]-α-D-glucopyranoside:[48] Triphenylphosphine (14.3 g, 55.0 mmol) was added portionwise at 0°C to solution of **18** (5.60 g, 10.9 mmol) in CH_2Cl_2. Then sulfuryl chloride (4.40 mL, 55.0 mmol) was added dropwise and the resulting mixture was stirred for 20 h at room temperature. The mixture was concentrated and purified over a short silica plug with hexane/EtOAc 1:1. From the resulting unstable sulfonyl chloride (4.28 g, 80%) a portion (1.90 g, 3.85 mmol) was immediately dissolved again in CH_2Cl_2 (35 mL). Sequentially triethylamine (2.44 mL, 17.5 mmol) and [6-(2,5-dihydro-1*H*-pyrrol-1-yl)-6-oxohexyl]amine[31] (650 mg, 3.50 mmol) were added. After stirring for 10 min at room temperature concentration of the solvent followed by flash chromatography (CH_2Cl_2/MeOH 40:1) afforded the desired product (1.40 g, 50% over 2 steps) as a colorless oil. R_f = 0.28 (CH_2Cl_2/MeOH 20:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5H), 5.90–5.84 (m, 1H), 5.81–5.75 (m, 1H), 5.21 (dd, J=11, 9 Hz, 1H), 5.11 (d, J=12 Hz, 1H), 5.04–4.99 (m, 2H), 4.89 (t, J=10 Hz, 1H), 4.77 (d, J=3 Hz, 1H), 4.54 (dd, J=7, 6 Hz, 1H), 4.32 (ddd, J=10, 10, 3 Hz, 1H), 4.22 (s, 4H), 4.00 (dt, J=10, 3 Hz, 1H), 3.49 (s, 3H), 3.23 (dd, J=15, 10 Hz, 1H), 3.10 (dd, J=15, 2 Hz, 1H), 3.17–3.07 (m, 2H), 2.32–2.22 (m, 2H), 2.04 (s, 3H), 1.89 (s, 3H), 1.68 (tt, J=15, 8 Hz, 2H), 1.59 (tt, J=15, 8 Hz, 2H), 1.49–1.33 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8, 170.5, 169.5, 155.5, 135.9, 128.3, 128.0, 127.8, 126.2, 124.6, 98.4, 70.7, 70.6, 66.9, 65.5, 56.0, 53.6, 53.3, 52.8, 52.0, 43.1, 33.9, 29.7, 26.1, 23.7, 20.7, 20.5 ppm; HRMS MALDI: m/z: calcd for $C_{29}H_{41}N_3O_{11}S$: 662.2354; found: 662.2343 $[M+Na]^+$.

Methyl 6-((*N*-(6-(3,4-dihydroxypyrrolidin-1-yl)-6-oxohexyl)sulfamoyl)-methyl-3,4-di-O-acetyl-2-deoxy-2-[(benzyloxycarbonyl)amino]-α-D-glucopyranoside (20): The isolated oil (1.32 g, 2.06 mmol) was dissolved in acetone/*tert*-butanol/water 15:6:2 (20 mL) was added *N*-methylmorpoline oxide (560 mg, 4.12 mmol) and potassium osmate (76.0 mg, 0.210 mmol). After 18 h at room temperature the reaction was quenched by adding sodium thiosulfate (360 mg, 2.10 mmol) and Florisil (360 mg). This was stirred for an additional hour. Filtration followed by flash chromatography (CH_2Cl_2/MeOH 20:1) afforded the desired product **20** (1.27 g, 91%) as a colorless oil. R_f = 0.38 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5H), 5.20 (dd, J=10, 10 Hz, 1H), 5.15–5.08 (m, 2H), 5.03 (d, J=12 Hz, 1H), 4.94 (dd, J=15, 10 Hz, 1H), 4.89–4.81 (m, 1H), 4.77 (dd, J=8, 4 Hz, 1H), 4.34 (dd, J=10, 2 Hz, 1H), 4.30–4.18 (m, 2H), 3.99 (ddt, J=11, 3, 4 Hz, 1H), 3.65 (dd, J=11, 6 Hz, 1H), 3.61–3.53 (m, 1H), 3.48 (s, 3H), 3.44 (dd, J=11, 6 Hz, 1H), 3.27 (ddd, J=15, 10, 10 Hz, 1H), 3.18–3.07 (m, 3H), 2.30–2.20 (m, 2H), 2.04 (s, 3H), 1.89 (s, 3H), 1.86–1.71 (m, 2H), 1.70–1.52 (2H), 1.47–1.34 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.0, 170.6, 169.7, 155.8, 135.9, 128.4, 128.2, 127.9, 98.4, 71.4, 70.8, 69.9, 67.1, 65.6, 56.2, 53.7, 52.3, 51.1, 50.4, 43.0, 33.7, 33.7, 29.4, 26.0, 23.8, 23.7, 20.8, 20.6 ppm; IR (neat): $\tilde{\nu}$ = 3316, 2940, 1741, 1617, 1525, 1451, 1371, 1323, 1222, 1145, 1039, 917, 737 cm^{-1}; HRMS MALDI: m/z: calcd for $C_{29}H_{43}N_3O_{13}S$: 674.2589; found: 674.2636 $[M+H]^+$.

Methyl 6-(*N*-(6-(3,4-dihydroxypyrrolidine-1-yl)-6-oxohexyl)sulfamoyl)-methyl-3,4-di-O-acetyl-2-deoxy-2-{[(9*H*-fluoren-9-ylmethyl)carbonyl]amino}-α-D-glucopyranoside (21): 10% Pd/C (19.3 mg, 0.180 mmol) was added to a solution of **20** (1.20 g, 1.80 mmol) under inert atmosphere in methanol (18.0 mL). Then a hydrogen-balloon (1.0 atm) was applied to the reaction, evacuation of the inert atmosphere, which was replaced by hydrogen, was performed three times. The reaction mixture was stirred vigorously for 18 h. Filtration over celite and concentration afforded the crude product and was used without further purification in the next step. The isolated product was dissolved in water/dioxane 1:1 (18.0 mL) and sodium bicarbonate (0.580 g, 5.40 mmol) and *N*-(9*H*-fluoren-2-ylmethoxyoxycarbonyl)succinimide (670 mg, 2.00 mmol) were added. After 30 min a white solid crashed out, this was filtered and washed with CH_2Cl_2 (60 mL) and water (60 mL). The organic phase was separated from the water layer, and the water layer was extracted with EtOAc (3×100 mL). The combined organic layers were washed with saturated NaCl (50 mL) and dried over $MgSO_4$. The organic phase was concentrated and flash chromatography (CH_2Cl_2/MeOH 10:1) afforded the desired product **21** (14.5 g, 26% over 2 steps) as a white foam. M.p. 92–95°C; R_f = 0.20 (CH_2Cl_2/MeOH 10:1); $[\alpha]_D^{24}$ = +58.3° (c = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, J=7 Hz, 2H), 7.55 (dd, J=7, 6 Hz, 2H), 7.41 (dd, J=7, 7 Hz, 2H), 7.32 (dd, J=7, 7 Hz, 2H), 5.25 (dd, J=10, 2 Hz, 1H), 5.18 (d, J=10 Hz, 1H), 4.94 (dt, J=14, 10 Hz, 1H), 4.78 (dd, J=9, 3 Hz, 1H), 4.70 (dd, J=13, 7 Hz, 1H), 4.42 (dd, J=10, 7 Hz, 1H), 4.36–4.14 (m, 5H), 4.01 (tt, J=10, 3 Hz, 1H), 3.68–3.62 (m, 2H), 3.61 (dd, J=10, 6 Hz, 1H), 3.52 (d, J=2 Hz, 4H), 3.45 (d, J=5 Hz, 1H), 3.41 (d, J=6 Hz, 1H), 3.32–3.18 (m, 2H), 3.16–3.08 (m, 3H), 2.25 (dt, J=7, 2 Hz, 2H), 2.06 (s, 3H), 1.96 (s, 3H), 1.70–1.53 (m, 4H), 1.42 ppm (dd, J=7, 7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1, 170.7, 169.7, 155.8, 143.4, 141.1, 127.7, 127.0, 124.9, 119.9, 98.4, 71.4, 70.8, 70.6, 69.9, 67.2, 65.6, 56.2, 53.8, 52.3, 51.1, 50.4, 47.0, 43.0, 33.7, 29.5, 26.0, 23.8, 20.8 ppm; IR (film): $\tilde{\nu}$=3330, 2942, 1747, 1619, 1523, 1450, 1367, 1325, 1240, 1148, 1044, 758 cm^{-1}; MALDI-FT: m/z: calcd for $C_{36}H_{47}N_3O_{13}S$: 784.2722; found: 784.2735 $[M+Na]^+$.

Methyl *N*-[(6-piperazinyl-6-oxohexylsulfamoyl)-methyl-2,3,4-tri-*O*-acetyl-α-D-glucopyranosyl]-AmB: Silica gel (312 mg) was suspended in CH_2Cl_2 (2.0 mL) and water (312 μL), then sodium periodate (44.0 mg, 203 μmol) was added to give a flocky suspension. To the reaction mixture **19** (59.0 mg, 101 μmol) was added and stirred at room temperature for 1 h. The suspension was filtered and the filter cake washed with CH_2Cl_2 (2× 5.0 mL) and EtOAc (2×5.0 mL). The solvents were removed under reduced pressure. To the resulting white solid, AmB (78.0 mg, 84.0 μmol) was added, followed by DMF (1.7 mL), conc. HCl (1 drop) and $NaBH_3CN$ (7.0 mg, 0.11 mmol) and the suspension that quickly cleared was stirred for 16 h. Amberlite IRA-743 (70.0 mg) was added and the suspension was stirred for an additional 1 h. After filtration the solvent was removed and the solid purified by flash chromatography ($CHCl_3$/MeOH/H_2O 20:6:1). The resulting yellow solid (91 mg, 73%) was dried by lyophilisation. R_f = 0.67 ($CHCl_3$/MeOH/H_2O 10:6:1); ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 6.98 (dd, J=6, 6 Hz, 1H), 6.48–6.20 (m, 8H), 6.16 (dd, J=4, 4 Hz, 2H), 6.12–6.03 (m, 2H), 5.98–5.91 (m, 1H), 5.80 (s, 1H), 5.44 (dd, J=15, 10 Hz, 1H), 5.32 (s, 1H), 5.27 (dd, J=10, 10 Hz, 1H), 5.23–5.18 (m, 1H), 4.93–4.84 (m, 3H), 4.81–4.72 (m, 3H), 4.65–4.58 (m, 1H), 4.40–4.3 (m, 3H), 4.27–4.15 (m, 3H), 4.14–4.09 (m, 1H), 4.08–4.03 (m, 1H), 4.01–3.93 (m, 1H), 3.81 (s, 1H), 3.57–3.49 (m, 1H), 3.49–3.42 (m, 2H), 3.38–3.28 (m, 4H), 3.24 (dd, J=15, 8 Hz, 2H), 3.21 (d, J=3 Hz, 1H), 3.14–3.06 (m, 3H), 2.97–2.80 (m, 4H), 2.37 (d, J= 9 Hz, 1H), 2.30–2.23 (m, 3H), 2.17 (d, J=6 Hz, 2H), 2.01 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H), 1.93–1.82 (m, 3H), 1.78–1.70 (m, 1H), 1.63–1.36 (m, 14H), 1.35–1.21 (m, 8H), 1.18 (d, J=6 Hz, 3H), 1.11 (d, J=6 Hz, 3H), 1.04 (d, J=6 Hz, 3H), 0.91 (d, J=7 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 170.4, 170.1, 169.5, 169.4, 169.3, 162.2, 136.6, 133.8, 133.6, 133.4, 133.1, 132.3, 132.0, 131.8, 131.1, 97.0, 95.9, 79.0, 77.0, 73.6, 73.5, 70.3, 69.6, 69.5, 69.2, 69.1, 68.7, 67.6, 67.5, 67.4, 66.1, 65.3, 64.6, 55.1, 51.9, 51.8, 50.1, 49.7, 46.1, 45.9, 44.6, 44.1, 42.2, 42.0, 41.9, 35.6, 35.0, 32.1, 30.7, 30.3, 29.3, 28.9, 25.8, 24.3, 20.4, 20.3, 20.2, 18.3, 18.0, 16.9, 11.9 ppm; IR (KBr): $\tilde{\nu}$ = 3386, 2933, 1752, 1663, 1437, 1371, 1326, 1224, 1042, 1011, 752 cm^{-1}; UV (H_2O): 416, 391, 371, 352 cm^{-1}; MALDI-FT: m/z: calcd for $C_{70}H_{109}N_3O_{28}S$: 1472.6991; found: 1472.701 $[M+H]^+$.

Methyl *N*-[(6-piperazinyl-6-oxohexylsulfamoyl)-methyl-α-D-glucopyranosyl]-AmB (22): The yellow solid (50 mg, 34 μmol) was dissolved in MeOH/H_2O 3:2 (1.7 mL) and powdered potassium carbonate (21 mg, 153 μmol) was added at room temperature. After 40 min the solvents were concentrated and flash chromatography ($CHCl_3$/MeOH/H_2O 10:6:1) afforded **22** as a yellow powder (30 mg, 65%). R_f = 0.42 ($CHCl_3$/MeOH/H_2O 10:6:1); ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 6.85–6.80 (m, 1H), 6.46–6.20 (m, 8H), 6.19–6.13 (m, 2H), 6.09 (d, J=11 Hz, 1H), 6.06 (d, J=10 Hz, 1H), 5.96 (dd, J=15, 9 Hz, 1H), 5.74 (s, 1H), 5.69–5.63 (m, 1H), 5.55–5.48 (m, 1H), 5.44 (dd, J=15, 10 Hz, 1H), 5.32 (s, 1H), 5.21 (d, J=5 Hz, 1H), 4.81–4.78 (m, 2H), 4.76 (d, J=4 Hz, 1H), 4.64 (d, J=5 Hz, 1H), 4.51 (d, J=4 Hz, 1H), 4.45–4.30 (m, 3H), 4.22 (s, 2H), 4.16 (t, J=9, 1H), 4.10–4.02 (m, 1H), 4.00–3.90 (m, 1H), 3.80 (dt, J=10, 1 Hz, 2H), 3.56–3.34 (m, 4H), 3.22 (dd, J=10, 4 Hz, 2H), 3.16–3.10 (m, 2H), 3.08 (d, J=10 Hz, 1H), 3.05 (d, J=9 Hz, 1H), 2.96–2.83 (m, 5H), 2.76–2.69 (m, 1H), 2.68–2.62 (m, 1H), 2.40 (d, J=10.1, 2H), 2.30 (dd, J=15, 7 Hz, 2H), 2.27–2.19 (m, 3H), 2.16 (d, J=6 Hz, 2H), 1.91–1.77 (m, 3H), 1.72 (d, J=7 Hz, 2H), 1.62–1.36 (m, 14H), 1.32–1.21 (m, 8H), 1.17 (d, J=6 Hz, 3H), 1.11 (d, J=6 Hz, 3H), 1.04 (d, J=6 Hz, 3H), 0.98 (d, J=7 Hz, 1H), 0.91 (d, J=7 Hz, 3H), 0.80 ppm (d, J=7 Hz, 1H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 170.5, 170.3, 133.9, 133.7, 133.2, 132.3, 132.1, 132.0, 131.8, 131.1, 99.7, 97.1, 96.1, 77.0, 73.5, 72.8, 72.2, 71.7, 69.7, 69.1, 68.8, 67.7, 67.1, 66.1, 65.3, 60.2, 56.9, 54.7, 53.2, 50.8, 49.5, 46.3, 46.1, 44.7, 44.3, 44.2, 42.3, 42.2, 42.1, 42.0, 41.9, 39.9, 39.7, 39.5, 35.0, 32.2, 29.3, 29.0, 28.9, 25.8, 25.7, 24.4, 18.4, 18.1, 16.9, 16.4, 12.2, 12.0, 10.6, 8.6 ppm; IR (neat): $\tilde{\nu}$ = 3332, 2929, 1715, 1623, 1586, 1415, 1316, 1144, 996, 823, 760 cm^{-1}; UV (H_2O): λ = 416, 391, 372, 352 nm; MALDI-FT: m/z: calcd for $C_{64}H_{103}N_3O_{25}S$: 1390.6313; found: 1390.630 $[M-H+Na_2]^+$.

Methyl *N*-[(6-piperazinyl-6-oxohexylsulfamoyl)-methyl]-2-deoxy-2-amino-α-D-glucopyranosyl]-AmB (23): Water (0.18 mL) and sodium periodate (27 mg, 0.13 mmol) were added under vigorous stirring to silica (0.18 g) in chloroform (1.5 mL); then **21** (50.0 mg, 65.6 μmol) was added and stirred at room temperature for 1 h. The suspension was filtered, washed with CH_2Cl_2 (2×5.0 mL) and EtOAc (2×5.0 mL). The filtrate was concentrated and the dialdehyde used without further purification. To sodium cyanoborohydride (4.4 mg, 71 μmol) in DMF (1.1 mL) was added the dialdehyde and AmB (51 mg, 55 μmol), followed by one drop of conc. HCl. This mixture was stirred for 18 h. The solvent was evaporated and flash chromatography ($CHCl_3$/MeOH/H_2O 40:8:1) afforded the protected AmB derivative (54 mg, 59%) as a yellow solid. The isolated yellow solid (25 mg, 15 μmol) was dissolved in MeOH/water 3:2 (0.30 mL) and potassium carbonate was added at room temperature. After stirring for 20 min at room temperature piperidine (45 μL, 0.45 mmol) was added and an additional 1 h was stirred. Evaporation of the solvent and flash chromatography ($CHCl_3$/MeOH/H_2O 10:6:1) afforded **23** (13 mg, 66%) as a yellow solid. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 6.87 (t, J=6 Hz, 1H), 6.49–6.20 (m, 8H), 6.17 (t, J= 4 Hz, 2H), 6.12–6.02 (m, 2H), 5.95 (dd, J=15, 9 Hz, 1H), 5.82 (s, 1H), 5.43 (dd, J=15, 10 Hz, 1H), 5.36 (s, 1H), 5.21 (d, J=5 Hz, 1H), 4.79 (s, 2H), 4.75 (s, 1H), 4.65 (s, 1H), 4.59 (s, 1H), 4.50–4.33 (m, 4H), 4.32 (s, 1H), 4.27–4.14 (m, 3H), 4.10–4.03 (m, 1H), 4.02–3.94 (m, 1H), 3.86–3.77 (m, 3H), 3.58–3.36 (m, 14H), 3.15–3.05 (m, 4H), 2.99–2.80 (m, 5H), 2.76–2.68 (m, 2H), 2.67–2.61 (m, 1H), 2.38 (d, J=10 Hz, 1H), 2.33–2.21 (m, 3H), 2.17 (d, J=6 Hz, 1H), 2.10–1.99 (m, 1H), 1.94–1.82 (m, 2H), 1.72 (d, J=7.0 Hz, 1H), 1.62–1.51 (m, 4H), 1.51–1.43 (m, 5H), 1.42–1.36 (m, 2H), 1.35–1.22 (m, 6H), 1.18 (d, J=6 Hz, 3H), 1.11 (d, J=6 Hz, 3H), 1.04 (d, J=6 Hz, 3H), 0.98 (t, J=7 Hz, 1H), 0.91 ppm (d, J=7 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 174.9, 170.4, 170.2, 136.7, 136.6, 133.8, 133.6, 133.4, 133.1, 132.3, 132.1, 131.8, 131.7, 131.1, 128.5, 97.0, 96.9, 77.1, 77.0, 74.2, 73.7, 73.5, 73.2, 73.1, 72.6, 69.6, 69.1, 68.8, 67.6, 67.3, 66.1, 65.3, 65.1, 57.2, 55.4, 54.8, 53.1, 50.6, 49.5, 46.1, 46.0, 44.7, 44.3, 44.2, 42.3, 42.2, 42.1, 42.0, 41.9, 36.7, 35.0, 32.1, 29.3, 29.0, 28.9, 25.8, 25.6, 24.4, 18.4, 18.1, 16.9, 12.0, 10.5 ppm; MALDI-FT: m/z: calcd for $C_{64}H_{104}N_4O_{24}S$: 1367.6653; found: 1367.663 $[M+Na]^+$.

***N*,*N*-Di-(3-hydroxypropyl)-AmB (25)**: To a solution of 3-(*tert*-butyldimethylsiloxy)propanal[77] (300 mg, 1.60 mmol) and AmB (**1**) (365 mg, 0.400 mmol) in DMF (3.00 mL) was added $NaBH_3CN$ (100 mg, 1.60 mmol) followed by a drop of conc. HCl. After 16 h at room temperature, Amberlite IRA-743 (400 mg) was added and the mixture was stirred for an hour. After filtration, the solution was concentrated down and added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and purified by flash chromatography ($CHCl_3$/MeOH/H_2O 40:8:1). The isolated yellow solid was dissolved in MeOH (5.00 mL) in a plastic bottle. At 0°C, diluted HF·pyridine solution (1.00 mL, prepared from 0.500 mL of the 70% HF·pyridine commercial solution and 0.500 mL of pyridine) was added. After 2 h at room temperature, the solution was concentrated and added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2×100 mL) providing the desired compound **25** as a yellow solid (104 mg, 28%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 6.47–6.06 (m, 13H), 5.94 (dd, J= 15, 9 Hz, 1H), 5.90 (s, 1H), 5.45 (dd, J=15, 10 Hz, 1H), 5.36 (s, 1H), 5.22–5.20 (m, 1H), 4.79–4.76 (m, 2H), 4.72 (s, 1H), 4.61 (s, 1H), 4.45–4.38 (m, 1H), 4.24–4.21 (m, 1H), 4.06–3.92 (m, 2H), 3.60–3.02 (m, OH), 2.31–2.26 (m, 1H), 2.18 (d, J=6 Hz, 1H), 2.00–1.97 (m, 1H), 1.90–1.87 (m, 1H), 1.76–1.72 (m, 2H), 1.60–1.52 (m, 2H), 1.42–1.21 (m, 18H), 1.11 (d, J=6 Hz, 3H), 1.04 (d, J=6 Hz, 3H), 0.92 ppm (d, J=7 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 174.2, 170.5, 136.7, 133.7, 133.5, 133.2, 133.1, 132.5, 132.3, 132.2, 132.0, 131.8, 131.1, 129.0, 97.2, 77.1, 74.6, 73.7, 73.5, 73.1, 69.1, 68.8, 67.6, 66.8, 66.2, 65.3, 65.0, 64.4, 58.7, 56.8, 46.0, 44.7, 44.2, 42.3, 42.0, 36.7, 35.0, 28.9, 18.4, 17.8, 16.9, 12.0 ppm; MALDI-FT: m/z: calcd for $C_{53}H_{85}NO_{19}$: 1040.5894; found: 1040.5789 $[M+H]^+$.

***N*,*N*-Di-(methyl-4-butanoate)-AmB (26)**: To a solution of methyl-4-oxobutanoate (520 mg, 4.50 mmol) and AmB (**1**) (820 mg, 0.890 mmol) in DMF (5.00 mL) was added $NaBH_3CN$ (280 mg, 4.50 mmol) followed by a drop of conc. HCl. After 18 h at room temperature, Amberlite IRA-743 (800 mg) was added and the mixture was stirred for an hour. After filtration, the solution was concentrated down and added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and purified by flash chromatography ($CHCl_3$/MeOH/H_2O 40:8:1) providing the desired compound **26** as a yellow solid (450 mg, 45%). R_f = 0.30 ($CHCl_3$/MeOH/H_2O 40:8:1); ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 6.46–6.06 (m, 13H), 5.95 (dd, J=15, 9 Hz, 1H), 5.82 (s, 1H), 5.45 (dd, J=15, 10 Hz, 1H), 5.32

(s, 1H), 5.21–5.19 (m, 1H), 4.80–4.74 (m, 2H), 4.62 (s, 1H), 4.43–4.36 (m, 1H), 4.32 (s, 1H), 4.25–4.17 (m, 2H), 4.06–3.96 (m, 2H), 3.75 (s, 1H), 3.58 (s, 6H), 3.55–3.35 (m, OH), 3.11–3.08 (m, 1H), 2.78–2.72 (m, 1H), 2.64–2.59 (m, 1H), 2.31 (t, $J=7$ Hz, 4H), 2.17 (d, $J=6$ Hz, 1H), 1.98–1.23 (m, 21H), 1.18 (d, $J=6$ Hz, 3H), 1.11 (d, $J=6$ Hz, 3H), 1.04 (d, $J=6$ Hz, 3H), 0.92 ppm (d, $J=7$ Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 173.6, 173.2, 170.5, 136.9, 136.7, 133.8, 133.6, 133.5, 133.1, 132.4, 132.3, 132.1, 132.0, 131.8, 131.6, 131.1, 128.7, 97.4, 97.1, 80.3, 77.1, 76.3, 75.7, 74.4, 73.8, 73.7, 73.5, 69.4, 69.2, 68.9, 67.9, 67.6, 66.2, 65.4, 63.9, 56.9, 51.0, 50.2, 46.2, 44.6, 44.2, 42.3, 42.0, 35.0, 31.0, 29.0, 24.0, 18.4, 18.2, 16.9, 12.0 ppm; MALDI-FT: m/z: calcd for $C_{55}H_{85}NO_{21}$: 1124.6005; found: 1124.5600 $[M+H]^+$.

***N,N*-Di-(4-butanoic acid)-AmB (27)**: To a solution of *N,N*-di-(methyl-4-butanoate)-AmB (**26**) (100 mg, 0.089 mmol) in THF (5.00 mL) and H_2O (3.00 mL) was added aqueous LiOH solution (2.00 mL, 1.00 M) at 0 °C. After 1 h, the reaction mixture was acidified to pH 5 with dilute aqueous hydrochloric acid solution. The solution was concentrated and added dropwise to diethyl ether (250 mL). The yellow-brown precipitate was filtered providing the desired compound **27** (42.0 mg, 43%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 12.22 (brs, 2H), 6.60–5.85 (m, 15H), 5.55–5.34 (s, 2H), 5.25–5.04 (m, 2H), 5.02–4.99 (m, 1H), 4.95–4.90 (m, 1H), 4.85–4.82 (m, 2H), 4.64–4.57 (m, 1H), 4.39 (s, 1H), 4.15–4.05 (m, 1H), 3.68 (m, OH), 3.33–3.12 (m, 1H), 2.37–2.30 (m, 2H), 2.17 (d, $J=6$ Hz, 1H), 2.00–1.90 (m, 1H), 1.71–1.28 (m, 21H), 1.18 (dd, $J=10$, 6 Hz, 3H), 1.11 (d, $J=6$ Hz, 3H), 1.04 (d, $J=6$ Hz, 3H), 0.91 ppm (d, $J=7$ Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 173.7, 173.5, 170.4, 136.9, 136.7, 133.8, 133.6, 133.5, 133.1, 132.4, 132.3, 132.1, 132.0, 131.8, 131.6, 131.1, 128.7, 97.8, 97.1, 93.9, 93.3, 80.7, 77.1, 76.4, 75.9, 75.2, 73.9, 73.5, 73.3, 72.4, 68.9, 68.5, 67.7, 66.4, 66.0, 64.8, 61.6, 51.0, 50.2, 46.2, 44.6, 42.3, 42.0, 35.0, 31.2, 18.5, 18.4, 16.9, 12.0 ppm; MALDI-FT: m/z: calcd for $C_{55}H_{85}NO_{21}$: 1094.5536; found: 1094.5541 $[M-H]^-$.

***N,N*-Di-{*N*-(9-fluorenylmethoxycarbonyl)-3-aminopropyl}-AmB (28)**: To a solution of *N*-(9-fluorenylmethoxycarbonyl)-3-aminopropanal[72] (150 mg, 0.510 mmol) and AmB (**1**) (157 mg, 0.170 mmol) in DMF (3.00 mL) was added $NaBH_3CN$ (32.0 mg, 0.510 mmol) followed by a drop of conc. HCl. After 16 h at room temperature, Amberlite IRA-743 (300 mg) was added and the mixture was stirred for an hour. After filtration, the solution was concentrated down and added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and purified by flash chromatography ($CHCl_3$/MeOH/H_2O 10:6:1) providing the desired compound **28** as a yellow solid (200 mg, 80%). R_f = 0.70 ($CHCl_3$/MeOH/H_2O 10:6:1); ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.87 (d, $J=8$ Hz, 4H), 7.68 (d, $J=8$ Hz, 4H), 7.40 (t, $J=8$ Hz, 4H), 7.31 (t, $J=8$ Hz, 4H), 6.46–6.06 (m, 12H), 5.96 (dd, $J=14$, 8 Hz, 1H), 5.84 (s, 1H), 5.44 (dd, $J=15$, 10 Hz, 1H), 5.33 (s, 1H), 5.21 (brs, 1H), 4.79–4.60 (m, 4H), 4.43–4.19 (m, 10H), 4.07–3.97 (m, 2H), 3.81 (s, 1H), 3.55–3.41 (m, 3H), 3.31 (brs, OH), 3.13–3.02 (m, 6H), 2.77 (s, 1H), 2.64 (s, 1H), 2.28 (s, 1H), 2.17 (d, $J=6$ Hz, 1H), 1.93–1.24 (m, 18H), 1.19 (d, $J=6$ Hz, 3H), 1.11 (d, $J=7$ Hz, 3H), 1.04 (d, $J=6$ Hz, 3H), 0.92 ppm (d, $J=7$ Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 177.6, 170.5, 162.2, 156.0, 143.9, 142.5, 140.6, 139.3, 137.3, 136.7, 133.8, 133.6, 133.4, 133.1, 132.4, 132.3, 132.1, 131.9, 131.8, 131.7, 131.2, 128.8, 127.5, 127.2, 127.0, 125.1, 121.3, 119.9, 101.2, 97.1, 77.1, 77.0, 73.9, 73.5, 69.5, 69.1, 68.8, 67.8, 67.5, 66.1, 65.2, 64.8, 58.2, 48.3, 46.7, 44.8, 44.6, 44.2, 42.0, 41.9, 38.4, 35.7, 35.0, 30.7, 28.9, 28.5, 18.4, 18.2, 16.9, 15.1, 12.0 ppm; MALDI-FT: m/z: calcd for $C_{87}H_{107}N_3O_{21}$: 1504.7295; found: 1504.7289 $[M+Na]^+$.

16-(*N*′-(2-Aminoethyl)-carboxamide)-*N,N*-di-(3-aminopropyl)-AmB (29): To a solution of **28** (170 mg, 0.115 mmol) in DMF (3.00 mL) was added *N*-Fmoc-ethylenediamine (49.0 mg, 0.172 mmol), 1-hydroxybenzotriazole (19.0 mg, 0.138 mmol), (benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (60.0 mg, 0.115 mmol) and diisopropylethylamine (40.0 μL, 0.230 mmol). After 36 h at room temperature, the solution was concentrated down and a flash chromatography ($CHCl_3$/MeOH/H_2O 40:8:1) provided the protected derivative of compound **29**. The yellow solid was dissolved in DMSO (3.00 mL) and was added piperidine (0.200 mL, 2.10 mmol). After 2 h at room temperature, the solution was added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2×100 mL) providing the desired compound **29** as a yellow solid (44.0 mg, 35%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 6.48–6.06 (m, 13H), 5.96–5.91 (m, 1H), 5.43 (dd, $J=15$, 10 Hz, 1H), 5.22 (brs, 1H), 4.89–4.65 (m, 3H), 4.46–4.40 (m, 1H), 4.30–4.18 (m, 2H), 4.09–4.00 (m, 1H), 3.94–3.88 (m, 1H), 3.88–3.44 (brs, OH), 3.14–3.00 (m, 7H), 2.88–2.64 (m, 3H), 2.31–2.26 (m, 1H), 2.17 (d, $J=6$ Hz, 1H), 1.62–1.23 (m, 18H), 1.19 (d, $J=6$ Hz, 3H), 1.11 (d, $J=6$ Hz, 3H), 1.04 (d, $J=6$ Hz, 3H), 0.92 ppm (d, $J=7$ Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 171.8, 170.5, 136.7, 133.8, 133.6, 133.3, 133.1, 132.4, 132.1, 131.8, 131.2, 128.5, 97.0, 77.1, 74.1, 73.8, 73.4, 69.0, 68.7, 67.8, 67.7, 67.6, 67.3, 66.1, 65.5, 64.8, 64.4, 54.2, 46.4, 45.8, 45.7, 44.7, 44.0, 42.4, 41.9, 38.0, 35.0, 29.0, 25.8, 18.4, 18.2, 16.8, 12.0 ppm; MALDI-FT: m/z: calcd for $C_{55}H_{93}N_5O_{16}$: 1080.6696; found: 1080.61690 $[M+H]^+$.

16-(*N*′-(1-Methylpiperazinyl)-carboxamide)-*N,N*-di-(3-aminopropyl)-AmB (30): To a solution of **28** (200 mg, 0.135 mmol) in DMF (2.00 mL) was added 1-methylpiperazine (0.100 mL, 1.00 mmol), 1-hydroxybenzotriazole (36.0 mg, 0.270 mmol), (benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (100 mg, 0.190 mmol). After 18 h at room temperature, the solution was concentrated down and the residue was added dropwise to diethyl ether (250 mL). The yellow precipitate was diluted in DMF (2.00 mL) and triethylamine (0.100 mL, 1.00 mmol) and Fmoc-Cl (100 mg, 0.360 mmol) was added. After 2 h, the mixture added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and purified by flash chromatography ($CHCl_3$/MeOH/H_2O 10:6:1). To the isolated solid in DMSO (3.00 mL) was added piperidine (0.200 mL, 2.10 mmol). After 2 h at room temperature, the solution was added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2×100 mL) providing the desired compound **30** as a yellow solid (10.0 mg, 7%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 6.48–6.06 (m, 12H), 5.97–5.92 (m, 1H), 5.43 (dd, $J=15$, 10 Hz, 1H), 5.23 (brs, 1H), 4.89–4.52 (m, 4H), 4.33–4.17 (m, 6H), 4.08–3.99 (m, 4H), 3.90 (s, 1H), 3.50 (brs, OH), 3.12–3.06 (m, 4H), 2.72–2.64 (m, 4H), 2.41–2.26 (m, 1H), 2.17 (d, $J=6$ Hz, 1H), 1.82–1.15 (m, 22H), 1.19 (d, $J=6$ Hz, 3H), 1.11 (d, $J=6$ Hz, 3H), 1.04 (d, $J=6$ Hz, 3H), 0.92 (d, $J=7$ Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 171.8, 170.5, 136.6, 134.0, 133.8, 133.4, 133.3, 132.7, 132.5, 132.4, 132.0, 131.4, 128.7, 96.9, 77.4, 74.3, 74.0, 73.7, 69.2, 69.0, 68.0, 67.9, 66.3, 65.9, 55.3, 54.9, 51.2, 47.7, 46.4, 45.7, 45.4, 44.9, 42.6, 42.1, 41.3, 35.2, 31.4, 30.8, 29.1, 26.2, 18.6, 18.5, 18.3, 17.1, 12.2 ppm; MALDI-FT: m/z: calcd for $C_{58}H_{97}N_5O_{16}$: 1120.4147; found: 1120.7003 $[M+H]^+$.

16-(*N*′-(3-Dimethylaminopropyl)-carboxamide)-*N,N*-di-(3-aminopropyl)-AmB (31): To a solution of **28** (100 mg, 0.068 mmol) in DMF (2.00 mL) was added 3-dimethylaminopropylamine (17.0 mg, 0.136 mmol), 1-hydroxybenzotriazole (11.0 mg, 0.082 mmol), (benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (35.0 mg, 0.068 mmol) and diisopropylethylamine (20.0 μL, 0.102 mmol). After 24 h at room temperature, the solution was concentrated down and the residue was added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2×100 mL). To the yellow solid in DMSO (3.00 mL) was added piperidine (0.200 mL, 2.10 mmol). After 2 h at room temperature, the solution was added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2×100 mL) providing the desired compound **31** as a yellow solid (36.0 mg, 47%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 6.48–6.07 (m, 13H), 5.97–5.93 (m, 1H), 5.43 (dd, $J=15$, 10 Hz, 1H), 5.23 (brs, 1H), 4.86–4.83 (m, 4H), 4.35–4.31 (m, 1H), 4.26–4.24 (m, 1H), 4.08–3.97 (m, 2H), 3.92–3.80 (m, 1H), 3.65–3.44 (m, 5H), 3.17–3.08 (m, 2H), 2.31–2.24 (m, 2H), 2.17 (d, $J=6$ Hz, 1H), 2.12 (s, 3H), 2.08 (s, 3H), 1.90–1.20 (m, 23H), 1.11 (d, $J=6$ Hz, 3H), 1.04 (d, $J=6$ Hz, 3H), 0.92 (d, $J=7$ Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 170.5, 162.2, 136.7, 136.3, 133.8, 133.6, 133.4, 133.1, 132.4, 132.2, 131.9, 131.8, 131.2, 128.5, 97.1, 77.0, 74.1, 73.8, 73.5, 69.1, 68.8, 67.9, 67.6, 66.1, 65.7, 62.7, 54.5, 47.9, 46.2, 45.8, 45.5, 44.9, 44.7, 44.0, 42.4, 42.0, 35.7, 35.0, 30.7, 30.6, 18.4, 18.1, 16.9, 12.0 ppm; MALDI-FT: m/z: calcd for $C_{58}H_{99}N_5O_{16}$: 1122.4306; found: 1122.7160 $[M+H]^+$.

16-(*N*′-(4-(3-Aminopropyl)morpholine)carboxamide)-*N,N*-di-(3-aminopropyl)-AmB (32): To a solution of **28** (100 mg, 0.068 mmol) in DMF (2.00 mL) was added 4-(3-aminopropyl)-morpholine (20.0 mg, 0.136 mmol), 1-hydroxybenzotriazole (11.0 mg, 0.082 mmol), (benzotria-

zol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (35.0 mg, 0.068 mmol) and diisopropylethylamine (20.0 μL, 0.102 mmol). After 18 h at room temperature, the solution was concentrated down and the residue was added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2×100 mL). To the yellow solid in DMSO (3.00 mL) was added piperidine (0.200 mL, 2.10 mmol). After 2 h at room temperature, the solution was added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2×100 mL) providing the desired compound **32** as a yellow solid (39.0 mg, 49%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ=6.48–6.06 (m, 12H), 5.97–5.93 (m, 1H), 5.43 (dd, J=15, 10 Hz, 1H), 5.22 (brs, 1H), 4.90–4.35 (m, 7H), 4.26–4.20 (m, 4H), 4.05–3.99 (m, 4H), 3.90–3.77 (m, 4H), 3.56–3.46 (m, 7H), 3.16–3.01 (m, 4H), 2.90–2.80 (m, 4H), 2.33–2.28 (m, 4H), 2.17 (d, J=6 Hz, 1H), 1.98–1.24 (m, 18H), 1.19 (d, J=6 Hz, 3H), 1.11 (d, J=6 Hz, 3H), 1.04 (d, J=6 Hz, 3H), 0.91 (d, J=7 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 171.9, 170.5, 136.7, 136.5, 133.7, 133.6, 133.3, 133.1, 132.4, 132.1, 131.9, 131.8, 131.2, 128.5, 97.0, 77.1, 74.2, 74.0, 73.8, 73.7, 73.4, 69.0, 68.7, 67.8, 67.7, 66.1, 64.8, 64.5, 55.9, 53.3, 47.8, 47.6, 47.4, 47.3, 46.1, 44.9, 44.7, 44.6, 42.4, 41.9, 38.2, 35.0, 29.0, 26.1, 18.4, 18.1, 16.9, 12.0 ppm; MALDI-FT: m/z: calcd for $C_{60}H_{101}N_5O_{17}$: 1164.4672; found: 1164.7265 $[M+H]^+$.

16-(N'-6-Aminohexanylcarboxamide)-*N*,*N*-di(3-aminopropyl)-AmB (33): To a solution of **28** (300 mg, 0.202 mmol) in DMF (2.0 mL) was added diisopropylamine (87 μL, 0.49 mmol), 1-hydroxybenzotriazole (38 mg, 0.28 mmol), (benzotriazol-1-yloxy)-tripyrrolidino-phosphonium hexafluorophosphate (126 mg, 0.242 mmol) and 6-(9-fluorenylmethoxycarbonyl)-1-diaminohexane monohydrochloride (114 mg, 0.303 mmol). After 18 h at room temperature, the solution was added dropwise to diethyl ether (200 mL). The yellow precipitate was filtered and washed with diethyl ether (2×10 mL). The yellow solid was purified by flash chromatography ($CHCl_3$/MeOH/H_2O 60:9:1). The isolated yellow solid was dissolved in DMSO (2 mL) and piperidine (0.100 mL) was added. After 10 min at room temperature, the solution was added dropwise to diethyl ether (200 mL). The yellow precipitate was filtered and washed with diethyl ether (2×10 mL) providing the desired compound **33** as a yellow solid (119 mg, 51%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.89 (s, 1H), 6.45 (dd, J=14, 11 Hz, 1H), 6.39–6.19 (m, 8H), 6.16 (s, 1H), 6.15 (d, J=4 Hz, 1H), 6.08 (dd, J=15, 11 Hz, 2H), 5.94 (dd, J=15, 9 Hz, 1H), 5.42 (dd, J=15, 10 Hz, 1H), 5.28–5.16 (m, 1H), 4.41–4.30 (m, 2H), 4.29–4.20 (m, 3H), 4.18 (s, 1H), 4.11–3.97 (m, 4H), 3.93–3.84 (m, 3H), 3.57–3.39 (14H), 3.20–3.12 (m, 2H), 3.08 (t, J=11 Hz, 3H), 2.98–2.89 (m, 2H), 2.88–2.74 (m, 3H), 2.46–2.37 (m, 1H), 2.33–2.22 (m, 2H), 2.16 (d, J=6 Hz, 2H), 2.00–1.92 (m, 1H), 1.92–1.80 (m, 2H), 1.76–1.67 (m, 1H), 1.63–1.44 (m, 9H), 1.44–1.36 (m, 6H), 1.35–1.29 (m, 5H), 1.29–1.21 (m, 6H), 1.17 (d, J=6 Hz, 3H), 1.10 (d, J=7, 3H), 1.03 (d, J=6 Hz, 3H), 0.90 ppm (d, J=7 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 171.5, 170.4, 136.7, 136.6, 133.8, 133.6, 133.3, 133.1, 132.3, 132.3, 132.1, 131.8, 131.7, 131.1, 128.3, 97.0, 77.1, 74.0, 73.8, 73.5, 69.0, 68.7, 67.7, 67.5, 66.1, 64.9, 64.4, 63.2, 57.0, 47.1, 46.2, 44.7, 44.6, 42.3, 41.9, 41.4, 38.4, 35.9, 35.0, 33.1, 30.3, 29.3, 29.0, 26.3, 26.1, 26.0, 18.4, 18.3, 16.8, 12.0 ppm; MALDI-FT: m/z: calcd for $C_{59}H_{101}N_5O_{16}$: 1136.7316; found 1136.730 $[M+H]^+$.

16-(N'-(2-Amino-*N*,*N*,*N*-trimethylethanaminium chloride)-carboxamide)-*N*,*N*-di-(3-aminopropyl)-AmB (34): To a solution of **28** (100 mg, 0.067 mmol) in DMF (2.00 mL) was added 2-amino-*N*,*N*,*N*-trimethylethanaminium chloride (19.0 mg, 0.134 mmol) in H_2O (0.250 mL), 1-hydroxybenzotriazole (18.0 mg, 0.134 mmol), (benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (35.0 mg, 0.067 mmol) and diisopropylethylamine (30.0 μL, 0.134 mmol). After 18 h at room temperature, the solution was concentrated down and the residue was added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2×100 mL). The yellow precipitate was filtered and purified by flash chromatography ($CHCl_3$/MeOH/H_2O 40:8:1). The isolated yellow solid was dissolved in DMSO (5.00 mL) and piperidine (0.200 mL, 2.10 mmol) was added. After 2 h at room temperature, the solution was added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2×100 mL) providing the desired compound **34** as a yellow solid (25.0 mg, 34%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 6.48–6.06 (m, 12H), 6.00–5.90 (m, 1H), 5.43 (dd, J=15, 10 Hz, 1H), 5.21 (brs, 1H), 4.98–4.69 (m, 3H), 4.43–4.35 (m, 1H), 4.26–4.23 (m, 2H), 4.09–3.90 (m, 2H), 3.70–3.40 (m, 7H), 3.15 (brs, 12H), 2.30–2.27 (m, 1H), 2.17 (d, J=6 Hz, 1H), 2.02–1.28 (m, 20H), 1.17 (dd, J=16, 6 Hz, 3H), 1.11 (d, J=6 Hz, 3H), 1.04 (d, J=6 Hz, 3H), 0.92 (d, J=7 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 172.7, 170.5, 136.7, 133.8, 133.7, 133.4, 133.1, 132.3, 132.1, 131.8, 131.1, 128.6, 97.1, 77.1, 74.6, 73.9, 73.7, 73.5, 69.1, 68.8, 68.5, 68.0, 67.6, 66.1, 64.9, 64.0, 61.8, 52.8, 52.7, 47.9, 46.2, 44.6, 42.4, 42.0, 37.7, 35.0, 28.9, 25.0, 18.4, 18.1, 16.9, 12.0 ppm; MS MALDI-FT: m/z: calcd for $C_{58}H_{100}N_5O_{16}$: 1122.7160; found: 1122.7106 $[M]^+$.

16-(N'-(Hexylcarboxamide)-*N*,*N*-di-(3-aminopropyl)-AmB (35): To a solution of **28** (150 mg, 0.100 mmol) in DMF (2.00 mL) was added 1-hexanamine (66.0 μL, 0.500 mmol), 1-hydroxybenzotriazole (27.0 mg, 0.200 mmol), (benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (52.0 mg, 0.100 mmol). After 18 h at room temperature, the solution was concentrated down and the residue was added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2×100 mL). To the yellow solid in DMSO (3.00 mL) was added piperidine (0.200 mL, 2.10 mmol). After 2 h at room temperature, the solution was added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2×100 mL) providing the desired compound **35** as a yellow solid (15.0 mg, 13%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 6.48–5.94 (m, 12H), 5.88–5.81 (m, 1H), 5.46–5.33 (m, 1H), 5.23 (brs, 1H), 4.78–4.58 (m, 4H), 4.37–4.21 (m, 6H), 4.06–3.96 (m, 2H), 3.33 (brs, OH), 3.16–3.05 (m, 5H), 2.96–2.92 (m, 2H), 2.32–2.26 (m, 2H), 2.17 (d, J=6 Hz, 1H), 1.75–1.15 (m, 23H), 1.11 (d, J=6 Hz, 3H), 1.04 (d, J=6 Hz, 3H), 0.91 (d, J=7 Hz, 3H), 0.87 (d, J=5 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 171.7, 170.5, 136.7, 135.4, 133.8, 133.6, 133.1, 132.5, 132.4, 132.1, 131.8, 131.4, 131.3, 128.4, 97.0, 77.1, 74.1, 73.8, 73.4, 73.0, 69.0, 68.7, 67.7, 66.3, 66.1, 65.5, 64.5, 55.7, 45.8, 45.7, 44.7, 44.6, 44.3, 44.1, 42.4, 42.0, 41.9, 38.4, 35.0, 31.0, 29.2, 26.1, 25.8, 22.0, 18.4, 18.0, 16.9, 13.8, 12.0 ppm; MS MALDI-FT: m/z: calcd for $C_{59}H_{100}N_4O_{16}$: 1121.4425; found: 1121.7207 $[M+H]^+$.

16-(N'-(1,2,4-Triazole-1-ethyl-carboxamide)-*N*,*N*-di-(3-aminopropyl)-AmB (36): To a solution of **28** (330 mg, 0.223 mmol) in DMF (2.00 mL) was added 1*H*-1,2,4-triazole-1-ethanamide monohydrochloride (50.0 mg, 0.450 mmol), 1-hydroxybenzotriazole (60.0 mg, 0.450 mmol), (benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (60.0 mg, 0.223 mmol) and diisopropylethylamine (0.100 mL, 0.500 mmol). After 18 h at room temperature, the solution was concentrated down and the residue was added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2×100 mL). The yellow precipitate was filtered and purified by flash chromatography ($CHCl_3$/MeOH/H_2O 40:8:1). The isolated yellow solid was dissolved in DMSO (5.00 mL) and piperidine (0.200 mL, 2.10 mmol) was added. After 2 h at room temperature, the solution was added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2×100 mL) providing the desired compound **36** as a yellow solid (51.0 mg, 20%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.48 (s, 1H), 8.20 (brs, 1H), 7.96 (s, 1H), 6.48–6.06 (m, 12H), 5.96–5.91 (m, 1H), 5.43 (dd, J=15, 10 Hz, 1H), 5.22 (brs, 1H), 4.53–3.90 (m, 15H), 3.52–3.41 (m, 5H), 3.11–3.07 (m, 2H), 2.92–2.73 (m, 4H), 2.29–2.73 (m, 2H), 2.17 (d, J=6 Hz, 1H), 1.89–1.26 (m, 21H), 1.17 (dd, J=16, 6 Hz, 3H), 1.11 (d, J=6 Hz, 3H), 1.04 (d, J=6 Hz, 3H), 0.91 ppm (d, J=7 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 172.5, 172.4, 170.5, 151.2, 144.3, 136.7, 136.6, 133.8, 133.6, 133.3, 133.1, 132.4, 132.2, 132.1, 131.8, 131.2, 128.4, 97.0, 77.1, 74.2, 73.8, 73.5, 73.2, 70.6, 69.0, 68.7, 67.7, 67.6, 66.1, 65.0, 64.8, 62.7, 62.5, 57.0, 48.0, 47.6, 46.1, 44.7, 44.4, 42.4, 41.9, 38.7, 35.0, 29.0, 18.4, 18.3, 18.1, 16.9, 12.0 ppm; MALDI-FT: m/z: calcd for $C_{57}H_{93}N_7O_{16}$: 1132.3856; found: 1132.6752 $[M+H]^+$.

***N*,*N*-Di-(3-aminopropyl)-AmB methyl ester (37)**: To a solution of *N*,*N*-di-(3-aminopropyl)-AmB (**3**) (150 mg, 0.140 mmol) in MeOH (10.0 mL) was added a 2M solution of trimethylsilyldiazomethane in diethyl ether (0.700 mL, 14.0 mmol). After 3 h at room temperature, the solution was concentrated down to a volume of 1.00 mL and then added dropwise to diethyl ether (250 mL). The yellow precipitate was filtered and washed with diethyl ether (2×100 mL) providing the desired compound **37** as a yellow solid (90.0 mg, 59%). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ =

6.45–5.93 (m, 13H), 5.44 (dd, $J=15$, 10 Hz, 1H), 5.34 (brs, 1H), 5.22 (brs, 1H), 4.92–4.69 (m, 3H), 4.35–4.18 (m, 3H), 4.06–4.02 (m, 1H), 3.81–3.76 (m, 1H), 3.63 (s, 3H), 3.34 (brs, OH), 3.10–3.04 (m, 3H), 2.82–2.63 (m, 3H), 2.39–2.24 (m, 1H), 2.17 (d, $J=6$ Hz, 1H), 1.89–1.28 (m, 18H), 1.18 (d, $J=6$ Hz, 3H), 1.11 (d, $J=6$ Hz, 3H), 1.04 (d, $J=6$ Hz, 3H), 0.91 ppm (d, $J=7$ Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 173.0, 170.4, 136.7, 134.1, 133.8, 133.1, 132.5, 132.1, 131.7, 131.2, 129.2, 97.2, 96.8, 80.2, 76.2, 75.6, 74.0, 73.1, 69.0, 68.1, 66.2, 65.3, 64.8, 64.0, 52.1, 51.1, 45.6, 44.8, 44.0, 42.1, 41.9, 28.8, 18.4, 18.2, 17.1, 16.9, 12.0 ppm; MALDI-FT: m/z: calcd for $C_{54}H_{89}N_3O_{17}$: 1052.6270; found: 1052.6265 $[M+H]^+$.

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