Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2015, **13**, 7193

5′-Methylene-triazole-substituted-aminoribosyl uridines as MraY inhibitors: synthesis, biological evaluation and molecular modeling†

Mickaël J. Fer,[a] Ahmed Bouhss,[b] Mariana Patrão,[a] Laurent Le Corre,[a] Nicolas Pietrancosta,[a] Ana Amoroso,[c] Bernard Joris,[c] Dominique Mengin-Lecreulx,[b] Sandrine Calvet-Vitale*[a] and Christine Gravier-Pelletier*[a]

Received 8th April 2015,
Accepted 6th May 2015

DOI: 10.1039/c5ob00707k

www.rsc.org/obc

The straightforward synthesis of 5′-methylene-[1,4]-triazole-substituted aminoribosyl uridines is described. Two families of compounds were synthesized from a unique epoxide which was regioselectively opened by acetylide ions (for compounds **II**) or azide ions (for compounds **III**). Sequential diastereoselective glycosylation with a ribosyl fluoride derivative, Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) with various complementary azide and alkyne partners afforded the targeted compounds after final deprotection. The biological activity of the 16 resulting compounds together with that of 14 previously reported compounds **I**, lacking the 5′ methylene group, was evaluated on the MraY transferase activity. Out of the 30 tested compounds, 18 compounds revealed MraY inhibition with IC_{50} ranging from 15 to 150 μM. A molecular modeling study was performed to rationalize the observed structure–activity relationships (SAR), which allowed us to correlate the activity of the most potent compounds with an interaction involving Leu191 of $MraY_{AA}$. The antibacterial activity was also evaluated and seven compounds exhibited a good activity against Gram-positive bacterial pathogens with MIC ranging from 8 to 32 μg mL^{-1}, including the methicillin resistant *Staphylococcus aureus* (MRSA).

Introduction

In view of the increasing resistance[1] of bacteria to commonly used antibiotics and the emergence of multidrug resistant bacterial strains, it is of prime importance to develop antibiotics with new mechanisms of action. Several strategies have been developed for discovering new antibiotics; they notably include the identification of new antibacterial targets by genomics approaches and the screening of synthetic libraries on these targets.[2] However, a main drawback of the latter strategy lies in the limited chemical diversity of the available libraries and in the use of non-validated and isolated bacterial targets.[3] A complementary approach deals with the manipulation of genes encoding enzymes involved in polyketides and non-ribosomal peptides, in order to generate new derivatives.[4] Indeed, many useful antibiotics belong to the latter two biosynthetic classes. New targets are also looked for in already known biological processes such as, for example, folate biosynthesis,[5] fatty acid biosynthesis,[6] peptide deformylase[7] and transfer ribonucleic acid synthetases.[8] The bacterial cell wall is also particularly interesting in this respect. Indeed, the multiple enzymes involved in peptidoglycan biosynthesis,[9] which are essential and specific to the bacterial world, constitute ideal targets in the search for new antibiotics, the inhibition of any step in this pathway provoking an arrest of growth and cell lysis. Thus, β-lactams and lipoglycopeptides are well-known antibiotics which interfere with the late polymerization steps of peptidoglycan biosynthesis. However, the ever increasing number of resistance mechanisms developed or acquired by pathogens towards these antibacterial agents[10] forces us to focus on upstream biosynthetic steps as potential alternative drug targets. For several years, our group focused on the MraY transferase, an integral membrane protein that is not targeted by any drug in clinical use so far, a major advantage expected to delay the emergence of resistance. The 3D structure of MraY

[a]*Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, UMR 8601 CNRS, Université Paris Descartes, Sorbonne Paris Cité, CICB-Paris (Centre Interdisciplinaire Chimie Biologie-Paris), 45 rue des Saints Pères, 75270 Paris 06, France. E-mail: christine.gravier-pelletier@parisdescartes.fr, sandrine.calvet-vitale@parisdescartes.fr*

[b]*Institute for Integrative Biology of the Cell (I2BC), CNRS, Université Paris Sud, CEA, F-91405 Orsay, France*

[c]*Unité de Physiologie et Génétique Bactériennes, Centre d'Ingénierie des Protéines, Département des Sciences de la Vie, Université de Liège, Sart Tilman, B4000 - Liège 1-Belgique, Belgium*

†Electronic supplementary information (ESI) available: (1) Numbering system, (2) ^{1}H and ^{13}C NMR spectra of all new compounds, (3) HPLC purity of previously reported compounds **27a–n**. See DOI: 10.1039/c5ob00707k

was unknown until recently, due principally to its transmembrane nature. Nevertheless, the challenge has recently been addressed and the 3D crystal structure of MraY from *Aquifex aeolicus* ($MraY_{AA}$) has been determined,[11] confirming key structural features that had been previously identified.[12,13] This enzyme, which catalyzes the first membrane-associated step of peptidoglycan biosynthesis, has been demonstrated to be essential[14] and is ubiquitous in the bacterial kingdom. It transfers the phospho-*N*-acetylmuramoyl-pentapeptide (P-Mur*N*Ac-pentapeptide) moiety from the cytoplasmic precursor UDP-Mur*N*Ac-pentapeptide to the membrane lipid acceptor undecaprenyl-phosphate (C_{55}-P), generating C_{55}-pyrophosphoryl-Mur*N*Ac-pentapeptide (lipid I) and uridine monophosphate (UMP) (Fig. 1).[12]

In addition to a few non-nucleosidic compounds recently described,[15] several families of natural nucleoside antibiotics such as FR-900493,[16] liposidomycins,[17] caprazamycins[18] and muraymycins[19] (Fig. 2) have been identified as MraY inhibitors and display interesting antibacterial activities.[20] Elegant synthetic approaches toward these compounds have been reported.[21,22] The common aminoribosyl-*O*-uridine scaffold shared by the natural nucleoside inhibitors has been proven to be essential for biological activity.[23]

Based on this aminoribosyl-*O*-uridine frame, our goal was to develop powerful MraY inhibitors, displaying simplified structure as compared to that of natural inhibitors and endowed with antibacterial activity.

We report here the diversity-oriented synthesis of new MraY inhibitors (Fig. 3), containing either a *C*-triazole (compounds **II**) or an *N*-triazole (compounds **III**). Both families exhibit a supplementary methylene group between the aminoribosyl uridine scaffold and the triazole linker as compared to the 5′-triazole-substituted aminoribosyl uridines (compounds **I**) we previously described.[24] The enhanced flexibility of compounds **II** and **III** was expected to improve the positioning of the resulting inhibitors within the active site of MraY and to result in a better inhibitory activity.[25] Identical R groups were used in both series allowing a comparison of the respective impacts of *C*- and *N*-triazole linkers. The *in vitro* and *in cellulo* biological activity of compounds **I**, **II** and **III** was evaluated and a molecular modeling study was performed to rationalize the obtained *in vitro* activities.

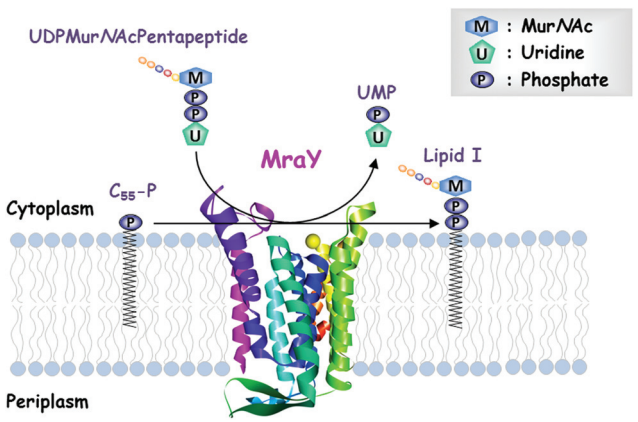


Fig. 1 Reaction catalyzed by the bacterial transferase MraY. The protein is represented according to PDB code 4J72 of $MraY_{AA}$, including the catalytic magnesium (yellow ball).

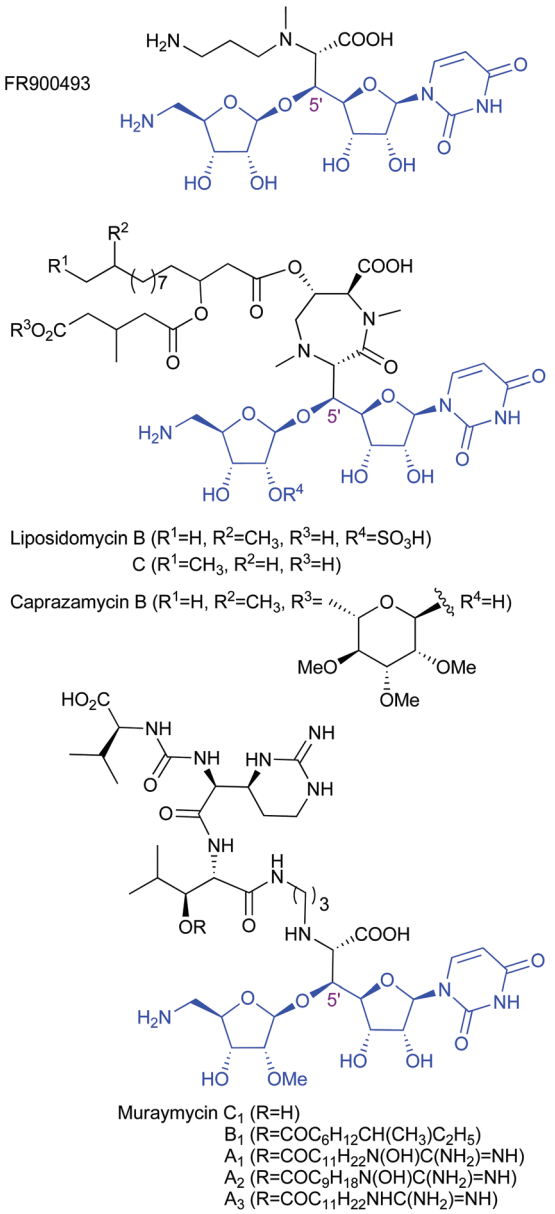


Fig. 2 MraY natural inhibitors.

Results and discussion

Chemical synthesis

The retrosynthesis we designed (Fig. 4) towards the targeted inhibitors **II** and **III** relies on the Cu(I)-catalyzed azide–alkyne cycloaddition[26] (CuAAC) involving individual azides or alkynes and complementary 5′-alkynylmethylenyl-aminoribosyl uridine

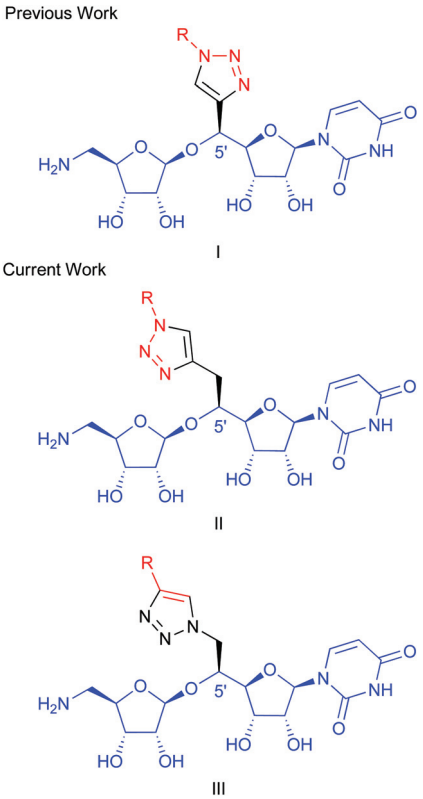


Fig. 3 Overall structure of targeted inhibitors.

A or 5′-azidomethylenyl-aminoribosyl uridine **B**, respectively. These building blocks **A** and **B** could result from *O*-glycosylation of the corresponding homopropargylic alcohol **C** or azidomethyl alcohol **D** by a known anomerically activated and amine protected 5-amino-5-deoxy-D-ribofuranoside. Both alcohols **C** and **D** could come from a unique epoxide **E**.

We recently described the multi-gram scale synthesis of epoxide **1** and its regioselective opening by various carbo- and hetero-nucleophiles.[27] In particular, nucleophilic opening of the epoxide **1** by lithium trimethylsilylacetylide in the presence of $BF_3{\cdot}Et_2O$ furnished the corresponding trimethylsilyl homopropargylic alcohol[27] that was deprotected in the presence of potassium carbonate in methanol to give **2** in 71% overall yield (Scheme 1). In a complementary manner, opening of the epoxide **1** by sodium azide in the presence of ammonium chloride afforded the azido alcohol **3**[27] in 85% yield. Both alcohols **2** and **3** were next subjected to glycosylation with the known amino ribose derivative **4**,[24] activated as a fluoride in anomeric position and protected at $C_{5'}$ as a phthalimido group to prevent any side reaction during further CuAAC reaction. This reaction was carried out in the presence of boron trifluoride etherate[28] at −78 °C in CH_2Cl_2 to provide the phthalimidoribosyl uridine derivatives **5** and **6** in 61% and 41% isolated yields, with a good β/α diastereoselectivity (80/20 and 85/15, respectively) thanks to the isopentylidene protective group of the diol, hindering the α face of the ribosyl donor. Assignment

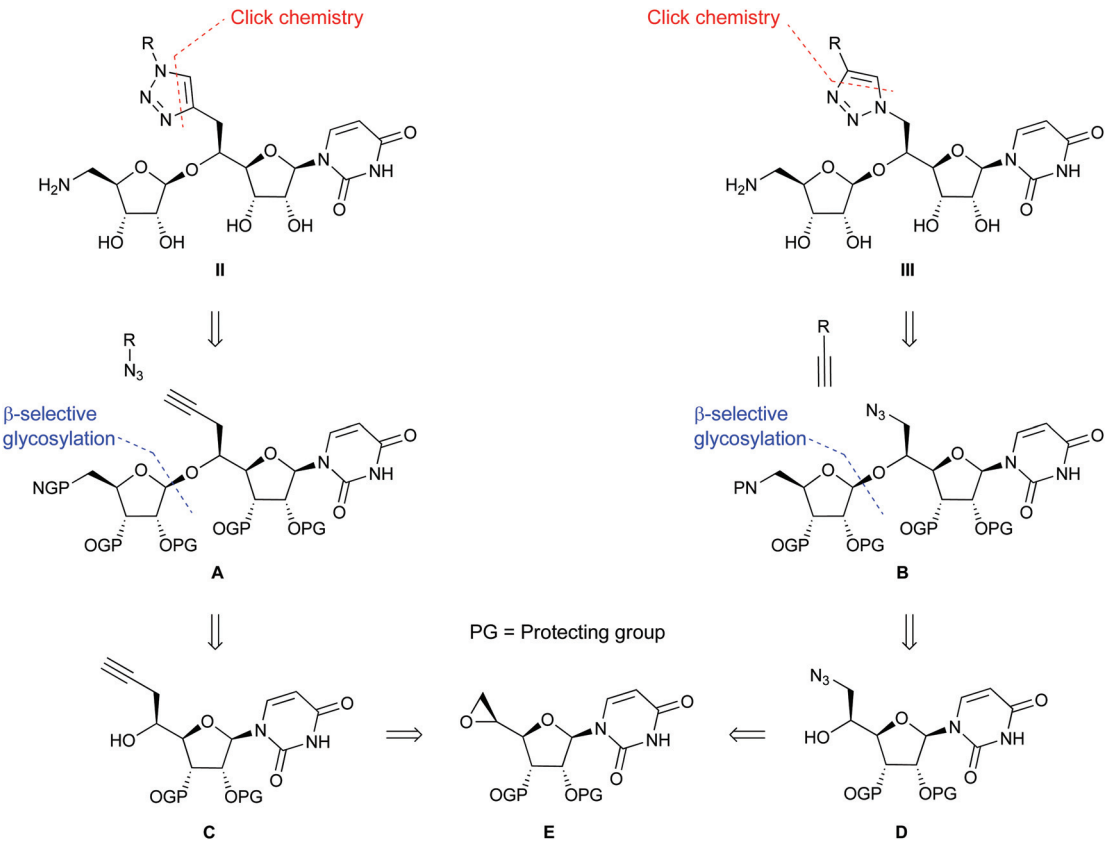
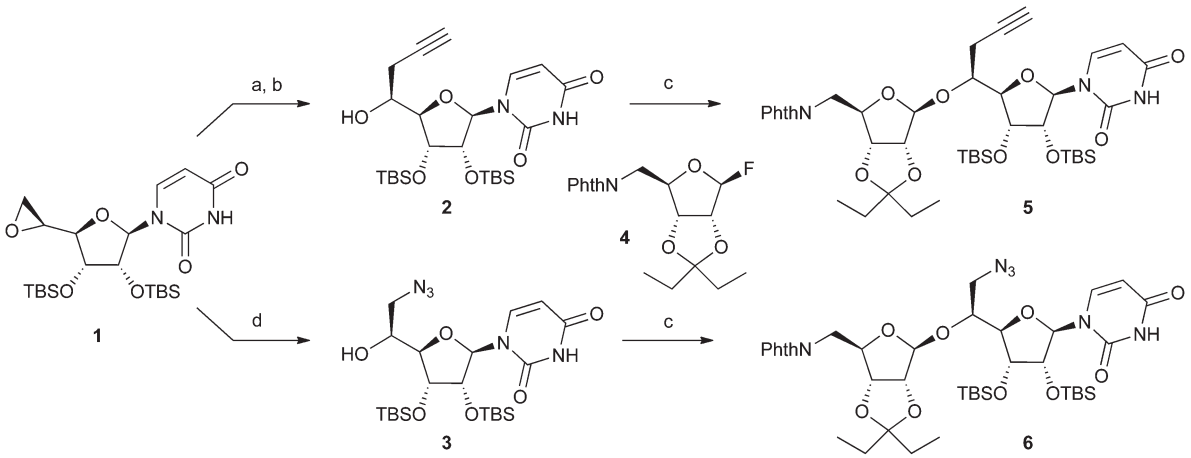


Fig. 4 Retrosynthetic analysis.



Scheme 1 Synthesis of alkyne **5** and azide **6**. Reagents and conditions: (a) trimethylsilylacetylene, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C to −10 °C, 16 h, 77%; (b) K_2CO_3, MeOH, 92%; (c) **4**, $BF_3{\cdot}EtO_2$, M.S. 4 Å, CH_2Cl_2, −78 °C, 81% as a 80/20 β/α mixture, 61% isolated for **5**, 55% as a 85/15 β/α mixture, 41% isolated for **6**; (d) NaN_3, NH_4Cl, DMF, 70 °C, 16 h, 85%.

of anomers for compounds **5** and **6** was made according to distinguishing characteristic ^{1}H NMR signals for $H_{1''}$ (a singlet at 5.24 ppm for the major β anomers **5** and **6** and a doublet at 5.29 and 5.33 ppm ($^3J_{H1''-H2''}$ = 2.5 Hz) for their corresponding minor α anomers, respectively).

With these key intermediates in hand, we next turned to the preparation of the complementary fragments for CuAAC, azido and alkynes building blocks with various structures and polarity (Fig. 4). Thus, apolar aliphatic or aromatic azides and alkynes **7a–b** and **8a–b** and polar hydroxylalkyl azides and alkynes with various chain lengths **7c–d** and **8c–d** were selected. Highly hydrophilic PEG-containing azide and alkyne **7e** and **8e**, prone to enhance water solubility, and phthalimidoalkyl azide and alkyne **7f** and **8f**, as masked primary amines, were also chosen. In addition, a few benzophenone containing azides and alkynes **7g–h**[24] and **8g–h** were included in the series. Indeed, the related compounds **I** (Fig. 3) bearing such a photoactivable group revealed promising inhibition of MraY activity[24] and the benzophenone moiety could further be exploited to promote, upon irradiation, the formation of a covalent linkage with the enzyme. Such an irreversible MraY-inhibitor complex should enhance the stability of the protein and promote its crystallization that would be a major leap for rational drug design of new antibiotics. All these complementary fragments (Fig. 5) were either purchased from commercial sources or synthesized in a few steps from alcohols or bromide derivatives.

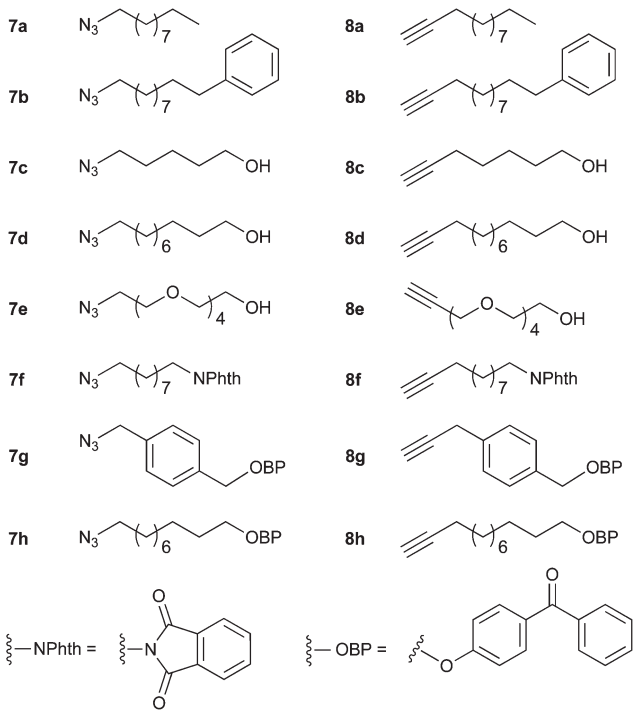
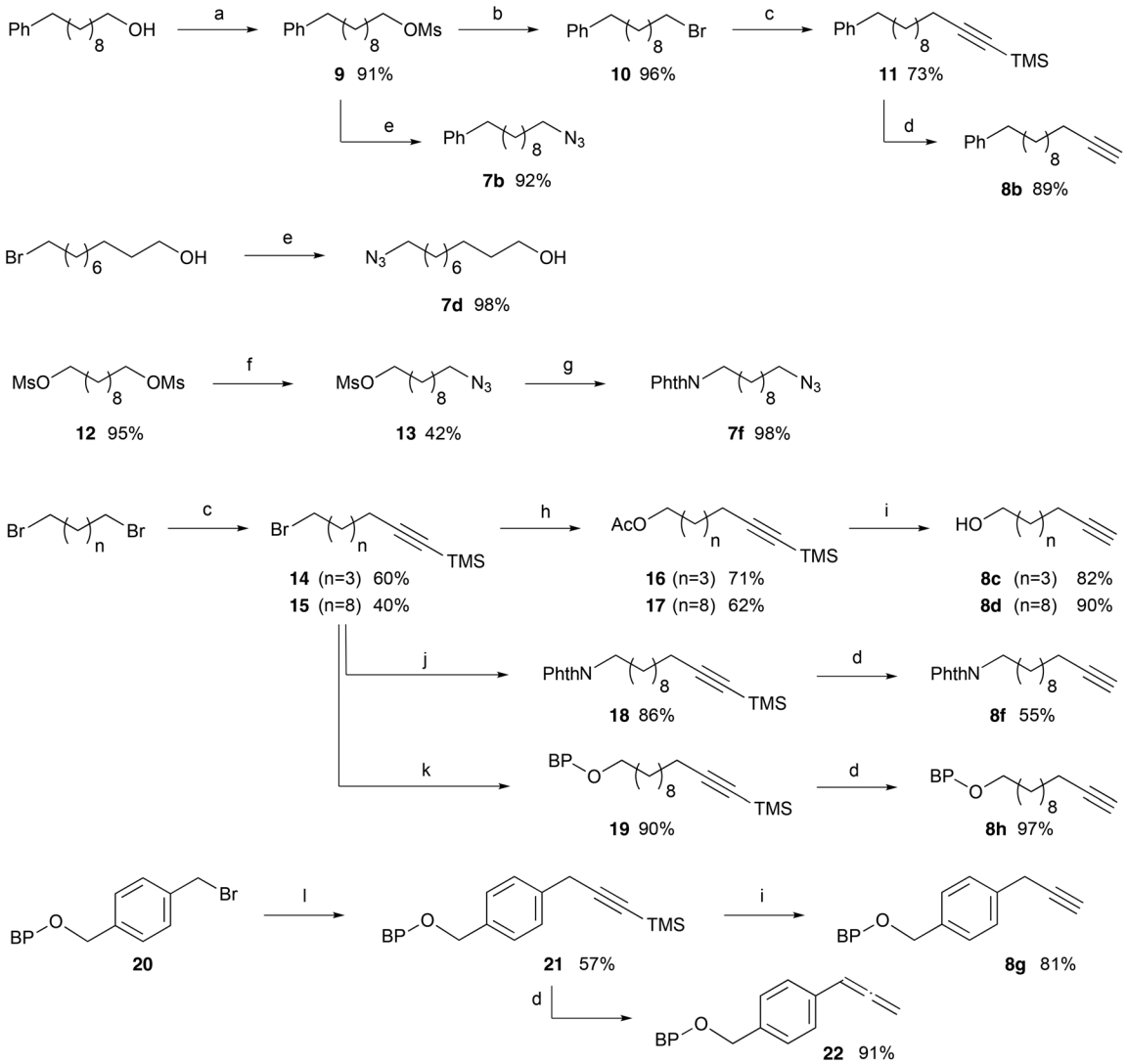


Fig. 5 Structure of complementary azides **7a–h** and alkynes **8a–h** fragments.

The synthesis of azides **7b,d,f** and alkynes **8b–d,f–h** is depicted in Scheme 2. From the mesylate **9**, readily obtained from phenyl decanol in 91% yield, the azide **7b** was prepared by direct nucleophilic substitution by sodium azide, while the nucleophilic substitution of the mesylate by lithium trimethylsilyl acetylide was revealed to be unsuccessful. Alkyne introduction required the intermediate formation of the corresponding bromide **10** followed by its substitution by lithium acetylide leading to **11** and subsequent TMS deprotection to provide the alkyne **8b** in 62% overall yield from **9**. The azide **7d** resulted from bromodecanol by sodium azide substitution. The phthalimidoalkyl azide **7f** resulted from dimesylate **12**[29] followed by nucleophilic substitution with sodium azide to give **13** and subsequent phthalimide introduction. The alkynes **8c,d,f,h** were obtained from the corresponding dibromoalkane through substitution with lithium

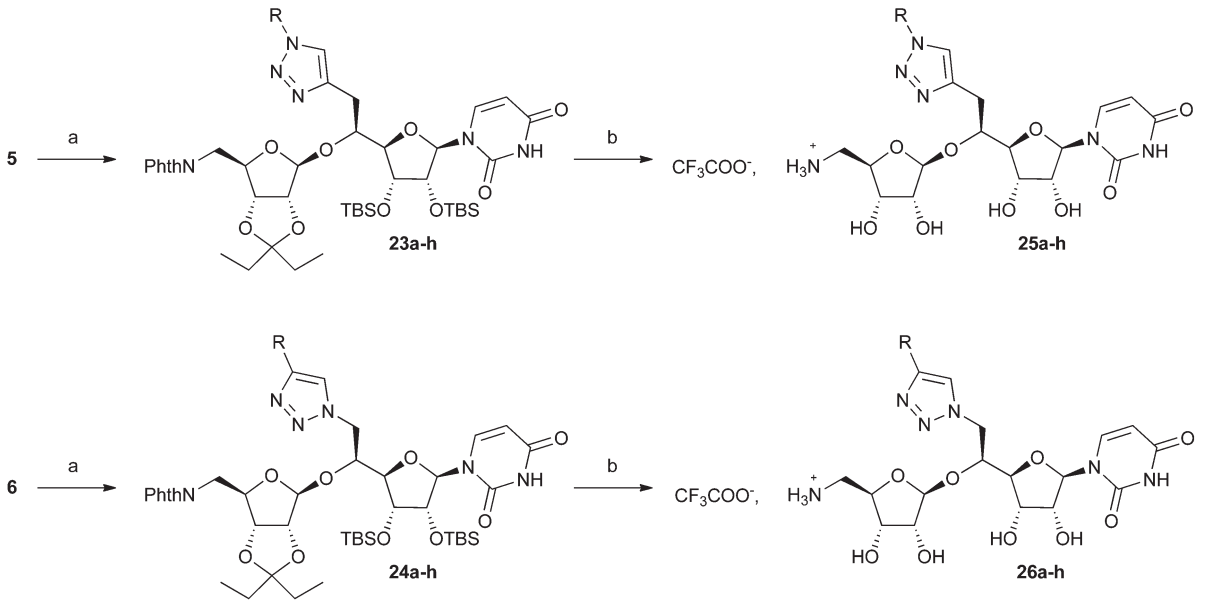


Scheme 2 Synthesis of azides **7b**, **7d**, **7f** and alkynes **8b–d**, **8f–h**. Reagents and conditions: (a) MsCl, TEA, DCM; (b) LiBr, acetone, reflux, 1.5 h; (c) TMS-acetylene, BuLi, HMPA, THF, −78 °C, r.t., 16 h; (d) TBAF, THF, r.t., 1 h; (e) NaN_3, NaI, DMF, 75 °C, 18 h; (f) NaN_3, CH_3CN, reflux, 18 h; (g) PhthNK, DMF, 80 °C, 18 h; (h) AcOK, DMF, 80 °C, 16 h; (i) K_2CO_3, MeOH, H_2O, r.t., 6 h; (j) PhthNK, DMF, r.t., 16 h; (k) 4-HO-BP, K_2CO_3, DMF, r.t., 16 h; (l) CuI, TBAI, K_2CO_3, TMS-acetylene, CH_3CN.

trimethylsilyl acetylide which intermediately gave **14** and **15**. The bromo derivative **14** was substituted by potassium acetate to afford **16** that was deprotected by potassium carbonate in methanol to furnish the alcohol **8c**. In the same manner, the bromo derivative **15** led to the alcohol **8d** through the acetate **17**. The phthalimido alkyne **8f** and the benzophenone **8h** were respectively prepared by nucleophilic substitution of the bromo derivative **15** with phthalimide potassium salt giving **18** and by 4-hydroxy-benzophenone in the presence of potassium carbonate leading to **19**, followed by TBAF deprotection. Attempts to prepare the alkyne **21** from the bromo derivative **20**[24] by nucleophilic substitution with sodium acetylide or lithium trimethylsilylacetylide resulted either in recovery of unchanged starting material or complete degradation. Finally, the alkyne **8g** was synthesized from bromide **20**, by copper-promoted coupling[30] with trimethylsilyl acetylene leading to alkyne **21**, followed by TMS deprotection in the presence of potassium carbonate in methanol. It is noteworthy that TBAF deprotection exclusively led to the formation of allene **22**.

We next turned to the synthesis of the triazole-containing targeted compounds **25a–h** and **26a–h** (Scheme 3).

Thus, azido and alkyne building blocks **5** and **6** were subjected to CuAAC conditions with their complementary partner **7a–h** and **8a–h**, respectively. The reaction was carried out in the presence of catalytic copper(I) *in situ* generated from copper sulphate and sodium ascorbate[26] in a 3/1 *tert*-BuOH/H_2O mixture with diisopropylethylamine as a base and afforded the expected *C*- and *N*-triazoles **23a–h** and **24a–h** in yields ranging from 43 to 68% (Table 1). Amine and alcohols deprotection were successively performed by methylamine in



Scheme 3 Synthesis of targeted compounds **25a–h** and **26a–h**. Reagents and conditions: (a) **7a–h** (R-N_3) or **8a–h** (R-≡), DIPEA, $CuSO_4{\cdot}5H_2O$ (0.1 equiv.), sodium ascorbate (0.3 equiv.), *tert*-BuOH/H_2O 3 : 1, r.t., 16 h; (b) CH_3NH_2, MeOH, r.t., 5 h and then TFA/H_2O 3 : 1, 0 °C, 10 min, and r.t., 18 h.

Table 1 Isolated yield of CuAAC and deprotection reactions for compounds **23–26**

	Yield (%)			Yield (%)	
Azide	**23**	**25**	Alkyne	**24**	**26**
7a	**a:** 58	**a:** 62	**8a**	**a:** 55	**a:** 56
7b	**b:** 57	**b:** 53	**8b**	**b:** 60	**b:** 52
7c	**c:** 56	**c:** 38	**8c**	**c:** 53	**c:** 34
7d	**d:** 59	**d:** 65	**8d**	**d:** 66	**d:** 42
7e	**e:** 43	**e:** 52	**8e**	**e:** 44	**e:** 69
7f	**f:** 61	**f:** 41	**8f**	**f:** 68	**f:** 45
7g	**g:** 67	**g:** 64	**8g**	**g:** 67	**g:** 72
7h	**h:** 57	**h:** 69	**8h**	**h:** 58	**h:** 64

methanol and acidic hydrolysis to give the targeted inhibitors **25a–h** and **26a–h** that were purified by preparative C-18 HPLC and isolated as their TFA salts in 34–72% yield over two steps. No trace of degradation product resulting from acidic cleavage of the glycosidic bond was detected.

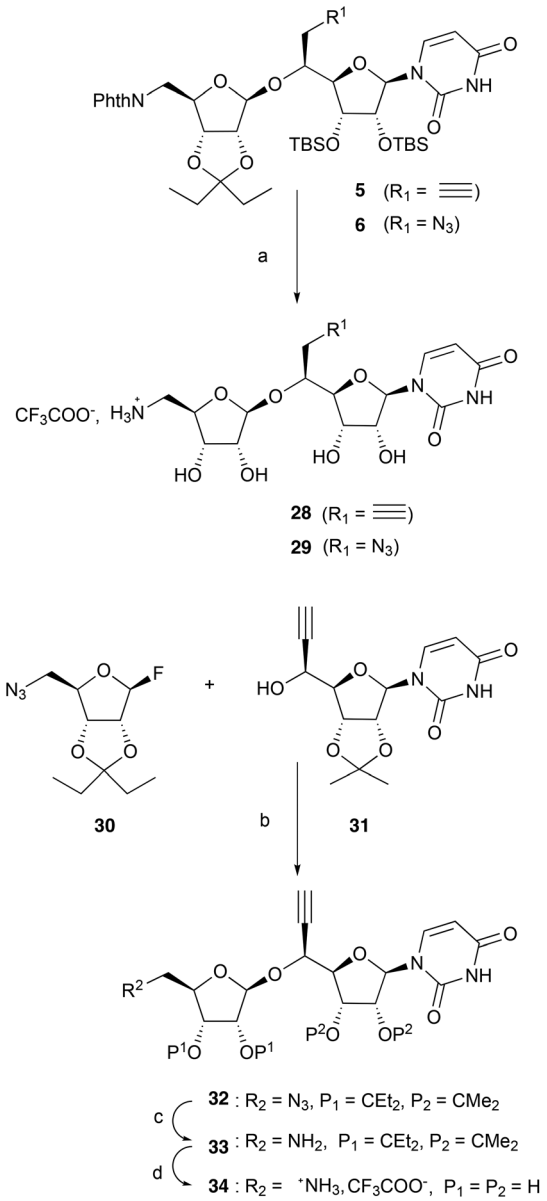
To perform a SAR study of these triazole-containing compounds as inhibitors of the MraY activity, biological activity of the *C*- and *N*-triazoles **25a–h** and **26a–h** (compounds **II** and **III**) was evaluated (Table 2) and compared to that of the previously described compounds **I**[24] (Table 3) displaying a triazole linker directly connected on the aminoribosyl uridine scaffold. The structures of the related compounds **27a–n** are depicted in Fig. 6.

Furthermore, to assess the impact of the polarity and the structure of the triazole substituent on the inhibitory activity, the unprotected alkynes **28** and **34** and azide **29** were synthesized as reference compounds (Scheme 4). On the one hand, alkyne **28** and azide **29** were readily prepared by amine and alcohols deprotection of alkyne **5** and azide **6** according to the same conditions as those described above for compounds **25** and **26**. On the other hand, the alkyne **34** was obtained in three steps involving glycosylation of the propargylic alcohol **31**[31] with 5-azidoribosyl fluoride **30**[28] as a ribosyl donor to give **32**, azide reduction under Staudinger conditions leading to **33** and acidic hydrolysis of ketal protective groups.

Biological evaluation

The inhibitory activity of compounds **I** (**27a–n**), **II** (**25a–h**), **III** (**26a–h**) and their unprotected precursors (**34**, **28**, **29**) was evaluated on purified MraY transferase. Concerning compounds **I** (Table 2), the introduction on the triazole of a short alkyl chain bearing a polar group such as a hydroxyl (**27e,f**), an amino group (**27g**), an imidazolyl (**27i**), a hindered cycloheptyl moiety (**27b**) or a more complex piperazinopyridine chain (**27j**) was revealed to be detrimental to the inhibitory activity (IC_{50} > 1000 μM), as compared to that of the parent compound **34** (IC_{50} = 100 μM). Indeed, in this series the best inhibitors were those containing either a benzophenone moiety (**27k–n**) or an alkyl chain (**27a,h**) with IC_{50} ranging from 50 to 150 μM, showing that a hydrophobic chain of sufficient length permitted us to maintain the enzyme inhibition in the 100 μM range. As exemplified for compounds **27c** and **27d**, a shorter or a more rigid hydrophobic R group led to weaker activities (IC_{50} of 250 and 400 μM, respectively).

Interestingly, the mode of inhibition was investigated and demonstrated to be competitive towards the nucleotide sub-

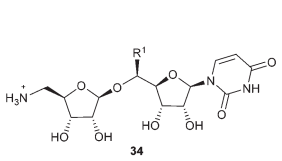


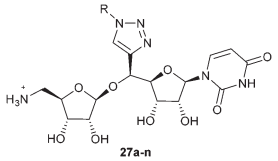
Scheme 4 Synthesis of reference compounds **28**, **29** and **34**. Reagents and conditions: (a) CH_3NH_2, MeOH, 5 h, r.t. and then TFA/H_2O: 3/1, 0 °C, 10 min, and r.t., 18 h, 31% for **28**, 52% for **29**; (b) $BF_3{\cdot}Et_2O$, M.S., CH_2Cl_2, −78 °C, 75% as a 13/1 β/α mixture, 45% isolated for **32**; (c) PPh_3, THF/H_2O: 6/1, 86%; (d) TFA/H_2O: 3/1, 0 °C, 10 min and then r.t., 1.5 h, 99%.

strate as exemplified for compound **27k** (Fig. 7) with a K_i value of 80 μM.

The *in vitro* activity of compounds **II** and **III** is depicted in Table 3. Commercially available tunicamycin from *Streptomyces* sp. was used as a positive control in the test and resulted in an IC_{50} value equal to 0.012 μM. From a general point of view, the inhibitory activity of compounds **II** and **III** on the MraY transferase was better than that of compounds **I**. Furthermore, the general tendency showed that the *C*-triazole-containing compounds **II** were more potent than the corresponding *N*-triazole-containing compounds **III**. The inhibitors

Table 2 Inhibitory activity of compounds **I** (**27a–n**) and **34** against MraY





Compound	R^1	IC_{50} [a] (μM)
34	-≡	100
Compounds I	**R**	
27a		140
27b		>1000
27c		250
27d		400
27e	OH	>1000
27f	OH	>1000
27g	NH_2	>1000
27h		150
27i		>1000
27j		>1000
27k	Bp	100, 125[b]
27l	Bp	100
27m	Bp	125
27n	Bp	50, 75[b]

[a] The activities of the compounds were tested against purified MraY from *Bacillus subtilis*. The assay was performed in a reaction mixture of 10 μL containing, in final concentrations, 100 mM Tris-HCl, pH 7.5, 40 mM $MgCl_2$, 1.1 mM C_{55}-P, 250 mM NaCl, 0.25 mM UDP-Mur*N*Ac-[^{14}C]pentapeptide (337 Bq), and 8.4 mM *N*-lauroyl sarcosine. The reaction was initiated by the addition of MraY enzyme (50 ng), and the mixture was incubated for 30 min at 37 °C under shaking. The reaction was stopped by heating at 100 °C for 1 min and the radiolabeled substrate (UDP-Mur*N*Ac-pentapeptide) and reaction product (lipid I) were separated by TLC on silica gel plates. The radioactive spots were located and quantified with a radioactivity scanner. Data represent the mean of independent triplicate determinations. [b] The activities were tested against purified MraY from *Aquifex aeolicus*. Bp = benzophenone.

bearing the longest alkyl chains (**25d**, **26d**) were more potent than their shorter homologs (**25c**, **26c**). For a same length, the compounds containing a hydroxyl group (**25d**, **26d**) were more active than those containing an amino group (**25f**, **26f**). In spite of their enhanced hydrosolubility, PEG-containing inhibitors (**25e**, **26e**) appeared to be poorly active. However, the introduction of a long hydrophobic chain on the triazole drastically

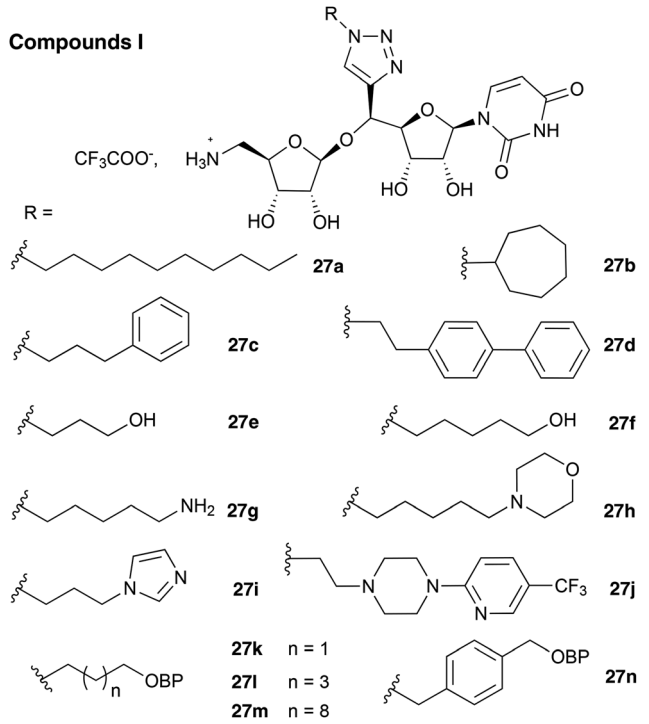


Fig. 6 Structure of compounds **27a–n**.

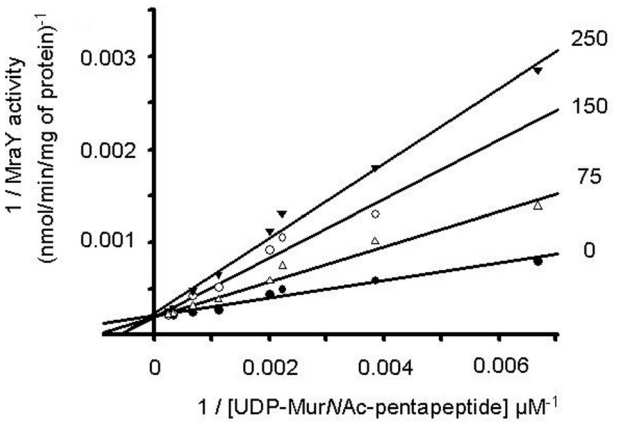
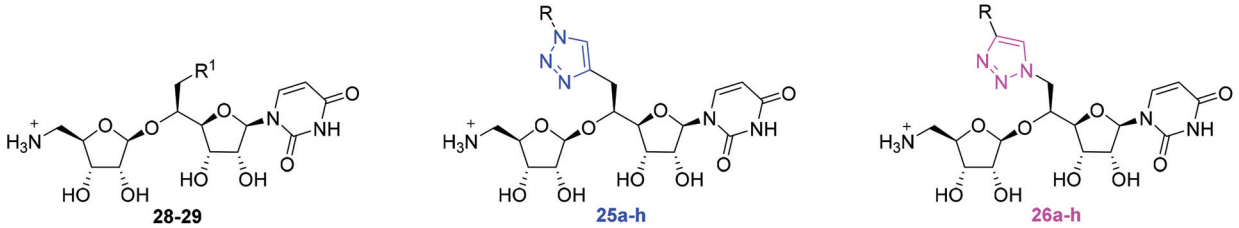


Fig. 7 Analysis of MraY inhibition by compound **27k**. Double reciprocal plot of initial velocity *versus* UDP-Mur*N*Ac-pentapeptide. Compound **27k** concentration was varied in the range 0–250 μM as indicated on the right (μM).

improved the inhibitory activity, yielding IC_{50} ranging from 15 to 25 μM for compounds **II** (**25a,b,g,h**) and from 25 to 100 μM for compounds **III** (**26a,b,g,h**). For these compounds, in both series, the introduction of a substituted *C* or *N*-triazole improved by up

Table 3 Inhibitory activity of compounds **II** (**25a–h**), **III** (**26a–h**), **28** and **29** against MraY



R^1	Compound	IC_{50} [a] (μM)	Compound	IC_{50} [a] (μM)
-≡	**28**	150	—	—
$-N_3$	—	—	**29**	>1000

R	Compounds **II**		Compounds **III**	
	25a	15	**26a**	35
Ph	**25b**	20	**26b**	30
OH	**25c**	400	**26c**	400
OH	**25d**	40	**26d**	75
OH	**25e**	750	—	—
OH	—	—	**26e**	450
NH_2	**25f**	200	**26f**	250
Bp	**25g**	20	**26g**	100
Bp	**25h**	25	**26h**	25

[a] The activities of the compounds were tested against purified MraY from *Aquifex aeolicus*. The assay was performed as described in Table 2. Data represent the mean of independent triplicate determinations. Bp = benzophenone.

to 10–40 fold the inhibitory potency as compared to that of the parent compounds (**28**, **29**). The promising results obtained for the inhibitors **25g,h** and **26g,h** demonstrated a tolerance for rather bulky groups such as benzophenone moieties.

The antibacterial activity of compounds **I**, **II**, and **III** was evaluated and the data are shown in Table 4. Several Gram-negative (*E. coli* ATCC 8730, *C. freundii* ATCC8090 and *P. aeruginosa* ATCC 27853) and Gram-positive pathogenic bacterial strains (*S. aureus* ATCC 25923, *E. faecium* ATCC 19434) were selected, including a methicillin resistant strain (*S. aureus* MRSA ATCC 43300). Piperacillin and vancomycin were used as the positive control in the tests. Interestingly, 9 out of the 33 tested compounds revealed antibacterial activity with minimum inhibitory concentration (MIC) values of 8–64 μg mL^{-1} on the three Gram-positive pathogens and on the Gram-negative *P. aeruginosa.* The best antibacterial activities were observed for compounds **26h** and **27m** bearing a hydrophobic decyloxybenzophenone R group with IC_{50} values of 25 and 100 μM, respectively (Tables 2 and 3). These promising antibacterial activities were obtained against *S. aureus* MRSA and the MIC values were 8 μg mL^{-1}. Despite the simplicity of the 5′ substituent borne by the aminoribosyl uridine scaffold, it is noteworthy that these antibacterial activities are comparable with that reported for muraymycins, natural MraY inhibitors with a much more complex structure.

Molecular modeling

Our SAR study revealed that a hydrophobic moiety was crucial for the inhibitory activity. To better understand how the synthesized compounds interact with the MraY protein and to evaluate the role of this hydrophobic counterpart, we took advantage that the X-ray crystal structure of MraY from *Aquifex aeolicus* ($MraY_{AA}$, PDB code: 4J72) had been recently solved,[11] paving the way for molecular docking studies. This structure revealed an active site opened towards the cytoplasm. It comprises a magnesium cation, 10 trans-membrane helices (TM1–10) and a deep hydrophobic pocket localized in the trans-membrane domain and surrounded by TM5 and TM9 (Fig. 8). We thus anticipated that this hydrophobic groove could play a major role in the interaction of our compounds, through their hydrophobic tail, within the enzyme active site.

After the preparation of both protein and ligands (compounds **25–27**), we performed a blind docking study of all compounds in the putative ligand binding site centered on the magnesium ion (*i.e.* Mg^{2+}, and key residues characterized by Bouhss *et al.*[13] such as Asp117 and Asp118). In parallel, all compounds were divided into three batches according to their *in vitro* potency: active compounds with an IC_{50} below or equal to 25 μM (compounds **25a,b,g,h** and **26h**), weakly active compounds which have no activity at 250 μM (compounds **25c,e**, **26c,e** and **27b,d–g,i,j**) and an intermediate set (compounds **25d,f**, **26a,b,d,f,g** and **27a,c,h,k–n**) with IC_{50} values ranging from 25 to 250 μM. 200 conformers of compounds were generated using the Caesar protocol of Discovery Studio 4.1 software[32] and have been docked using the cDOCKER protocol.[33] Finally, 5840 poses were generated after conformers docking and were analysed based on their interactions with hydrophobic groove residues. In particular, we monitored poses in which compounds bind with the key leucine residue (Leu191)

Table 4 Antibacterial activity of compounds I, II and III

		MIC[a] (μg mL^{-1})					
		Gram −			Gram +		
Compound	R	*Escherichia coli* ATCC 8730	*Citrobacter freundii* ATCC 8090	*Pseudomonas aeruginosa* ATCC 27853	*Staphylococcus aureus* ATCC 25923	*Staphylococcus aureus MRSA* ATCC 43300	*Enterococcus faecium* ATCC 19434
Piperacillin		4	4	8	4	>128	4
Vancomycin		—	—	—	1	1	0.5
27l	$-(CH_2)_5OBP$	>128	>128	>128	>128	**64**	>128
27m	$-(CH_2)_{10}OBP$	>128	>128	>128	**8**	**8**	>128
27n	$-CH_2PhCH_2OBP$	>128	>128	>128	>128	**32**	>128
25a	$-(CH_2)_9CH_3$	>128	>128	>128	**128**	**64**	>128
25b	$-(CH_2)_{10}Ph$	>128	>128	>128	**32**	**16**	64
25g	$-CH_2PhCH_2OBP$	>128	>128	>128	64	**32**	>128
26a	$-(CH_2)_9CH_3$	>128	>128	**128**	**16**	**64**	>128
26b	$-(CH_2)_{10}Ph$	>128	>128	**64**	**64**	**16**	**32**
26h	$-(CH_2)_{10}OBP$	>128	>128	>128	**16**	**8**	**128**

[a] Determination of the antibacterial activity was performed on microtitric plates, in 200 μL (final volume) of Müeller–Hinton broth (MHB), following the EUCAST (European Committee on Antimicrobial Susceptibility testing)/CLSI (Clinical and Laboratory Standard Institute) recommended procedure. Compounds were solubilized in DMSO and then diluted in MHB just before utilization. Inocula were prepared for each strain, resuspending isolated colonies from 18 h cultured plates. Equivalents of 0.5 McFarland turbidity standard (approximately 1×10^8 CFU mL^{-1}) were prepared in saline solution (NaCl 0.085%) and then diluted 200 fold in MHB. MIC values were determined as the lowest dilution of product showing no visual turbidity.

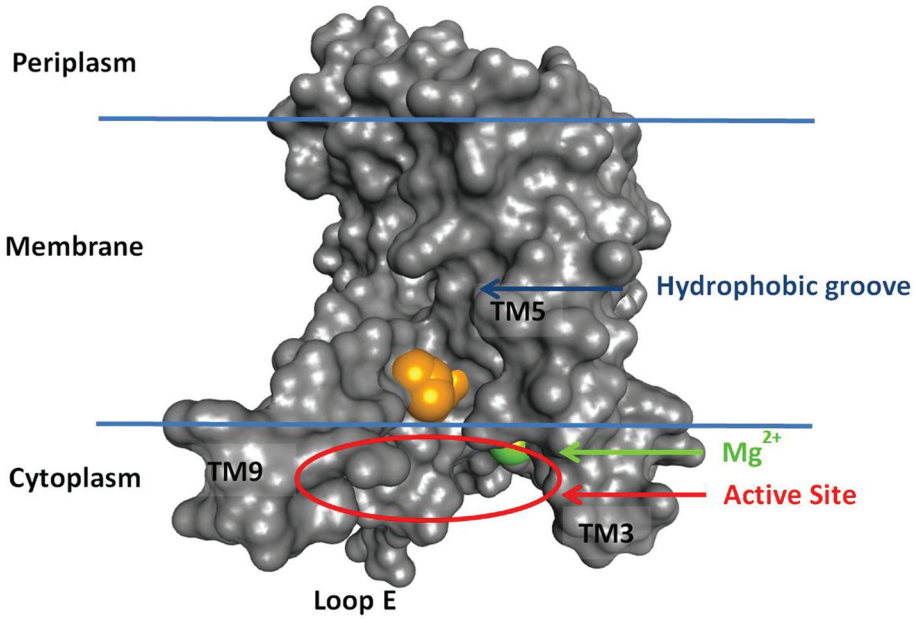


Fig. 8 The active site of $MraY_{AA}$. Molecular surface of MraY was obtained by the superimposition of atom-centered spheres, where the spheres' radii are given by the atomic van der Waals radii. The putative active site (red circle) described by Chung *et al.*[11] is located predominantly in the cytosolic extra-membrane portion and partially into the trans-membrane domain of the protein. The catalytic Mg^{2+} is represented by a green sphere and the hydrophobic groove is shown by a blue arrow. The access of this cleft is monitored by the Leu191 (in yellow).

localized at the entrance of the groove (Fig. 8). Comparison using the scoring function appeared to be inappropriate in our case because of the micromolar activities of our compounds (IC_{50} > 10 μM), so we selected the best interaction energy poses (based on cDOCKER Interaction Energy[33]) for our binding studies. Interestingly, our study revealed that an interaction with Leu191, and consequently with the hydrophobic groove, was sufficient to discriminate between active compounds and others, either intermediate or weakly active, as illustrated by compounds **25a** and **25f** (Fig. 9).

Furthermore, the results of docking experiments showed that active compounds bound according to two modes. These two binding modes are illustrated with compound **25a** (Fig. 10). Both of them revealed a good interaction between the amino-ribosyl part of inhibitor **25a** and the Mg^{2+} cation (green ball, Fig. 10) as well as a varied and complex network of low electrostatic interactions with residues located in the active site and known to be important for substrate recognition,[13] such as Asp265 or Lys121. A major difference between both modes of interaction is the positioning of

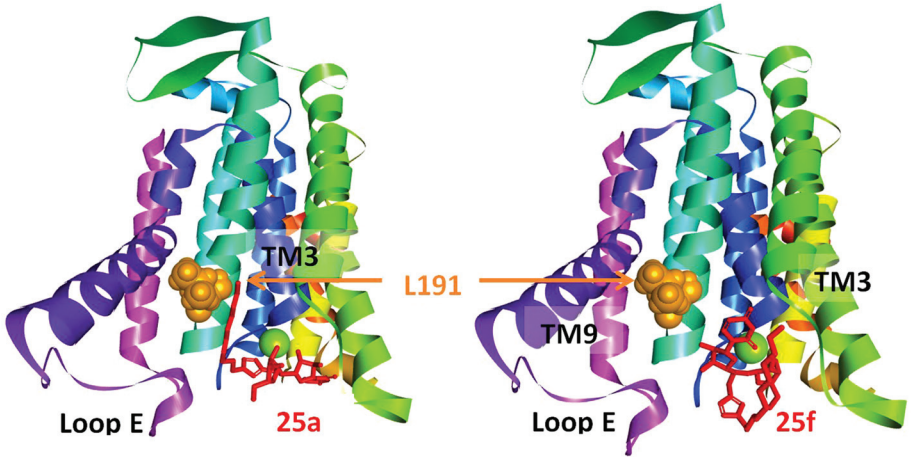


Fig. 9 Interaction of active compound **25a** (IC_{50} = 15 μM) and analog **25f** from the intermediate set (IC_{50} = 200 μM) with the hydrophobic groove. Both docked compounds **25a** and **25f** (red stick) bind to MraY and chelate the magnesium (green ball) *via* a hydroxyl group of the ribose. However, **25a** only interacts with Leu191 (yellow).

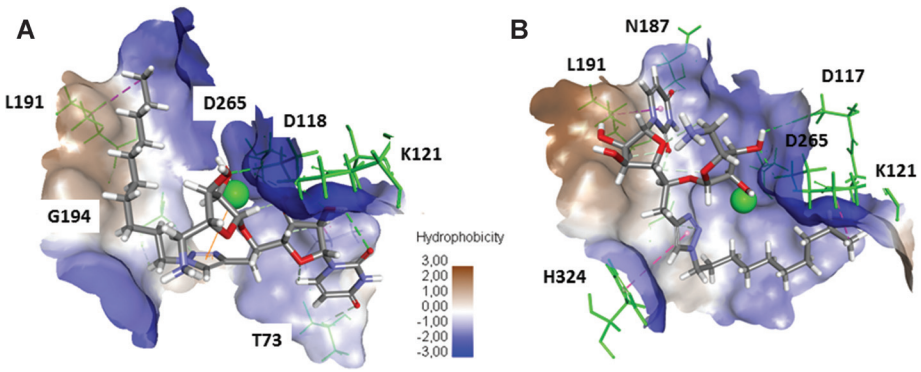


Fig. 10 Docking modes of compound **25a**: mode A (with the hydrophobic tail into the hydrophobic groove, in contact with Leu191) and mode B (with the uracil moiety into the hydrophobic groove, in contact with Leu191).

active compounds within the active site. Indeed, the interaction with the hydrophobic groove can involve the hydrophobic tail of the active inhibitors (Mode A, Fig. 10A), as one can expect, or, more surprisingly, their uracil moiety (Mode B, Fig. 10B).

The effect of introducing a hydrophobic moiety on an aminoribosyl scaffold has already been reported.[34,35] On the one hand, Dini *et al.*[34] reported an interesting SAR study of aminoribosyl uridine derivatives lacking the hydroxyl group at C-3′ and bearing various substituents at C-5′. Their study showed that the introduction of a hydrophobic chain at C-5′ led to a five- to ten-fold increase of *in vitro* potency compared to that of the parent compound. These results are in good agreement with a positioning of the inhibitors according to the mode A suggested by our docking experiments. On the other hand, Matsuda *et al.*[35] reported the synthesis of muraymycins analogues with an elaborate urea-dipeptide motif introduced on an amino acid at the C-5′ position of an aminoribosyl uridine scaffold. Biological evaluation of several analogs differing in the hydrophobic chain introduced on this urea-dipeptide was also reported and showed that the presence of a long hydrophobic chain decreased the inhibitory activity by a factor 30, while the antibacterial activity was improved due to a better membrane penetration. According to the authors, this urea-dipeptide moiety could interact with the carbohydrate recognition domain in the cytoplasmic loop 5, while the aminoribosyl moiety could interact with the vicinal Asp located on the cytoplasmic loop 2, close to the magnesium cation. The resulting positioning, locating the uracil moiety next to the hydrophobic groove, would be in good agreement with our binding mode B. Thus, the two modes of binding revealed by our docking study could explain the contrasting conclusions of the SAR reported by Dini[34] and Matsuda.[35]

Conclusion

We report the synthesis of 16 inhibitors of the bacterial transferase MraY displaying a 5′-methylene-[1,4]-triazole-substituted aminoribosyl uridine structure from a conveniently protected epoxyuridine derivative. Key steps of the synthesis involved the regioselective opening of this epoxide by acetylide or azide ions followed by a sequential β-selective glycosylation with a ribosyl donor, Cu(I)-catalyzed azide–alkyne cycloaddition with various complementary azide and alkyne partners, to introduce chemical and structural diversity, and deprotection to afford *C*-triazole (compounds **II**) or a *N*-triazole (compounds **III**). The biological activity of the 16 resulting compounds was evaluated *in vitro* on purified MraY and *in cellulo* on different Gram (+) and Gram (−) bacterial strains and was compared to that of 14 previously synthesized compounds lacking the 5′ methylene group (compounds **I**). The latter was revealed to be weakly active on MraY, except those bearing either a benzophenone moiety, for which the IC_{50} ranged from 50 to 125 μM, or a hydrophobic chain with an IC_{50} of about 150 μM. In contrast, all compounds **II** and **III** proved to be inhibitors of the enzymatic activity of MraY, with IC_{50} ranging from 15 to 25 μM for the most potent, showing a meaningful improvement of the inhibitory activity related to the enhanced flexibility of compounds **II** and **III** as compared to that of compounds **I**. A slight superiority of compounds **II** as compared to compounds **III** was observed, revealing the influence of the positioning of the triazole ring within the active site, the mode of inhibition of these inhibitors having been demonstrated to be competitive towards the nucleotide substrate. The introduction of a long hydrophobic chain on the triazole drastically improved the inhibitory activity. A molecular modeling study was performed to rationalize the observed structure–activity relationships (SAR), which allowed us to correlate the activity of the most potent compounds with an interaction involving Leu191 of $MraY_{AA}$ and which was consistent with two possible modes of positioning for the most active inhibitors within the enzymatic active site, with either the hydrophobic chain in the hydrophobic groove or the uracil moiety. The antibacterial activity was also evaluated, and out of the 30 tested compounds, seven of them exhibited a good activity against Gram-positive bacterial pathogens with MIC ranging from 8 to 32 μg mL^{-1}, including methicillin resistant *Staphylococcus aureus* (MRSA).

Experimental

General experimental methods

When needed, reactions were carried out under an argon atmosphere. They were monitored by thin-layer chromatography with precoated silica on aluminium foil. Flash chromatography was performed with silica gel 60 (40–63 μm); the solvent systems are given in v/v. Spectroscopic ^{1}H and ^{13}C NMR, MS and/or analytical data were obtained using chromatographically homogeneous samples. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded in $CDCl_3$ unless otherwise indicated. Chemical shifts (δ) are reported in ppm and coupling constants are given in Hz. For each compound, detailed peak assignments have been made according to COSY, HSQC and HMBC experiments. The numbering of molecules is indicated in the ESI.† Optical rotations were measured with a sodium (589 nm) lamp at 20 °C. Melting points were measured on a hot bench. IR spectra were recorded on an FT-IR spectrophotometer and the wavelengths are reported in cm^{-1}. Purification of tested compounds was achieved by either recrystallization or semi-preparative reverse phase HPLC (column: Cluzeau, C_{18}-stability, 10 μm, 250 mm × 20 mm). Unless otherwise indicated, methods used for purification were: method A: flow rate: 15 mL min^{-1}, H_2O–TFA 0.1%/MeOH (60/40 to 10/90 v/v in 12 min); method B: flow rate: 15 mL min^{-1}, H_2O–TFA 0.1%/MeOH (60/40 for 5 min to 10/90 v/v in 10 min). Purity of tested compounds (>95%) was controlled by analytical reverse phase HPLC (column: Cluzeau, C18-stability, 5 μm, 250 mm × 4.6 mm). Unless otherwise indicated, methods used were: method C: flow rate: 1 mL min^{-1}, H_2O–TFA 0.1%/MeOH (60/40 to 10/90 v/v in 12 min) or method D: flow rate: 1 mL min^{-1}, H_2O–TFA 0.1%/MeOH (60/40 for 5 min to 10/90 v/v in 10 minutes). Products were detected at 254 nm; low resolution mass spectra (LRMS) were recorded with an ion trap mass analyzer under electrospray ionization (ESI) in positive ionization mode detection or atmospheric pressure chemical ionization (APCI). High resolution mass spectra (HRMS) were recorded with a TOF mass analyzer under electrospray ionization (ESI) in positive ionization mode detection, atmospheric pressure chemical ionization or atmospheric pressure photoionization (APPI). For MraY activity, the radioactive spots were located and quantified with a radioactivity scanner (model Multi-Tracemaster LB285).

Chemical synthesis

5′(*S*)-*C*-(Acetylenylmethyl)-2′,3′-di-*O*-(*tert*-butyldimethylsilyl) uridine 2. At −78 °C, to a solution of ethynyltrimethylsilane (2.29 g, 23.35 mmol, 4 equiv.) in dry THF (35 mL) was dropwise added *n*-BuLi (1.9 M in hexane, 12.3 mL, 23.35 mmol, 4 equiv.). The resulting solution was stirred at −78 °C for 1 h. At −78 °C, to this resulting solution were successively added dropwise a solution of epoxide **1** (2.83 g, 5.84 mmol, 1 equiv.) in freshly distilled THF (35 mL) and $BF_3{\cdot}Et_2O$ (2.9 mL, 23.35 mmol, 4 equiv.). The resulting solution was allowed to warm from −78 °C to −10 °C and the mixture was diluted in DCM. Saturated aqueous solution of NH_4Cl was then added (20 mL) and the aqueous phase was extracted with DCM (3 × 40 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane/EtOAc = 8/2 to 7/3) afforded the desired homopropargylic alcohol as a white powder (2.63 g, 77% yield). This compound (2.6 g, 4.46 mmol, 1 equiv.) was then dissolved in methanol (52 mL) and potassium carbonate (3.1 g, 22.3 mmol, 5 equiv.) was added. The mixture was stirred at r.t. for 2.5 h and quenched by addition of saturated aqueous solution of NH_4Cl (30 mL). After removal of volatiles *in vacuo*, the aqueous phase was extracted with EtOAc (5 × 50 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography (cyclohexane/EtOAc 6/4) of the residue afforded alcohol **2** as a white solid (2.1 g, 92% yield): R_f 0.30 (cyclohexane/EtOAc 1/1); mp 198–204 °C; $[\alpha]_D$ −11 (*c* 1.0, CH_2Cl_2); IR (film) 3474br, 2857m, 1693s, 1158w; ^{1}H NMR δ 8.54–8.38 (m, 1H, NH), 7.58 (d, 1H, $J_{H6–H5}$ = 8.5 Hz, H_6), 5.73 (dd, 1H, $J_{H5–H6}$ = 8.5 Hz, $J_{H5–NH}$ = 2.5 Hz, H_5), 5.46 (d, 1H, $J_{H1′–H2′}$ = 6.0 Hz, $H_{1′}$), 4.59 (dd, 1H, $J_{H2′–H1′}$ = 6.0 Hz, $J_{H2′–H3′}$ = 4.0 Hz, $H_{2′}$), 4.18–4.16 (m, 2H, $H_{3′}$, $H_{4′}$), 3.88–3.85 (m, 1H, $H_{5′}$), 3.58–3.47 (br s, 1H, OH), 2.58 (ddd, 1H, $J_{H6′a–H6′b}$ = 16.5 Hz, $J_{H6′a–H5′}$ = 7.5 Hz, $J_{H6′a–H8′}$ = 2.5 Hz, $H_{6′a}$), 2.44 (ddd, 1H, $J_{H6′b–H6′a}$ = 16.5 Hz, $J_{H6′b–H5′}$ = 7.5 Hz, $J_{H6′b–H8′}$ = 2.5 Hz, $H_{6′b}$), 2.08 (t, 1H, $J_{H8′–H6′a}$ = $J_{H8′–H6′b}$ = 2.5 Hz, $H_{8′}$), 0.92 (s, 9H, –C(CH_3)$_3$), 0.87 (s, 9H, –C(CH_3)$_3$), 0.16 (s, 9H, –Si–(CH_3)$_3$), 0.09, 0.06, 0.01 (3s, 12H, –Si–*t*-Bu–(CH_3)$_2$); ^{13}C NMR δ 162.8 (C_4), 150.4 (C_2), 143.4 (C_6), 102.4 (C_5), 94.1 ($C_{1′}$), 86.6 ($C_{4′}$), 80.6 ($C_{7′}$), 73.1, 73.1 ($C_{2′}$, $C_{3′}$), 71.0 ($C_{8′}$), 69.7 ($C_{5′}$), 26.0, 25.9 (–C(CH_3)$_3$), 24.5 ($C_{6′}$), 18.2, 18.1 (–C(CH$_3$)$_3$), −4.3, −4.4, −4.5, −4.8 (–Si–*t*-Bu–(CH_3)$_2$); HRMS ESI^+ calcd for $C_{24}H_{43}N_2O_6Si_2^+$ $(M + H)^+$ 511.2654, found 511.2650.

1″,5″-Dideoxy-2″,3″-*O*-isopentylidene-5″-phthalimido-1″-[2′,3′-*O*-isopropylidene-5′(*S*)-acetylenylmethyl-uridinyl]-β-D-ribofuranose 5. Fluoride 4 (684 mg, 1.96 mmol, 2 equiv.) and alkyne 2 (500 mg, 0.98 mmol, 1 equiv.) were dried together by coevaporation with toluene (3 × 10 mL) and dissolved in DCM (26 mL). The flask was flushed with argon and molecular sieves 4 Å was added (5 g) in one portion. The suspension was stirred at r.t. for 1 h and then cooled to −78 °C. Boron trifluoride diethyletherate (248 μL, 1.96 mmol, 2 equiv.) was added at −78 °C and the reaction medium was stirred at this temperature for 10 min and was then allowed to warm to r.t. for 16 h. The reaction mixture was filtered on a celite pad and the cake was washed with DCM (50 mL). The reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution (50 mL) and the aqueous phase was extracted with DCM (5 × 60 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting white foam was purified by flash chromatography (toluene/acetone 95/5) to give the phthalimido-ribosyl-uridine **5** as a β/α mixture (β/α = 85/15) as a white foam (668 mg, 81% combined yield). After crystallization in a minimum amount of cyclohexane/EtOAc 9/1, the β-anomer was isolated with 61% yield: R_f 0.26 (cyclohexane/EtOAc 6/4); m.p. 122–125 °C; $[\alpha]_D$ −34 (*c* 1.0, CH_2Cl_2); IR (film)

3268br, 2857w, 1774w, 1718s, 1696m, 1394m; ^{1}H NMR δ 8.47 (br s, 1H, NH), 7.90–7.87 (m, 2H, $H_{11''}$), 7.84 (d, 1H, J_{H6-H5} = 8.0 Hz, H_6), 7.78–7.74 (m, 2H, $H_{12''}$), 6.17 (dd, 1H, J_{H5-H6} = 8.0 Hz, J_{H5-NH} = 2.0 Hz, H_5), 5.92 (d, 1H, $J_{H1'-H2'}$ = 4.5 Hz, $H_{1'}$), 5.24 (s, 1H, $H_{1''}$), 4.75 (d, 1H, $J_{H2''-H3''}$ = 6.0 Hz, $H_{2''}$), 4.64 (d, 1H, $J_{H3''-H2''}$ = 6.0 Hz, $H_{3''}$), 4.53 (dd, 1H, $J_{H4''-H5''b}$ = 10.5 Hz, $J_{H4''-H5''a}$ = 6.0 Hz, $H_{4''}$), 4.47 (dd, 1H, $J_{H4'-H5'}$ = 1.0 Hz, $J_{H4'-H3'}$ = 4.5 Hz, $H_{4'}$), 4.18 (t, 1H, $J_{H2'-H3'}$ = $J_{H2'-H1'}$ = 4.5 Hz, $H_{2'}$), 4.02 (t, 1H, $J_{H3'-H2'}$ = $J_{H3'-H4'}$ = 4.5 Hz, $H_{3'}$), 3.87 (ddd, 1H, $J_{H5'-H4'}$ = 1.0 Hz, $J_{H5'-H6'a}$ = 4.5 Hz, $J_{H5'-H6'b}$ = 11.0 Hz, $H_{5'}$), 3.81 (dd, 1H, $J_{H5''a-H5''b}$ = 13.5 Hz, $J_{H5''a-H4''}$ = 6.0 Hz, $H_{5''a}$), 3.77 (dd, 1H, $J_{H5''b-H5''a}$ = 13.5 Hz, $J_{H5''b-H4''}$ = 10.5 Hz, $H_{5''b}$), 2.98 (ddd, 1H, $J_{H6'a-H6'b}$ = 16.5 Hz, $J_{H6'a-H5'}$ = 4.5 Hz, $J_{H6'a-H8'}$ = 2.5 Hz, $H_{6'a}$), 2.66 (ddd, 1H, $J_{H6'b-H6'a}$ = 16.5 Hz, $J_{H6'b-H5'}$ = 11.0 Hz, $J_{H6'b-H8'}$ = 2.5 Hz, $H_{6'b}$), 2.06 (t, 1H, $J_{H8'-H6'a}$ = $J_{H8'-H6'b}$ = 2.5 Hz, $H_{8'}$), 1.72–1.60 (m, 2H, $H_{7''}$), 1.56–1.48 (m, 2H, $H_{7''}$), 0.94 (s, 9H, –C(CH_3)$_3$), 0.91 (s, 9H, –C(CH_3)$_3$), 0.88 (t, 3H, $J_{H8''-H7''}$ = 7.5 Hz, $H_{8''}$), 0.82 (t, 3H, $J_{H8''-H7''}$ = 7.5 Hz, $H_{8''}$), 0.13, 0.10 (2s, 12H, –Si–*t*-Bu–(CH_3)$_2$); ^{13}C NMR δ 168.2 ($C_{9''}$), 163.3 (C_4), 150.3 (C_2), 139.8 (C_6), 134.5 ($C_{12''}$), 131.9 ($C_{10''}$), 123.9 ($C_{11''}$), 117.7 ($C_{6''}$), 112.5 ($C_{1''}$), 102.8 (C_5), 88.6 ($C_{1'}$), 86.3 ($C_{3''}$), 84.6 ($C_{4''}$), 83.8 ($C_{4'}$), 82.1 ($C_{2''}$), 79.6 ($C_{5'}$), 79.4 ($C_{7'}$), 75.6 ($C_{2'}$), 72.2 ($C_{3'}$), 71.4 ($C_{8'}$), 40.4 ($C_{5''}$), 29.4, 28.9 ($C_{7''}$), 25.9, 25.9 (–C(*C*H$_3$)$_3$), 22.8 ($C_{6'}$), 18.2 (–*C*(CH$_3$)$_3$), 8.5, 7.4 ($C_{8''}$), –3.9, –4.3, –4.6, –4.6 (–Si–*t*-Bu–(*C*H$_3$)$_2$); HRMS ESI$^+$ calcd for $C_{42}H_{62}N_3O_{11}Si_2^+$ (M + H)$^+$ 840.3917, found 840.3915.

1″,5″-Dideoxy-2″,3″-*O*-isopentylidene-5″-phthalimido-1″-[2′,3′-*O*-isopropylidene-5′(*S*)-azidomethyl-uridinyl]-β-D-ribofuranose 6. Fluoride 4 (1.19 g, 3.39 mmol, 2.1 equiv.) and azide 3 (852 mg, 1.61 mmol, 1 equiv.) were dried together by co-evaporation with toluene (3 × 10 mL) and dissolved in DCM (26 mL). The flask was flushed with argon and molecular sieves 4 Å was added (8 g) in one portion. The suspension was stirred at r.t. for 1 h and then cooled to −78 °C. Boron trifluoride diethyletherate (426 μL, 3.39 mmol, 2.1 equiv.) was added at −78 °C and the reaction medium was stirred at this temperature for 10 min and was then allowed to warm to r.t. for 16 h. The reaction mixture was filtered on a celite pad and the cake was washed with DCM (50 mL). The reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution (50 mL) and the aqueous phase was extracted with DCM (5 × 60 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting white foam was purified by flash chromatography (toluene/acetone 95/5) to give the phthalimido-ribosyl-uridine **6** as a β/α mixture (β/α = 85/15) as a white foam (761 mg, 55% combined yield). The β-anomer was isolated with 41% yield: R_f 0.52 (toluene/acetone 8/2); m.p. 102–106 °C; $[\alpha]_D$ −9 (*c* 0.6, CH_2Cl_2); IR (film) 2928br, 2856br, 1715s, 1698m, 1394m; ^{1}H NMR δ 8.45 (br s, 1H, NH), 7.91–7.89 (m, 2H, $H_{11''}$), 7.85 (d, 1H, J_{H6-H5} = 8.5 Hz, H_6), 7.79–7.76 (m, 2H, $H_{12''}$), 6.14 (dd, 1H, J_{H5-H6} = 8.5 Hz, J_{H5-NH} = 1.0 Hz, H_5), 5.85 (d, 1H, $J_{H1'-H2'}$ = 4.0 Hz, $H_{1'}$), 5.24 (s, 1H, $H_{1''}$), 4.75 (d, 1H, $J_{H2''-H3''}$ = 5.5 Hz, $H_{2''}$), 4.65 (d, 1H, $J_{H3''-H2''}$ = 5.5 Hz, $H_{3''}$), 4.55 (dd, 1H, $J_{H4''-H5''b}$ = 10.5 Hz, $J_{H4''-H5''a}$ = 5.5 Hz, $H_{4''}$), 4.25 (dd, 1H, $J_{H4'-H5'}$ = 1.5 Hz, $J_{H4'-H3'}$ = 4.0 Hz, $H_{4'}$), 4.19 (t, 1H, $J_{H2'-H3'}$ = $J_{H2'-H1'}$ = 4.0 Hz, $H_{2'}$), 4.04 (t, 1H, $J_{H3'-H2'}$ = $J_{H3'-H4'}$ = 4.0 Hz, $H_{3'}$), 3.88–3.70 (m, 4H, $H_{5'}$, $H_{6'a}$, $H_{5''a}$, $H_{5''b}$), 3.60 (dd, 1H, $J_{H6'b-H6'a}$ = 12.5 Hz, $J_{H6'b-H5'}$ = 9.0 Hz, $H_{6'b}$), 1.73–1.64 (m, 2H, $H_{7''}$), 1.55–1.49 (m, 2H, $H_{7''}$), 0.94 (s, 9H, –C(CH_3)$_3$), 0.92 (s, 9H, –C(CH_3)$_3$), 0.88 (t, 3H, $J_{H8''-H7''}$ = 7.5 Hz, $H_{8''}$), 0.83 (t, 3H, $J_{H8''-H7''}$ = 7.5 Hz, $H_{8''}$), 0.16, 0.13, 0.13 (3s, 12H, –Si–*t*-Bu–(CH_3)$_2$); ^{13}C NMR δ 168.2 ($C_{9''}$), 163.2 (C_4), 150.2 (C_2), 139.8 (C_6), 134.6 ($C_{12''}$), 131.9 ($C_{10''}$), 123.9 ($C_{11''}$), 117.8 ($C_{6''}$), 112.5 ($C_{1''}$), 102.6 (C_5), 89.1 ($C_{1'}$), 86.2 ($C_{3''}$), 84.6 ($C_{4''}$), 82.9 ($C_{4'}$), 82.1 ($C_{2''}$), 78.6 ($C_{5'}$), 75.6 ($C_{2'}$), 71.6 ($C_{3'}$), 51.5 ($C_{6'}$), 40.4 ($C_{5''}$), 29.4, 28.9 ($C_{7''}$), 25.9 (–C(*C*H$_3$)$_3$), 18.2, 18.2 (–*C*(CH$_3$)$_3$), 8.5, 7.5 ($C_{8''}$), −3.9, −4.2, −4.7, −4.7 (–Si–*t*-Bu–(*C*H$_3$)$_2$); HRMS ESI$^+$ calcd for $C_{40}H_{61}N_6O_{11}Si_2^+$ (M + H)$^+$ 857.3931, found 857.3945.

10-Phenyldecyl methanesulfonate 9. To a solution of 10-phenyldecanol (625 mg, 2.67 mmol, 1 equiv.) in dichloromethane (2 mL) was added triethylamine (593 μL, 4.26 mmol, 1.6 equiv.). At 0 °C, to this resulting solution was then added dropwise methanesulfonyl chloride (310 μL, 4.0 mol, 1.5 equiv.). The mixture was stirred at 0 °C for 30 min and then at r.t. for 2 h. The precipitate was filtered out and the filtrate was concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane/EtOAc 8/2 to 6/4) afforded the mesylate **9** as a colorless oil (760 mg, 91% yield): R_f 0.52 (cyclohexane/EtOAc 6/4); IR (film) 2854m 1354s, 1110s, 972m, 952m, 831w; ^{1}H NMR δ 7.34–7.31 (m, 2H, H_3), 7.24–7.24 (m, 3H, H_2, H_4), 4.28 (t, 2H, J_{Ha-Hb} = 6.5 Hz, H_a), 3.05 (s, 3H, CH_3), 2.66 (t, 2H, J_{Hj-Hi} = 7.5 Hz, H_j), 1.82–1.77 (m, 2H, H_i), 1.69–1.64 (m, 2H, H_b), 1.47–1.42 (m, 2H, H_c), 1.39–1.30 (m, 10H, H_d, H_e, H_f, H_g, H_h); ^{13}C NMR δ 143.0 (C_1), 128.5 (C_3), 128.4 (C_2), 125.7 (C_4), 51.7 (C_a), 37.5 (CH_3), 36.1 (C_j), 31.6 (C_i), 26.6, 29.4, 29.3, 28.9, 26.9 (C_b, C_c, C_d, C_e, C_f, C_g, C_h); HRMS ESI$^+$ calcd for $C_{17}H_{28}O_3SNa^+$ (M + Na)$^+$ 335.1651, found 335.1652.

1-Bromo-10-phenyl-decane 10. To a solution of mesylate **9** (150 mg, 0.48 mmol, 1 equiv.) in acetone (3.0 mL) was added lithium bromide (84 mg, 0.96 mmol, 2.0 equiv.). The mixture was refluxed for 2 h, cooled to r.t., and concentrated *in vacuo*. The residue was filtered through a silica gel pad and washed with DCM (50 mL) to furnish **10** as a colorless oil (137 mg, 96% yield): R_f 0.62 (cyclohexane/EtOAc 9/1); IR (film) 3026w, 2925s, 2853m, 1603w, 1453m, 699s; ^{1}H NMR δ 7.30–7.27 (m, 2H, H_3), 7.19–7.17 (m, 3H, H_2, H_4), 3.42 (t, 2H, J_{Ha-Hb} = 7.0 Hz, H_a), 2.62 (t, 2H, J_{Hj-Hi} = 7.5 Hz, H_j), 1.86 (qt, 2H, J_{Hb-Ha} = J_{Hb-Hc} = 7.0 Hz, H_b), 1.66–1.58 (m, 2H, H_i), 1.46–1.40 (m, 2H, H_c), 1.36–1.28 (m, 10H, H_d, H_e, H_f, H_g, H_h); ^{13}C NMR δ 143.0 (C_1), 128.5 (C_3), 128.4 (C_2), 125.7 (C_4), 36.1 (C_j), 34.2 (C_a), 32.8 (C_b), 31.6 (C_i), 29.6, 29.6, 29.4, 28.9, 28.3 (C_c, C_d, C_e, C_f, C_g, C_h); HRMS APPI calcd for $C_{16}H_{25}Br^+$ (M)$^+$ 296.1140, found 296.1130. Spectral data were in agreement with the literature.[36]

12-Phenyl-1-trimethylsilyl-dodec-1-yne 11. A flame dried flask flushed with argon was cooled to −78 °C and charged with a solution of ethynyltrimethylsilane (413 mg, 4.21 mmol, 2.5 equiv.) in dry THF (10 mL). The mixture was stirred at −78 °C for 5 min and *n*-BuLi was then added dropwise (2.5 M in hexane, 1.69 mL, 4.21 mmol, 2.5 equiv.). The medium was stirred at −78 °C for 1 h and HMPA (731 μL, 4.21 mmol, 1 equiv.) was then added. Finally, at −78 °C, to this resulting solution was added dropwise a solution of freshly purified

1-bromo-10-phenyl-decane **10** (500 mg, 1.68 mmol, 1 equiv.) in THF (5 mL). The resulting orange solution was stirred at −78 °C and then at r.t. for 16 h, quenched with a saturated aqueous solution of NH_4Cl (10 mL) and volatiles were removed *in vacuo*. The aqueous phase was extracted with DCM (3 × 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* Flash chromatography of the residue (cyclohexane) afforded alkyne **11** as a colorless oil (387 mg, 73% yield): R_f 0.24 (cyclohexane); IR (film) 2928m, 2848m, 2167w, 1448w, 843m, 744s; ^{1}H NMR δ 7.28–7.24 (m, 2H, H_{3ar}), 7.16–7.14 (m, 3H, H_{2ar}, H_{4ar}), 2.58 (t, 2H, $J_{Ha–Hb}$ = 7.5 Hz, H_a), 2.19 (t, 2H, $J_{Hj–Hi}$ = 7.5 Hz, H_j), 1.62–1.56 (m, 2H, H_b), 1.49 (qt, 2H, $J_{Hi–Hj}$ = $J_{Hi–Hh}$ = 7.5 Hz, H_i), 1.38–1.23 (m, 12H, H_c, H_d, H_e, H_f, H_g, H_h); ^{13}C NMR δ 143.1 (C_{1ar}), 128.5 (C_{3ar}), 128.4 (C_{2ar}), 125.7 (C_{4ar}), 107.9 (C_2), 84.4 (C_1), 36.1 (C_a), 31.7 (C_b), 29.6, 29.6, 29.5, 29.2, 28.9, 28.8, 25.5 (C_c, C_d, C_e, C_f, C_g, C_h, C_i), 20.0 (C_j); HRMS APPI calcd for $C_{18}H_{26}^+$ $(M - TMS + H)^+$ 242.2035, found 242.2028.

10-Azido-decyl methanesulfonate 13. To a suspension of dimesylate **12**[29] (1 g, 3.03 mmol, 1 equiv.) in acetonitrile (16 mL) was added sodium azide (197 mg, 3.03 mmol, 2.5 equiv.). The mixture was refluxed for 18 h and cooled to r.t. The precipitate was then filtered out and the filtrate was concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane/EtOAc 8/2) afforded the starting material **12** as a white solid (254 mg, 25%) and azido mesylate **13** as a colorless oil (354 mg, 42%, 56% yield based on the recovered starting material): R_f 0.35 (cyclohexane/EtOAc 8/2); IR (film) 2096s, 1350s, 1169m, 955m; ^{1}H NMR δ 4.22 (t, 2H, $J_{Ha–Hb}$ = 6.5 Hz, H_a), 3.26 (t, 2H, $J_{Hj–Hi}$ = 7.0 Hz, H_j), 2.99 (s, 3H, CH_3), 1.77–1.72 (m, 2H, H_b), 1.62–1.56 (m, 2H, H_i), 1.42–1.27 (m, 12H, H_c, H_d, H_e, H_f, H_g, H_h); ^{13}C NMR δ, 70.3 (C_a), 51.6 (C_j), 37.5 (CH_3), 29.4, 29.4, 29.2, 29.2, 29.1, 28.9, 26.8, 25.5 (C_b, C_c, C_d, C_e, C_f, C_g, C_h, C_i); HRMS ESI$^+$ calcd for $C_{11}H_{24}NO_3S^+$ $(M - N_2 + H)^+$ 250.1471, found 250.1469.

7-Bromo-1-trimethylsilyl-hept-1-yne 14. A flame dried flask flushed with argon was cooled to −78 °C and charged with a solution of ethynyltrimethylsilane (178 mg, 1.81 mmol, 1 equiv.) in dry THF (5 mL). The mixture was stirred at −78 °C for 5 min and *n*-BuLi was then added dropwise (2.5 M in hexane, 724 μL, 1.81 mmol, 1 equiv.). The medium was stirred at −78 °C for 1 h and HMPA (315 μL, 1.81 mmol, 1 equiv.) was then added. Finally, at −78 °C, to this resulting solution was added dropwise a solution of 1,5-dibromopentane (500 mg, 2.17 mmol, 1.2 equiv.) in THF (5 mL). The mixture was stirred at −78 °C for 5 min and then at r.t. for 16 h, quenched with a saturated aqueous solution of NH_4Cl (10 mL) and volatiles were removed *in vacuo*. The aqueous phase was extracted with DCM (3 × 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* Flash chromatography of the residue (cyclohexane) afforded **14** as a white fine powder (270 mg, 60% yield): R_f 0.22 (cyclohexane); m.p. 72 °C; IR (film) 1556m, 1274w, 1262w, 829m, 749s; ^{1}H NMR δ 3.42 (t, 2H, $J_{Ha–Hb}$ = 6.5 Hz, H_a), 2.27–2.23 (m, 2H, H_e), 1.93–1.86 (m, 2H, H_b), 1.57–1.54 (m, 4H, H_c, H_d), 0.16 (s, 9H, (–Si–(CH_3)$_3$)); ^{13}C NMR δ 107.2 (C_2), 84.9 (C_1), 33.7 (C_a), 32.4 (C_b), 27.8 (C_d), 27.5 (C_c), 19.9 (C_e), 0.3 (–Si–(CH_3)$_3$); HRMS APPI calcd for $C_7H_{11}Br^+$ $(M - TMS + H)^+$ 174.0044, found 174.0042.

12-Bromo-1-trimethylsilyl-dodec-1-yne 15. A flame dried flask flushed with argon was cooled to −78 °C and charged with a solution of ethynyltrimethylsilane (208 mg, 2.12 mmol, 1 equiv.) in dry THF (3 mL). The mixture was stirred at −78 °C for 5 min and *n*-BuLi was then added dropwise (2.5 M in hexane, 847 μL, 2.12 mmol, 1 equiv.). The medium was stirred at −78 °C for 1 h and HMPA (368 μL, 2.12 mmol, 1 equiv.) was then added. Finally, at −78 °C, to this resulting pale yellow solution was added dropwise a solution of 1,10-dibromodecane (953 mg, 3.18 mmol, 1.5 equiv.) in THF (3 mL). The mixture was stirred at −78 °C for 16 h, quenched with a saturated aqueous solution of NH_4Cl (10 mL) and volatiles were removed *in vacuo*. The aqueous phase was extracted with DCM (3 × 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* Flash chromatography of the residue (cyclohexane) afforded **15** as a colorless oil (413 mg, 41% yield): R_f 0.19 (cyclohexane); IR (film) 2174w, 1248m, 702s, 840s, 759w; ^{1}H NMR δ 3.42 (t, 2H, $J_{Ha–Hb}$ = 6.5 Hz, H_a), 2.21 (t, 2H, $J_{Hj–Hi}$ = 7.0 Hz, H_j), 1.87 (qt, 2H, $J_{Hb–Ha}$ = $J_{Hb–Hc}$ = 7.0 Hz, H_b), 1.52 (qt, 2H, $J_{Hi–Hj}$ = $J_{Hi–Hh}$ = 6.5 Hz, H_i), 1.46–1.40 (m, 2H, H_c), 1.40–1.38 (m, 2H, H_h), 1.34–1.28 (m, 8H, H_d, H_e, H_f, H_g), 0.16 (s, 9H, (–Si–(CH_3)$_3$)); ^{13}C NMR δ 107.9 (C_2), 84.5 (C_1), 34.2 (C_a), 32.9 (C_b), 29.5, 29.2, 28.9, 28.8, 28.3 (C_c, C_d, C_e, C_f, C_g, C_h, C_i), 20.0 (C_j), 0.4 (–Si–(CH_3)$_3$); HRMS APPI calcd for $C_{12}H_{21}Br^+$ $(M - TMS + H)^+$ 244.0827, found 244.0822. Spectral data were in agreement with the literature.[37]

7-*O*-Acetyl-1-trimethylsilyl-hept-1-yne 16. Potassium acetate (595 mg, 6.07 mmol, 15 equiv.) was added to a solution of alkyne **14** (100 mg, 0.40 mmol, 1 equiv.) in DMF (6 mL). The reaction mixture was stirred at 80 °C for 12 h, cooled to r.t. and quenched by addition of a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous phase was extracted with ether (4 × 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* Flash chromatography of the residue (cyclohexane/EtOAc 9/1) afforded **16** as a colorless oil (65 mg, 71% yield): R_f 0.10 (cyclohexane/EtOAc 9/1); IR (film) 2956w, 2174w, 1742s, 1365w, 1248s, 1049w, 838s, 759m; ^{1}H NMR δ 4.05 (t, 2H, $J_{Ha–Hb}$ = 6.5 Hz, H_a), 2.22 (t, 2H, $J_{He–Hd}$ = 7.0 Hz, H_e), 2.03 (s, 3H, –OCOCH_3), 1.64 (qt, 2H, $J_{Hb–Ha}$ = $J_{Hb–Hc}$ = 6.5 Hz, H_b), 1.57–1.49 (m, 2H, H_d), 1.48–1.42 (m, 2H, H_c), 0.13 (s, 9H, (–Si–(CH_3)$_3$)); ^{13}C NMR δ 171.2 (–$OCOCH_3$), 107.2 (C_2), 84.8 (C_1), 64.5 (C_a), 28.3 (C_b), 28.2 (C_d), 25.2 (C_c), 21.1 (–OCOCH_3), 19.8 (C_e), 0.3 (–Si–(CH_3)$_3$; HRMS APCI$^+$ calcd for $C_{12}H_{22}NaO_2Si^+$ $(M + Na)^+$ 249.1281, found 249.1283. Spectral data were in agreement with the literature.[38]

12-*O*-Acetyl-1-trimethylsilyl-dodec-1-yne 17. Potassium acetate (360 mg, 3.64 mmol, 15 equiv.) was added to a solution of alkyne **15** (77 mg, 0.24 mmol, 1 equiv.) in DMF (1 mL). The reaction mixture was stirred at 80 °C for 12 h, cooled to r.t. and quenched by addition of saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous phase was extracted with ether (4 × 15 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* Flash chromato-

graphy of the residue (cyclohexane/EtOAc 98/2) afforded **17** as a colorless oil (45 mg, 63% yield): R_f 0.37 (cyclohexane/EtOAc 98/2); IR (film) 2929w, 1742m, 1247m, 1236m, 838s; ^{1}H NMR δ 4.06 (t, 2H, $J_{Ha–Hb}$ = 7.0 Hz, H_a), 2.21 (t, 2H, $J_{Hj–Hi}$ = 7.0 Hz, H_j), 2.04 (s, 3H, –OCOCH_3), 1.62 (qt, 2H, $J_{Hb–Ha}$ = $J_{Hb–Hc}$ = 7.0 Hz, H_b), 1.52 (qt, 2H, $J_{Hi–Hj}$ = $J_{Hi–Hh}$ = 7.0 Hz, H_i), 1.39–1.26 (m, 12H, H_c, H_d, H_e, H_f, H_g, H_h), 0.15 (s, 9H, (–Si–(CH_3)$_3$)); ^{13}C NMR δ 171.4 (–O*C*OCH$_3$), 107.9 (C_2), 84.4 (C_1), 64.8 (C_a), 29.6, 29.5, 29.4, 29.2, 28.9, 28.8, 26.1 (C_b, C_c, C_d, C_e, C_f, C_g, C_h, C_i), 21.2 (–OCO*C*H$_3$), 19.9 (C_j), 0.3 (–Si–(*C*H$_3$)$_3$); HRMS, ESI$^+$ calcd for $C_{17}H_{33}O_2Si^+$ $(M + H)^+$ 297.2244, found 297.2248.

12-*N*-Phthalimido-1-trimethylsilyl-dodec-1-yne 18. To a solution of bromo alkyne **15** (111 mg, 0.35 mmol, 1 equiv.) in DMF (3.5 mL) was added phthalimide potassium salt (194 mg, 1.05 mmol, 3 equiv.). The mixture was stirred at 80 °C for 16 h, cooled to r.t., quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane/EtOAc 95/5) afforded **18** as a colorless oil (115 mg, 86% yield). Additionally, partial deprotection of the TMS group was observed, and thus terminal alkyne **8f** was also isolated in 3% yield. Data for **18**: R_f 0.36 (cyclohexane/EtOAc 95/5); IR (film) 1713s, 1395m, 1247w, 842s; ^{1}H NMR δ 7.85–7.84 (m, 2H, H_{3ar}), 7.72–7.70 (m, 2H, H_{4ar}), 3.69 (t, 2H, $J_{Ha–Hb}$ = 7.5 Hz, H_a), 2.21 (t, 2H, $J_{Hj–Hi}$ = 7.0 Hz, H_j), 1.70–1.65 (m, 2H, H_b), 1.52 (qt, 2H, $J_{Hi–Hj}$ = $J_{Hi–Hh}$ = 7.0 Hz, H_i), 1.39–1.25 (m, 12H, H_c, H_d, H_e, H_f, H_g, H_h), 0.15 (s, 9H, (–Si–(CH_3)$_3$); ^{13}C NMR δ 168.6 (C_{1ar}), 133.9 (C_{4ar}), 132.4 (C_{2ar}), 123.3 (C_{3ar}), 107.9 (C_2), 84.4 (C_1), 38.2 (C_a), 29.6, 29.3, 29.2, 28.9, 28.8, 28.8, 27.0 (C_b, C_c, C_d, C_e, C_f, C_g, C_h, C_i), 20.0 (C_j), 0.3 (–Si–(*C*H$_3$)$_3$); HRMS, APCI$^+$ calcd for $C_{20}H_{26}NO_2^+$ $(M - TMS + 2H)^+$ 312.1958, found 312.1963.

12-*O*-*p*-Benzophenonyl-1-trimethylsilyl-dodec-1-yne 19. To a solution of bromo alkyne **15** (96 mg, 0.30 mmol, 2.4 equiv.) in DMF (1 mL) was added 4-hydroxy-benzophenone (25 mg, 0.12 mmol, 1 equiv.) and potassium carbonate (87 mg, 0.63 mmol, 5 equiv.). The mixture was stirred at r.t. for 16 h, quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane/DCM 6/4) afforded **19** as a colorless oil (49 mg, 90% yield): R_f 0.22 (cyclohexane/DCM 6/4); IR (film) 2174w, 1654w, 1600w, 1250s, 852s; ^{1}H NMR δ 7.83–7.81 (m, 2H, H_{7ar}), 7.77–7.75 (m, 2H, H_{3ar}), 7.58–7.55 (m, 1H, H_{9ar}), 7.49–7.46 (m, 2H, H_{8ar}), 6.96–6.94 (m, 2H, H_{2ar}), 4.04 (t, 2H, $J_{Ha–Hb}$ = 7.0 Hz, H_a), 2.21 (t, 2H, $J_{Hj–Hi}$ = 7.5 Hz, H_j), 1.82 (qt, 2H, $J_{Hb–Ha}$ = $J_{Hb–Hc}$ = 7.0 Hz, H_b), 1.52 (qt, 2H, $J_{Hi–Hj}$ = $J_{Hi–Hh}$ = 7.0 Hz, H_i), 1.49–1.45 (m, 2H, H_c), 1.35–1.26 (m, 10H, H_d, H_e, H_f, H_g, H_h), 0.16 (s, 9H, (–Si–(CH_3)$_3$)); ^{13}C NMR δ 195.6 (C_{5ar}), 163.0 (C_{1ar}), 138.5 (C_{6ar}), 132.7 (C_{3ar}), 131.9 (C_{9ar}), 130.0 (C_{4ar}), 129.8 (C_{7ar}), 128.3 (C_{8ar}), 114.1 (C_{2ar}), 107.8 (C_2), 84.4 (C_1), 68.4 (C_a), 29.6, 29.5, 29.5, 29.3, 29.2, 28.9, 28.7 (C_b, C_d, C_e, C_f, C_g, C_h, C_i), 26.1 (C_c), 19.9 (C_j), 0.3 (–Si–(*C*H$_3$)$_3$); HRMS ESI calcd for $C_{28}H_{39}O_2Si^+$ $(M + H)^+$ 435.2714, found 435.2727.

1-Trimethylsilyl-3-[4-*O*-(benzophenonyl)-benzyl]-prop-1-yne 21. To a suspension of bromide derivative **20**[24] (100 mg, 0.26 mmol, 1 equiv.), copper iodide (50 mg, 0.26 mmol, 1 equiv.), TBAI (96 mg, 0.26 mmol, 1 equiv.), and potassium carbonate (72 mg, 0.52 mmol, 2 equiv.) in dry acetonitrile (1.5 mL) was added trimethylsilylacetylene (45 µL, 0.31 mmol, 1.2 equiv.). The mixture was stirred at 40 °C for 24 h, quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with DCM (4 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane/DCM 7/3 to 4/6) afforded **21** as a colorless film (60 mg, 57% yield): R_f 0.39 (cyclohexane/DCM 1/1); IR (film) 2130m, 1632s, 1600w, 1250s, 855s; ^{1}H NMR δ 7.85–7.83 (m, 2H, H_{3ar}), 7.77–7.75 (m, 2H, H_{7ar}), 7.59–7.55 (m, 1H, H_{9ar}), 7.49–7.46 (m, 2H, H_{8ar}), 7.42–7.38 (m, 4H, H_c, H_d), 7.06–7.03 (m, 2H, H_{2ar}), 5.14 (s, 2H, H_a), 3.68 (s, 2H, H_f), 0.21 (s, 9H, (–Si–(CH_3)$_3$)); ^{13}C NMR δ 195.6 (C_{5ar}), 162.5 (C_{1ar}), 138.4 (C_e), 136.7 (C_{6ar}), 134.7 (C_b), 132.7 (C_{3ar}), 132.0 (C_{9ar}), 130.5 (C_{4ar}), 129.9 (C_{7ar}), 128.4 (C_{8ar}), 128.3, 127.9 (C_c, C_d), 114.5 (C_{2ar}), 104.1 (C_2), 87.3 (C_1), 70.1 (C_a), 26.1 (C_f), 0.2 (–Si–(*C*H$_3$)$_3$); HRMS ESI$^+$ calcd for $C_{26}H_{27}O_2S_i^+$ $(M + H)^+$ 399.1775, found 399.1768.

3-[4-*O*-(Benzophenonyl)-benzyl]-propadiene 22. To a solution of alkyne **21** (49 mg, 0.12 mmol, 1 equiv.) in dry THF (1.5 mL) was added, at 0 °C, tetrabutyl ammonium fluoride trihydrate. The flashing dark purple solution was stirred for 10 min at 0 °C and then at r.t. for 1 h. After removal of volatiles *in vacuo*, the crude residue was purified by flash chromatography (cyclohexane/DCM = 9/1 to 7/3). Under these conditions, allene **22** was obtained as a white powder (37 mg, 91% yield): R_f 0.32 (cyclohexane/DCM 7/3); IR (film) 2859br, 1938w, 1728br, 1650s, 1597s, 1257s; ^{1}H NMR δ 7.84–7.82 (m, 2H, H_{3ar}), 7.77–7.74 (m, 2H, H_{7ar}), 7.59–7.55 (m, 1H, H_{9ar}), 7.49–7.46 (m, 2H, H_{8ar}), 7.39–7.37 (m, 2H, H_d), 7.34–7.31 (m, 2H, H_c), 7.05–7.02 (m, 2H, H_{2ar}), 6.18 (t, 1H, $J_{Hf–H2}$ = 7.0 Hz, H_f), 5.17 (d, 2H, $J_{H2–Hf}$ = 7.0 Hz, H_2), 5.14 (s, 1H, H_a); ^{13}C NMR δ 210.1 (C_1), 195.7 (C_{5ar}), 162.5 (C_{1ar}), 138.4 (C_e), 134.9 (C_{6ar}), 134.2 (C_b), 132.7 (C_{3ar}), 132.0 (C_{9ar}), 130.5 (C_{4ar}), 129.9 (C_{7ar}), 128.3 (C_{8ar}), 128.0 (C_c), 127.1 (C_d), 114.6 (C_{2ar}), 93.7 (C_f), 79.1 (C_2), 70.1 (C_a); HRMS, ESI$^+$ calcd for $C_{23}H_{19}O_2^+$ $(M + H)^+$ 327.1380, found 327.1372.

1-Azido-10-phenyl-decane 7b. To a solution of mesylate **9** (220 mg, 0.70 mmol, 1 equiv.) in DMF (1.5 mL) were successively added sodium azide (114 mg, 13.2 mmol, 2.5 equiv.) and sodium iodide (53 mg, 0.35 mmol, 0.5 equiv.). The mixture was stirred at 75 °C for 18 h, cooled to r.t., and diluted with Et_2O (20 mL) and water (20 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography of the resulting pale yellow oil (cyclohexane/EtOAc 95/5 to 9/1) afforded azide **7b** as a colorless oil (168 mg, 92% yield): R_f 0.72 (cyclohexane/EtOAc 9/1); IR (film) 3026w, 2099s, 1603w, 746m; ^{1}H NMR δ 7.28–7.25 (m, 2H, H_3), 7.18–7.15 (m, 3H, H_2, H_4), 3.25 (t, 2H, $J_{Ha–Hb}$ = 7.0 Hz, H_a), 2.59 (t, 2H, $J_{Hj–Hi}$ = 7.5 Hz, H_j), 1.63–1.56 (m, 4H, H_b, H_i), 1.37–1.26 (m, 12H, H_c, H_d, H_e, H_f, H_g, H_h); ^{13}C NMR δ 143.0 (C_1), 128.5

(C_3), 128.4 (C_2), 125.7 (C_4), 70.3 (C_a), 37.5 (C_j), 36.1 (C_i), 31.6, 29.6, 29.5, 29.4, 29.3, 29.1, 25.5 (C_b, C_c, C_d, C_e, C_f, C_g, C_h); HRMS ESI$^+$ calcd for $C_{16}H_{26}N^+$ $(M - N_2 + H)^+$ 232.2060 found 232.2056. Spectral data were in agreement with the literature.[39]

10-Azido-decan-1-ol 7d. To a solution of 10-bromo-decan-1-ol (633 mg, 2.40 mmol, 1 equiv.) in DMF (7.6 mL) was added sodium azide (312 mg, 4.80 mmol, 2 equiv.) and sodium iodide (180 mg, 1.20 mmol, 0.5 equiv.). The suspension was stirred at 80 °C for 18 h, cooled to r.t. and diluted with ether (20 mL) and water (20 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic layers were washed with brine (2 × 20 mL) and water (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane/EtOAc 6/4) afforded azide **7d** as a colorless oil (469 mg, 98%): R_f 0.37 (cyclohexane/EtOAc 6/4); IR (film) 3056br, 2092m, 1276m, 1251m, 741s; ^{1}H NMR δ 3.66–3.62 (m, 2H, H_j), 3.28–3.24 (m, 2H, H_a), 1.63–1.54 (m, 4H, H_b, H_i), 1.37–1.29 (m, 12H, H_c, H_d, H_e, H_f, H_g, H_h); ^{13}C NMR δ 63.2 (C_j), 51.6 (C_a), 32.9 (C_i), 29.6, 29.5, 29.5, 29.3, 28.9, 26.8, 25.8 (C_b, C_c, C_d, C_e, C_f, C_g, C_h); HRMS ESI$^+$ calcd for $C_{10}H_{22}NO^+$ $(M - N_2 + H)^+$ 172.1696, found 172.1694.

1-Azido-10-phthalimido-decane 7f. To a solution of azido mesylate **13** (200 mg, 0.72 mmol, 1 equiv.) in DMF (2 mL) was added potassium phthalimide (400 mg, 2.16 mmol, 3 equiv.). The suspension was stirred at 80 °C for 18 h, cooled to r.t. and diluted with ether (15 mL) and water (15 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL) and the combined organic layers were washed with brine (2 × 20 mL) and water (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane/EtOAc 8/2) afforded azide **7f** as a colorless oil (233 mg, 98%): R_f 0.49 (cyclohexane/EtOAc 7/3); IR (film) 2094w, 1708s, 1345m, 719m; ^{1}H NMR δ 7.86–7.82 (m, 2H, H_3), 7.72–7.69 (m, 2H, H_4), 3.68 (t, 2H, $J_{Hj–Hi}$ = 7.5 Hz, H_j), 3.25 (t, 2H, $J_{Ha–Hb}$ = 7.0 Hz, H_a), 1.70–1.64 (m, 2H, H_i), 1.61–1.55 (m, 2H, H_b), 1.39–1.22 (m, 12H, H_c, H_d, H_e, H_f, H_g, H_h); ^{13}C NMR δ 168.6 (C_1), 133.9 (C_4), 132.4 (C_2), 123.3 (C_3), 51.6 (C_a), 38.2 (C_j), 29.5, 29.5, 29.2, 29.2, 28.9, 28.7, 26.9, 26.8 (C_b, C_c, C_d, C_e, C_f, C_g, C_h, C_i); HRMS APCI$^+$ calcd for $C_{18}H_{25}N_2O_2^+$ $(M - N_2 + H)^+$ 301.1911, found 301.1911.

General procedure for TMS deprotection and preparation of compounds 8b, 8f, 8h

To a solution of the silylated alkyne (1 equiv.) in THF (0.1 M) was added in one portion tetrabutyl ammonium fluoride trihydrate (1.1 to 1.6 equiv.). The solution was stirred at r.t. for 1 h and volatiles were removed *in vacuo*. Flash chromatography of the residue afforded the corresponding terminal alkyne.

12-Phenyl-dodec-1-yne 8b. Alkyne **8b** was obtained from protected alkyne **11** (327 mg, 1.04 mmol, 1 equiv.) according to the general procedure for terminal alkyne synthesis. Flash chromatography of the residue (cyclohexane) afforded **8b** as a colorless oil (223 mg, 89% yield): R_f 0.22 (cyclohexane); IR (film) 3075m, 2140m, 1602m, 1452m, 1290m, 1253s, 1175w; ^{1}H NMR δ 7.30–7.26 (m, 2H, H_{3ar}), 7.20–7.17 (m, 3H, H_{2ar}, H_{4ar}), 2.62 (t, 2H, $J_{Ha–Hb}$ = 7.5 Hz, H_a), 2.19 (dt, 2H, $J_{Hj–Hi}$ = 7.5 Hz, $J_{Hj–H2}$ = 3.0 Hz, H_j), 1.95 (t, 1H, $J_{H2–Hj}$ = 3.0 Hz, H_2), 1.66–1.60 (m, 2H, H_b), 1.55 (qt, 2H, $J_{Hi–Hj}$ = $J_{Hi–Hh}$ = 7.5 Hz, H_i), 1.43–1.38 (m, 2H, H_c), 1.38–1.26 (m, 10H, H_d, H_e, H_f, H_g, H_h); ^{13}C NMR δ 143.1 (C_{1ar}), 128.5 (C_{3ar}), 128.4 (C_{2ar}), 125.7 (C_{4ar}), 84.9 (C_1), 68.2 (C_2), 36.1 (C_a), 31.6 (C_b), 29.6, 29.5, 29.5, 29.5, 29.2, 28.9, 28.7 (C_c, C_d, C_e, C_f, C_g, C_h, C_i), 18.6 (C_j); HRMS APPI calcd for $C_{18}H_{26}^+$ $(M)^+$ 242.2035, found 242.2030.

Heptyn-1-ol 8c. To a suspension of ester **16** (71 mg, 0.31 mmol, 1 equiv.) in MeOH (2 mL) and water (0.2 mL) was added potassium carbonate (216 mg, 1.57 mmol, 5 equiv.). The reaction mixture was stirred at r.t. for 5 h and then quenched by addition of saturated aqueous solution of NH_4Cl (10 mL). The aqueous phase was extracted with EtOAc (4 × 15 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* Flash chromatography of the residue (cyclohexane/EtOAc 8/2) afforded **8c** as a white solid (29 mg, 82% yield): R_f 0.21 (cyclohexane/EtOAc 8/2); IR (film) 3061br, 2919w, 1278m, 1252m, 743s; ^{1}H NMR δ 3.66 (t, 2H, $J_{Ha–Hb}$ = 6.5 Hz, H_a), 2.21 (dt, 2H, $J_{He–Hd}$ = 7.0 Hz, $J_{He–H2}$ = 2.5 Hz, H_e), 1.94 (t, 1H, $J_{H2–He}$ = 2.5 Hz, H_2), 1.62–1.54 (m, 4H, H_b, H_d), 1.52–1.47 (m, 2H, H_c); ^{13}C NMR δ 84.6 (C_2), 68.5 (C_1), 62.9 (C_a), 32.4 (C_b), 28.4 (C_d), 25.1 (C_c), 18.5 (C_e); HRMS, APCI$^+$ calcd for $C_7H_{13}O^+$ $(M + H)^+$ 113.0966, found 113.0961. Spectral data were in agreement with the literature.[40]

Dodec-11-yn-1-ol 8d. To a suspension of ester **17** (36 mg, 0.12 mmol, 1 equiv.) in MeOH (1 mL) and water (0.1 mL) was added potassium carbonate (84 mg, 0.61 mmol, 5 equiv.). The reaction mixture was stirred at r.t. for 5 h and then quenched by addition of saturated aqueous solution of NH_4Cl (10 mL). The aqueous phase was extracted with EtOAc (4 × 15 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* Flash chromatography of the residue (cyclohexane/EtOAc 9/1) afforded **8d** as a white solid (20 mg, 90% yield): R_f 0.12 (cyclohexane/EtOAc 9/1); m.p 26–28 °C; IR (film) 3065br, 2923w, 1275m, 1256m, 744s; ^{1}H NMR δ 3.49 (t, 2H, $J_{Ha–Hb}$ = 7.0 Hz, H_a), 2.03 (dt, 2H, $J_{Hj–Hi}$ = 7.0 Hz, $J_{Hj–H2}$ = 2.5 Hz, H_j), 1.79 (t, 1H, $J_{H2–Hj}$ = 2.5 Hz, H_2), 1.45–1.35 (m, 4H, H_b, H_i), 1.28–1.11 (m, 12H, H_c, H_d, H_e, H_f, H_g, H_h); ^{13}C NMR δ 84.9 (C_2), 68.2 (C_1), 63.2 (C_a), 32.9 (C_b), 29.7, 29.6, 29.2, 28.9, 28.6, 25.8 (C_c, C_d, C_e, C_f, C_g, C_h, C_i), 18.5 (C_j); HRMS, APCI$^+$ calcd for $C_{12}H_{23}O^+$ $(M + H)^+$ 183.1743, found 183.1746. Spectral data were in agreement with the literature.[41]

12-*N*-Phthalimido-dodec-1-yne 8f. Alkyne **8f** was obtained from protected alkyne **18** (114 mg, 0.29 mmol, 1 equiv.) according to the general procedure for terminal alkyne synthesis. Flash chromatography of the residue (cyclohexane/EtOAc 95/5) afforded **8f** as a white film (51 mg, 55% yield): R_f 0.28 (cyclohexane/EtOAc 95/5); IR (film) 2937s, 2100m, 1767w, 1710s, 1394m; ^{1}H NMR δ 7.85–7.82 (m, 2H, H_{3ar}), 7.72–7.68 (m, 2H, H_{4ar}), 3.67 (t, 2H, $J_{Ha–Hb}$ = 7.5 Hz, H_a), 2.17 (dt, 2H, $J_{Hj–Hi}$ = 7.0 Hz, $J_{Hj–H2}$ = 2.5 Hz, H_j), 1.93 (t, 2H, $J_{H2–Hj}$ = 2.5 Hz, H_2), 1.69–1.64 (m, 2H, H_b), 1.51 (qt, 2H, $J_{Hi–Hj}$ = $J_{Hi–Hh}$ = 7.0 Hz, H_i), 1.40–1.26 (m, 12H, H_c, H_d, H_e, H_f, H_g, H_h); ^{13}C NMR δ 168.6 (C_{1ar}), 133.9 (C_{4ar}), 132.3 (C_{2ar}), 123.3 (C_{3ar}), 107.9 (C_2), 84.4 (C_1), 68.2 (C_2), 38.2 (C_a), 29.6, 29.5, 29.3, 29.2, 28.8, 28.7, 28.6,

26.9 (C_b, C_c, C_d, C_e, C_f, C_g, C_h, C_i), 18.5 (C_j); HRMS, ESI$^+$ calcd for $C_{20}H_{26}NO_2^+$ $(M + H)^+$ 312.1958, found 312.1961.

3-[4-*O*-(Benzophenonyl)-benzyl]-prop-1-yne 8g. To a suspension of protected alkyne **21** (100 mg, 0.25 mmol, 1 equiv.) in methanol (3 mL) was added potassium carbonate in one portion (173 mg, 1.25 mmol, 5 equiv.). The suspension was stirred at r.t. for 5 h and the suspension was then diluted with EtOAc (15 mL). After addition of saturated aqueous solution of NH_4Cl (10 mL), the aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane to cyclohexane/EtOAc 95/5) afforded **8g** as a white film (66 mg, 81% yield): R_f 0.42 (cyclohexane/EtOAc 9/1); IR (film) 2325w, 1645s, 1602s, 1281s, 1173m; ^{1}H NMR δ 7.77–7.74 (m, 2H, H_{3ar}), 7.70–7.66 (m, 2H, H_{7ar}), 7.49 (t, 1H, $J_{H9ar–H8ar}$ = 7.0 Hz, H_{9ar}), 7.39 (t, 2H, $J_{H8ar–H9ar}$ = 7.0 Hz, H_{8ar}), 7.34–7.31 (m, 4H, H_c, H_d), 6.97–6.94 (m, 2H, H_{2ar}), 5.06 (s, 1H, H_a), 3.55 (d, 2H, $J_{Hf–H2}$ = 3.0 Hz, H_f), 2.13 (t, 2H, $J_{H2–Hf}$ = 3.0 Hz, H_f); ^{13}C NMR δ 195.7 (C_{5ar}), 162.5 (C_{1ar}), 138.4 (C_e), 136.4 (C_{6ar}), 134.9 (C_b), 132.7 (C_{3ar}), 132.0 (C_{9ar}), 130.5 (C_{4ar}), 129.9 (C_{7ar}), 128.4 (C_{8ar}), 128.3, 127.9 (C_c, C_d), 114.6 (C_{2ar}), 81.8 (C_2), 70.7 (C_a), 70.1 (C_1), 24.7 (C_f); HRMS, ESI$^+$ calcd for $C_{23}H_{19}O_2^+$ $(M + H)^+$ 327.1380, found 327.1374.

12-*O*-*p*-Benzophenonyl-dodec-1-yne 8h. Alkyne **8h** was obtained from protected alkyne **19** (54 mg, 0.12 mmol, 1 equiv.) according to the general procedure for terminal alkyne synthesis. Flash chromatography of the residue (cyclohexane/EtOAc 9/1) afforded **8h** as a white film (44 mg, 97% yield): R_f 0.51 (cyclohexane/EtOAc 9/1); IR (film) 2919w, 1639s, 1602m, 1307s, 1290m, 1253s, 1175w; ^{1}H NMR δ 7.84–7.81 (m, 2H, H_{3ar}), 7.77–7.75 (m, 2H, H_{7ar}), 7.59–7.55 (m, 1H, H_{9ar}), 7.49–7.46 (m, 2H, H_{8ar}), 6.96–6.94 (m, 2H, H_{2ar}), 4.04 (t, 2H, $J_{Ha–Hb}$ = 6.5 Hz, H_a), 2.19 (dt, 2H, $J_{Hj–Hi}$ = 7.0 Hz, $J_{Hj–H2}$ = 2.5 Hz, H_j), 1.82 (qt, 2H, $J_{Hb–Ha}$ = $J_{Hb–Hc}$ = 6.5 Hz, H_b), 1.54 (qt, 2H, $J_{Hi–Hj}$ = $J_{Hi–Hh}$ = 7.0 Hz, H_i), 1.49–1.45 (m, 2H, H_c), 1.42–1.30 (m, 10H, H_d, H_e, H_f, H_g, H_h); ^{13}C NMR δ 195.7 (C_{5ar}), 163.0 (C_{1ar}), 138.5 (C_{6ar}), 132.7 (C_{3ar}), 131.9 (C_{9ar}), 130.1 (C_{4ar}), 129.8 (C_{7ar}), 128.3 (C_{8ar}), 114.2 (C_{2ar}), 84.9 (C_1), 68.4 (C_a), 68.2 (C_2), 29.6, 29.5, 29.5, 29.3, 29.2, 28.8, 28.6 (C_b, C_d, C_e, C_f, C_g, C_h, C_i), 26.1 (C_c), 18.5 (C_j); HRMS, ESI$^+$ calcd for $C_{25}H_{31}O_2^+$ $(M + H)^+$ 363.2319, found 363.2313.

General procedure for Cu(I)-catalyzed azide–alkyne cycloaddition: preparation of compounds 23a–h

To a solution of alkyne **5** (1 equiv.) and azide partner **7a–h** (1–2 equiv.) in *tert*-BuOH/H_2O (1.5 mL/500 μL) were successively added $CuSO_4$ (0.1 equiv.), sodium ascorbate (0.3 equiv.) and *N*-diisopropylethylamine (2.2 equiv.). The suspension was sonicated for 5 min to solubilise all reagents. The mixture was stirred at r.t. for 18 h and diluted with DCM (30 mL) and NH_4Cl (15 mL). The aqueous phase was extracted with DCM (6 × 30 mL) and the combined organic layers were washed with 10^{-3} M solution of tetra-sodium EDTA, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was then purified by flash chromatography to give the corresponding *C*-triazole **23a–h**.

Compound 23a. Triazole **23a** was synthesized according to the general procedure for Cu(I)-catalyzed azide–alkyne cycloaddition from alkyne **5** (114 mg, 0.14 mmol) and azide **7a** (50 mg, 0.27 mmol, 2 equiv.). Flash chromatography (cyclohexane/EtOAc 6/4) afforded **23a** as a white foam (81 mg, 58% yield): R_f 0.28 (cyclohexane/EtOAc 6/4); m.p. 102–106 °C; $[\alpha]_D$ −30 (*c* 0.5, CH_2Cl_2); IR (film) 3060m, 2928m, 2856m, 1714s, 1386m; ^{1}H NMR δ 8.76 (d, 1H, $J_{NH–H5}$ = 2.0 Hz, NH), 7.90–7.84 (m, 3H, $H_{11''}$, H_6), 7.77–7.74 (m, 2H, $H_{12''}$), 7.37 (s, 1H, $H_{8'}$), 6.18 (dd, 1H, $J_{H5–H6}$ = 8.0 Hz, $J_{H5–NH}$ = 2.0 Hz, H_5), 5.95 (d, 1H, $J_{H1'–H2'}$ = 5.5 Hz, $H_{1'}$), 5.34 (s, 1H, $H_{1''}$), 4.77 (d, 1H, $J_{H2''–H3''}$ = 6.0 Hz, $H_{2''}$), 4.67 (d, 1H, $J_{H3''–H2''}$ = 6.0 Hz, $H_{3''}$), 4.52 (dd, 1H, $J_{H4''–H5''a}$ = 7.0 Hz, $J_{H4''–H5''b}$ = 9.0 Hz, $H_{4''}$), 4.35–4.25 (m, 2H, $H_{9'}$), 4.19–4.16 (m, 2H, $H_{2'}$, $H_{5'}$), 4.00 (t, 1H, $J_{H3'–H2'}$ = $J_{H3'–H4'}$ = 3.5 Hz, $H_{3'}$), 3.88–3.82 (m, 3H, $H_{5''a}$, $H_{5''b}$, $H_{4'}$), 3.49 (dd, 1H, $J_{H6'a–H6'b}$ = 14.0 Hz, $J_{H6'a–H5'}$ = 4.5 Hz, $H_{6'a}$), 3.07 (dd, 1H, $J_{H6'b–H6'a}$ = 14.0 Hz, $J_{H6'b–H5'}$ = 10.5 Hz, $H_{6'b}$), 1.91–1.81 (m, 2H, $H_{10'}$), 1.72–1.60 (m, 2H, $H_{7''}$), 1.55–1.47 (m, 2H, $H_{7''}$), 1.33–1.20 (m, 14H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16'}$, $H_{17'}$), 0.88 (t, 3H, $J_{H8''–H7''}$ = 7.5 Hz, $H_{8''}$), 0.86 (t, 3H, $J_{H18'–H17'}$ = 7.5 Hz, $H_{18'}$), 0.85 (s, 9H, –C(CH_3)$_3$), 0.83 (s, 9H, –C(CH_3)$_3$), 0.81 (t, 3H, $J_{H8''–H7''}$ = 7.5 Hz, $H_{8''}$), 0.07, 0.07, 0.05, −0.02 (4s, 12H, –Si–*t*-Bu–(CH_3)$_2$); ^{13}C NMR δ 168.2 ($C_{9''}$), 163.3 (C_4), 150.6 (C_2), 142.9 ($C_{7'}$), 139.9 (C_6), 134.5 ($C_{12''}$), 131.9 ($C_{10''}$), 123.8 ($C_{11''}$), 122.2 ($C_{8'}$), 117.7 ($C_{6''}$), 112.4 ($C_{1''}$), 103.2 (C_5), 87.7 ($C_{1'}$), 86.4 ($C_{3''}$), 84.5 ($C_{4''}$), 84.3 ($C_{4'}$), 82.6 ($C_{2''}$), 80.8 ($C_{2'}$), 75.4 ($C_{5'}$), 72.6 ($C_{3'}$), 50.5 ($C_{9'}$), 40.5 ($C_{5''}$), 31.9 ($C_{10'}$), 30.5 ($C_{7''}$), 29.6, 29.5, 29.5, 29.4, 29.1, 28.9, 28.9 ($C_{7''}$, $C_{6'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$), 25.9, 25.8 (–C(CH_3)$_3$), 22.8 ($C_{17'}$), 18.1, 18.0 (–*C*(CH$_3$)$_3$), 14.2 ($C_{18'}$), 8.4, 7.5 ($C_{8''}$), −4.2, −4.5, −4.5, −4.6 (–Si–*t*-Bu–(CH_3)$_2$); HRMS, ESI$^+$ calcd for $C_{52}H_{83}N_6O_{11}Si_2^+$ $(M + H)^+$ 1023.5653, found 1023.5652.

Compound 23b. Triazole **23b** was synthesized according to the general procedure for Cu(I)-catalyzed azide–alkyne cycloaddition from alkyne **5** (60 mg, 0.07 mmol) and azide **7b** (37.5 mg, 0.14 mmol, 2 equiv.). Flash chromatography (cyclohexane/EtOAc 1/1) afforded **23b** as a white foam (45 mg, 57% yield): R_f 0.25 (cyclohexane/EtOAc 1/1); m.p. 100–102 °C; $[\alpha]_D$ −27 (*c* 1.0, CH_2Cl_2); IR (film) 2929m, 1717s, 1696s, 1394w, 1088w, 838w; ^{1}H NMR δ 8.30 (br s, 1H, NH), 7.90–7.88 (m, 3H, $H_{11''}$, H_6), 7.77–7.75 (m, 2H, $H_{12''}$), 7.36 (s, 1H, $H_{8'}$), 7.28–7.25 (m, 2H, $H_{20'}$), 7.18–7.15 (m, 3H, $H_{21'}$, $H_{22'}$), 6.20 (dd, 1H, $J_{H5–H6}$ = 8.0 Hz, $J_{H5–NH}$ = 2.0 Hz, H_5), 5.97 (d, 1H, $J_{H1'–H2'}$ = 6.0 Hz, $H_{1'}$), 5.36 (s, 1H, $H_{1''}$), 4.79 (d, 1H, $J_{H2''–H3''}$ = 6.0 Hz, $H_{2''}$), 4.69 (d, 1H, $J_{H3''–H2''}$ = 6.0 Hz, $H_{3''}$), 4.55–4.52 (m, 1H, $H_{4''}$), 4.35–4.26 (m, 2H, $H_{9'}$), 4.19–4.17 (m, 2H, $H_{2'}$, $H_{5'}$), 4.00 (t, 1H, $J_{H3'–H2'}$ = $J_{H3'–H4'}$ = 3.5 Hz, $H_{3'}$), 3.89–3.84 (m, 3H, $H_{5''}$, $H_{4'}$), 3.50 (dd, 1H, $J_{H6'a–H6'b}$ = 14.0 Hz, $J_{H6'a–H5'}$ = 5.0 Hz, $H_{6'a}$), 3.07 (dd, 1H, $J_{H6'b–H6'a}$ = 14.0 Hz, $J_{H6'b–H5'}$ = 11.0 Hz, $H_{6'b}$), 2.59 (t, 2H, $J_{H18'–H17'}$ = 7.5 Hz, $H_{18'}$), 1.89–1.84 (m, 2H, $H_{10'}$), 1.61–1.59 (m, 2H, $H_{17'}$), 1.55–1.52 (m, 2H, $H_{7''}$), 1.32–1.25 (m, 12H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16'}$), 0.89 (t, 3H, $J_{H8''–H7''}$ = 8.0 Hz, $H_{8''}$), 0.87 (s, 9H, –C(CH_3)$_3$), 0.84 (s, 9H, –C(CH_3)$_3$), 0.83 (t, 3H, $J_{H8''–H7''}$ = 8.0 Hz, $H_{8''}$), 0.08, 0.08, 0.07, −0.02 (4s, 12H, –Si–*t*-Bu–(CH_3)$_2$); ^{13}C NMR δ 168.3 ($C_{9''}$), 163.1 (C_4), 150.4 (C_2), 143.0 ($C_{19'}$), 142.9 ($C_{7'}$), 139.9 (C_6), 134.5 ($C_{12''}$), 131.9 ($C_{10''}$), 128.5 ($C_{21'}$), 128.3

($C_{20'}$), 125.7 ($C_{22'}$), 123.8 ($C_{11''}$), 122.1 ($C_{8'}$), 117.7 ($C_{6''}$), 112.4 ($C_{1''}$), 103.2 (C_5), 87.6 ($C_{1'}$), 86.4 ($C_{3''}$), 84.5 ($C_{4''}$), 84.4 ($C_{4'}$), 82.6 ($C_{2''}$), 80.9 ($C_{2'}$), 75.4 ($C_{5'}$), 72.7 ($C_{3'}$), 50.4 ($C_{9'}$), 40.5 ($C_{5''}$), 36.1 ($C_{18'}$), 31.6 ($C_{10'}$), 30.6 ($C_{7''}$), 29.6, 29.6, 29.5, 29.5, 29.4, 29.1, 28.9, 26.6 ($C_{7''}$, $C_{6'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$, $C_{17'}$), 25.9, 25.9 (–C(CH_3)$_3$), 18.1, 18.1 (–C(CH_3)$_3$), 8.5, 7.5 ($C_{8''}$), −4.2, −4.5, −4.5 (–Si–*t*-Bu–(CH_3)$_2$); HRMS, ESI$^+$ calcd for $C_{58}H_{87}N_6O_{11}Si_2^+$ $(M + H)^+$ 1099.5966, found 1099.5969.

Compound 23c. Triazole **23c** was synthesized according to the general procedure for Cu(I)-catalyzed azide–alkyne cycloaddition from alkyne **5** (72 mg, 0.086 mmol) and azidopentanol **7c** (22 mg, 0.17 mmol, 2 equiv.). Flash chromatography (cyclohexane/EtOAc 3/7 to EtOAc) afforded **23c** as a white foam (47 mg, 56% yield): R_f 0.40 (cyclohexane/EtOAc 1/9); m.p. 104–108 °C; $[\alpha]_D$ −27 (c 1.0, CH_2Cl_2); IR (film) 3046br, 2307w, 1715s, 1464m, 1169w; ^{1}H NMR δ 8.77–8.37 (br s, 1H, NH), 7.91–7.80 (m, 2H, $H_{11''}$), 7.86 (d, 1H, $J_{H6–H5}$ = 8.5 Hz, H_6), 7.79–7.74 (m, 2H, $H_{12''}$), 7.39 (s, 1H, $H_{8'}$), 6.19 (d, 1H, $J_{H5–H6}$ = 8.5 Hz, H_5), 5.96 (d, 1H, $J_{H1'–H2'}$ = 6.0 Hz, $H_{1'}$), 5.35 (s, 1H, $H_{1''}$), 4.77 (d, 1H, $J_{H2''–H3''}$ = 6.0 Hz, $H_{2''}$), 4.68 (d, 1H, $J_{H3''–H2''}$ = 6.0 Hz, $H_{3''}$), 4.53 (dd, 1H, $J_{H4''–H5''a}$ = 6.0 Hz, $J_{H4''–H5''b}$ = 10.0 Hz, $H_{4''}$), 4.39–4.29 (m, 2H, $H_{9'}$), 4.20–4.17 (m, 2H, $H_{2'}$, $H_{5'}$), 4.00 (dd, 1H, $J_{H3'–H2'}$ = 4.0 Hz, $J_{H3'–H4'}$ = 3.0 Hz, $H_{3'}$), 3.90–3.81 (m, 3H, $H_{5''}$, $H_{4'}$), 3.65 (t, 2H, $J_{H13'–H12'}$ = 6.0 Hz, $H_{13'}$), 3.48 (dd, 1H, $J_{H6'a–H6'b}$ = 14.0 Hz, $J_{H6'a–H5'}$ = 4.0 Hz, $H_{6'a}$), 3.06 (dd, 1H, $J_{H6'b–H6'a}$ = 14.0 Hz, $J_{H6'b–H5'}$ = 10.5 Hz, $H_{6'b}$), 1.92 (qt, 2H, $J_{H10'–H9'}$ = $J_{H10'–H11'}$ = 7.0 Hz, $H_{10'}$), 1.73–1.64 (m, 2H, $H_{7''}$), 1.64–1.58 (m, 2H, $H_{12'}$), 1.56–1.50 (m, 2H, $H_{7''}$), 1.44–1.38 (m, 2H, $H_{11'}$), 0.88 (t, 3H, $J_{H8''–H7''}$ = 7.5 Hz, $H_{8''}$), 0.87 (s, 9H, –C(CH_3)$_3$), 0.84 (s, 9H, –C(CH_3)$_3$), 0.83 (t, 3H, $J_{H8''–H7''}$ = 7.5 Hz, $H_{8''}$), 0.08, 0.07, −0.01 (3s, 12H, –Si–*t*-Bu–(CH_3)$_2$); ^{13}C NMR δ 168.3 ($C_{9''}$), 163.2 (C_4), 150.6 (C_2), 143.1 ($C_{7'}$), 140.0 (C_6), 134.5 ($C_{12''}$), 131.9 ($C_{10''}$), 123.8 ($C_{11''}$), 122.3 ($C_{8'}$), 117.7 ($C_{6''}$), 112.3 ($C_{1''}$), 103.3 (C_5), 87.6 ($C_{1'}$), 86.4 ($C_{3''}$), 84.6 ($C_{4''}$), 84.4 ($C_{4'}$), 82.3 ($C_{2''}$), 80.8 ($C_{2'}$), 75.3 ($C_{5'}$), 72.7 ($C_{3'}$), 62.5 ($C_{13'}$), 50.2 ($C_{9'}$), 40.5 ($C_{5''}$), 31.9 ($C_{7''}$), 30.2 ($C_{10'}$), 29.5 ($C_{11'}$), 28.9 ($C_{6'}$), 28.9 ($C_{7''}$), 25.8, 25.8 (–C(CH$_3$)$_3$), 22.9 ($C_{12'}$), 18.1, 18.1 (–C(CH_3)$_3$), 8.4, 7.5 ($C_{8''}$), −4.2, −4.8, −4.5 (–Si–*t*-Bu–(CH$_3$)$_2$); HRMS, ESI$^+$ calcd for $C_{47}H_{73}N_6O_{12}Si_2^+$ $(M + H)^+$ 969.4820, found 969.4812.

Compound 23d. Triazole **23d** was synthesized according to the general procedure for Cu(I)-catalyzed azide–alkyne cycloaddition from alkyne **5** (62 mg, 0.074 mmol) and azidodecanol **7d** (29 mg, 0.15 mmol, 2 equiv.). Flash chromatography (cyclohexane/EtOAc 2/8) afforded **23d** as a white foam (45 mg, 59% yield): R_f 0.40 (cyclohexane/EtOAc 2/8); m.p. 112–114 °C; $[\alpha]_D$ −28 (c 0.7, CH_2Cl_2); IR (film) 2931br, 2301m, 1711s, 1457w, 1262w; ^{1}H NMR δ 8.17–8.80 (br d, 1H, NH), 7.90–7.80 (m, 2H, $H_{11''}$), 7.81 (d, 1H, $J_{H6–H5}$ = 7.0 Hz, H_6), 7.79–7.74 (m, 2H, $H_{12''}$), 7.48–7.38 (br s, 1H, $H_{8'}$), 6.18 (br d, 1H, $J_{H5–H6}$ = 7.0 Hz, H_5), 5.96 (d, 1H, $J_{H1'–H2'}$ = 3.5 Hz, $H_{1'}$), 5.35 (s, 1H, $H_{1''}$), 4.78 (d, 1H, $J_{H2''–H3''}$ = 5.5 Hz, $H_{2''}$), 4.68 (d, 1H, $J_{H3''–H2''}$ = 5.5 Hz, $H_{3''}$), 4.53 (dd, 1H, $J_{H4''–H5''a}$ = 3.0 Hz, $J_{H4''–H5''b}$ = 9.0 Hz, $H_{4''}$), 4.37–4.29 (m, 2H, $H_{9'}$), 4.25–4.17 (m, 2H, $H_{2'}$, $H_{5'}$), 4.00–3.90 (m, 1H, $H_{3'}$), 3.89–3.81 (m, 3H, $H_{5''}$, $H_{4'}$), 3.64 (t, 2H, $J_{H18'–H17'}$ = 7.0 Hz, $H_{18'}$), 3.51–3.45 (m, 1H, $H_{6'a}$), 3.14–3.06 (m, 1H, $H_{6'b}$), 1.93–1.58 (m, 2H, $H_{17'}$), 1.73–1.63 (m, 2H, $H_{7''}$), 1.55–1.49 (m, 4H, $H_{10'}$, $H_{7''}$), 1.35–1.24 (m, 12H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16'}$), 0.89 (t, 3H, $J_{H8''–H7''}$ = 7.0 Hz, $H_{8''}$), 0.87 (s, 9H, –C(CH_3)$_3$), 0.85 (s, 9H, –C(CH_3)$_3$), 0.83 (t, 3H, $J_{H8''–H7''}$ = 7.0 Hz, $H_{8''}$), 0.08, 0.00 (2s, 12H, –Si–*t*-Bu–(CH_3)$_2$); ^{13}C NMR δ 168.3 ($C_{9''}$), 162.9 (C_4), 150.4 (C_2), 142.9 ($C_{7'}$), 140.1 (C_6), 134.5 ($C_{12''}$), 131.9 ($C_{10''}$), 123.8 ($C_{11''}$), 122.3 ($C_{8'}$), 117.7 ($C_{6''}$), 112.4 ($C_{1''}$), 103.3 (C_5), 87.6 ($C_{1'}$), 86.4 ($C_{3''}$), 84.6 ($C_{4''}$), 84.5 ($C_{4'}$), 84.5 ($C_{2''}$), 82.3 ($C_{2'}$), 75.4 ($C_{5'}$), 72.3 ($C_{3'}$), 63.2 ($C_{18'}$), 50.5 ($C_{9'}$), 40.5 ($C_{5''}$), 32.9 ($C_{10'}$), 32.5 ($C_{7''}$), 30.5 ($C_{17'}$), 29.5, 29.5, 29.4, 29.1, 29.0, 29.0, 26.6 ($C_{7''}$, $C_{6'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$), 25.9, 25.8 (–C(CH$_3$)$_3$), 18.1, 18.1 (–C(CH_3)$_3$), 8.5, 7.5 ($C_{8''}$), −4.2, −4.4, −4.5 (–Si–*t*-Bu–(CH$_3$)$_2$); HRMS, ESI$^+$ calcd for $C_{52}H_{83}N_6O_{12}Si_2^+$ $(M + H)^+$ 1039.5602, found 1039.5606.

Compound 23e. To a suspension of azide **7e** (11.5 mg, 0.043 mmol, 1 equiv.), alkyne **5** (55 mg, 0.065 mmol, 1.5 equiv.), $CuSO_4{\cdot}5H_2O$ (1.1 mg, 0.004 mmol, 0.1 equiv.) in *tert*-butanol/H_2O (1.5 mL/500 μL) were successively added sodium ascorbate (2.6 mg, 0.013 mmol, 0.3 equiv.) and diisopropylethylamine (16 μL, 0.09 mmol, 2.2 equiv.). The resulting brown mixture was sonicated for 5 min, stirred at r.t. for 18 h and diluted with DCM (30 mL) and NH_4Cl (15 mL). The aqueous phase was extracted with DCM (6 × 30 mL) and the combined organic layers were washed with 10^{-3} M solution of tetrasodium EDTA, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was then purified by flash chromatography (EtOAc/MeOH 100/0 to 90/10) to afford **23e** as a pale red film (20.5 mg, 43% yield): R_f 0.10 (EtOAc/MeOH 90/10); $[\alpha]_D$ −23 (c 0.5, CH_2Cl_2); IR (film) 2930br, 2853w, 1713s, 1394w, 1100m; ^{1}H NMR δ 8.55–8.45 (br m, 1H, NH), 7.92–7.89 (m, 2H, $H_{11''}$), 7.86 (d, 1H, $J_{H6–H5}$ = 7.0 Hz, H_6), 7.79–7.75 (m, 2H, $H_{12''}$), 7.64–7.54 (br s, 1H, $H_{8'}$), 6.19 (br d, 1H, $J_{H5–H6}$ = 6.5 Hz, H_5), 6.06–5.95 (br s, 1H, $H_{1'}$), 5.38 (s, 1H, $H_{1''}$), 4.78 (d, 1H, $J_{H2''–H3''}$ = 6.0 Hz, $H_{2''}$), 4.70 (d, 1H, $J_{H3''–H2''}$ = 6.0 Hz, $H_{3''}$), 4.60–4.48 (m, 3H, $H_{9'}$, $H_{4''}$), 4.28–4.17 (m, 2H, $H_{2'}$, $H_{5'}$), 4.06–3.98 (m, 1H, $H_{3'}$), 3.90–3.77 (m, 5H, $H_{5''}$, $H_{4'}$, $H_{10'}$), 3.77–3.48 (m, 18H, $H_{6'a}$, $H_{6'b}$, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16'}$, $H_{17'}$, $H_{18'}$), 3.11–3.03 (br s, 1H, OH), 1.72–1.63 (m, 2H, $H_{7''}$), 1.59–1.43 (m, 2H, $H_{7''}$), 0.89 (t, 3H, $J_{H8''–H7''}$ = 7.5 Hz, $H_{8''}$), 0.87 (s, 9H, –C(CH_3)$_3$), 0.84 (s, 9H, –C(CH_3)$_3$), 0.83 (t, 3H, $J_{H8''–H7''}$ = 7.0 Hz, $H_{8''}$), 0.08, 0.07, −0.01 (3s, 12H, –Si–*t*-Bu–(CH_3)$_2$); ^{13}C NMR δ 168.3 ($C_{9''}$), 163.2 (C_4), 150.5 (C_2), 140.1 ($C_{7'}$), 140.0 (C_6), 134.5 ($C_{12''}$), 131.9 ($C_{10''}$), 123.8 ($C_{11''}$), 123.8 ($C_{8'}$), 117.7 ($C_{6''}$), 112.3 ($C_{1''}$), 103.4 (C_5), 87.3 ($C_{1'}$), 86.4 ($C_{3''}$), 84.6 ($C_{4''}$), 84.5 ($C_{4'}$), 82.4 ($C_{2''}$), 80.8 ($C_{2'}$), 75.3 ($C_{5'}$), 73.0 ($C_{3'}$), 72.8, 70.7, 70.6, 70.4, 69.6, 61.7 (C_{PEG}), 50.5 ($C_{9'}$), 40.5 ($C_{5''}$), 29.5 ($C_{7''}$), 28.9 ($C_{7''}$), 25.9, 25.9 (–C(CH$_3$)$_3$), 18.1, 18.1 (–C(CH_3)$_3$), 8.5, 7.5 ($C_{8''}$), −4.2, −4.4, −4.5, −4.5 (–Si–*t*-Bu–(CH$_3$)$_2$); HRMS, ESI$^+$ calcd for $C_{52}H_{83}N_6O_{16}Si_2^+$ $(M + H)^+$ 1103.5399, found 1103.5425.

Compound 23f. Triazole **23f** was synthesized according to the general procedure for Cu(I)-catalyzed azide–alkyne cycloaddition from alkyne **5** (67 mg, 0.08 mmol) and azide **7f** (52.3 mg, 0.14 mmol, 2 equiv.). Flash chromatography (cyclohexane/EtOAc 1/1) afforded **23f** as a white foam (57 mg, 61% yield): R_f 0.20 (cyclohexane/EtOAc 1/1); m.p. 114–118 °C; $[\alpha]_D$ −29 (c 1.0, CH_2Cl_2); IR (film) 2930m, 1773w, 1701s, 1395m, 1086m, 837m, 721m; ^{1}H NMR δ 8.56 (d, 1H, $J_{NH–H5}$ = 2.0 Hz,

NH), 7.89–7.87 (m, 3H, $H_{11''}$, H_6), 7.84–7.81 (m, 2H, $H_{21'}$), 7.78–7.74 (m, 2H, $H_{22'}$), 7.72–7.69 (m, 2H, $H_{12''}$), 7.36 (s, 1H, $H_{8'}$), 6.20 (dd, 1H, J_{H5-H6} = 8.0 Hz, J_{H5-NH} = 2.0 Hz, H_5), 5.96 (d, 1H, $J_{H1'-H2'}$ = 5.5 Hz, $H_{1'}$), 5.35 (s, 1H, $H_{1''}$), 4.78 (d, 1H, $J_{H2''-H3''}$ = 6.0 Hz, $H_{2''}$), 4.68 (d, 1H, $J_{H3''-H2''}$ = 6.0 Hz, $H_{3''}$), 4.54–4.51 (m, 1H, $H_{4''}$), 4.34–4.25 (m, 2H, $H_{9'}$), 4.19–4.16 (m, 2H, $H_{2'}$, $H_{5'}$), 3.99 (t, 1H, $J_{H3'-H2'}$ = $J_{H3'-H4'}$ = 3.5 Hz, $H_{3'}$), 3.88–3.82 (m, 3H, $H_{5''}$, $H_{4'}$), 3.68 (t, 2H, $J_{H18'-H17'}$ = 7.0 Hz, $H_{18'}$), 3.50 (dd, 1H, $J_{H6'a-H6'b}$ = 14.0 Hz, $J_{H6'a-H5'}$ = 5.0 Hz, $H_{6'a}$), 3.07 (dd, 1H, $J_{H6'b-H6'a}$ = 14.0 Hz, $J_{H6'b-H5'}$ = 11.0 Hz, $H_{6'b}$), 1.89–1.84 (m, 2H, $H_{10'}$), 1.69–1.62 (m, 4H, $H_{17'}$, $H_{7''}$), 1.55–1.57–1.42 (m, 2H, $H_{7''}$), 1.24–1.19 (m, 12H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16'}$), 0.82 (t, 3H, $J_{H8''-H7''}$ = 8.0 Hz, $H_{8''}$), 0.79 (s, 9H, –C(CH_3)$_3$), 0.76 (s, 9H, –C(CH_3)$_3$), 0.75 (t, 3H, $J_{H8''-H7''}$ = 8.0 Hz, $H_{8''}$), 0.01, 0.00, −0.01, −0.1 (4s, 12H, –Si–*t*-Bu–(CH_3)$_2$); ^{13}C NMR δ 168.6, 168.2 ($C_{19'}$, $C_{9''}$), 163.2 (C_4), 150.5 (C_2), 142.9 ($C_{7'}$), 139.9 (C_6), 134.5 ($C_{12''}$), 133.9 ($C_{22'}$), 132.3 ($C_{20'}$), 131.9 ($C_{10''}$), 123.8 ($C_{11''}$), 123.3 ($C_{21'}$), 122.0 ($C_{8'}$), 117.7 ($C_{6''}$), 112.3 ($C_{1''}$), 103.2 (C_5), 87.6 ($C_{1'}$), 86.4 ($C_{3''}$), 84.5 ($C_{4''}$), 84.3 ($C_{4'}$), 82.2 ($C_{2''}$), 80.8 ($C_{2'}$), 75.4 ($C_{5'}$), 72.7 ($C_{3'}$), 50.4 ($C_{9'}$), 40.5 ($C_{5''}$), 38.2 ($C_{18'}$), 30.5 ($C_{7''}$), 29.5, 29.4, 29.4, 29.2, 29.1, 28.9, 28.7, 26.9, 26.6 ($C_{7''}$, $C_{6'}$, $C_{10'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$, $C_{17'}$), 25.9, 25.8 (–C(*C*H_3)$_3$), 18.1, 18.1 (–*C*(CH$_3$)$_3$), 8.4, 7.5 ($C_{8''}$), −4.2, −4.5, −4.5, −4.6 (–Si–*t*-Bu–(*C*H_3)$_2$); HRMS ESI$^+$ calcd for $C_{60}H_{86}N_7O_{13}Si_2^+$ (M + H)$^+$ 1168.5817, found 1168.5839.

Compound 23g. Triazole **23g** was synthesized according to the general procedure for Cu(I)-catalyzed azide–alkyne cycloaddition from alkyne **5** (140 mg, 0.17 mmol) and azide **7g** (110 mg, 0.33 mmol, 2 equiv.). Flash chromatography (cyclohexane/EtOAc 6/4) afforded **23g** as a white foam (133 mg, 67% yield): R_f 0.26 (cyclohexane/EtOAc 6/4); m.p. 122–128 °C; $[\alpha]_D$ −26 (*c* 0.5, CH_2Cl_2); IR (film) 2930m, 2351w, 1710s, 1693s, 1393m; ^{1}H NMR δ 8.22 (br d, 1H, J_{NH-H5} = 2.0 Hz, NH), 7.89–7.86 (m, 2H, $H_{11''}$), 7.85–7.82 (m, 3H, H_6, $H_{17'}$), 7.77–7.74 (m, 4H, $H_{12''}$, $H_{22'}$), 7.58–7.55 (m, 1H, $H_{23'}$), 7.48 (d, 2H, $J_{H21'-H22'}$ = 8.0 Hz, $H_{21'}$), 7.45 (d, 2H, $J_{H11'-H12'}$ = 8.5 Hz, $H_{11'}$), 7.36 (s, 1H, $H_{8'}$), 7.28 (d, 2H, $J_{H12'-H11'}$ = 8.5 Hz, $H_{12'}$), 7.03–6.99 (m, 2H, $H_{16'}$), 6.17 (dd, 1H, J_{H5-H6} = 8.0 Hz, J_{H5-NH} = 2.0 Hz, H_5), 5.95 (d, 1H, $J_{H1'-H2'}$ = 6.0 Hz, $H_{1'}$), 5.56 (d, 1H, $J_{H9'a-H9'b}$ = 15.0 Hz, $H_{9'a}$), 5.47 (d, 1H, $J_{H9'b-H9'a}$ = 15.0 Hz, $H_{9'b}$), 5.34 (s, 1H, $H_{1''}$), 5.14 (s, 2H, $H_{14'}$), 4.78 (d, 1H, $J_{H2''-H3''}$ = 6.0 Hz, $H_{2''}$), 4.67 (d, 1H, $J_{H3''-H2''}$ = 6.0 Hz, $H_{3''}$), 4.52 (dd, 1H, $J_{H4''-H5''a}$ = 6.5 Hz, $J_{H4''-H5''b}$ = 9.5 Hz, $H_{4''}$), 4.20–4.17 (m, 2H, $H_{2'}$, $H_{5'}$), 4.00 (dd, 1H, $J_{H3'-H2'}$ = 4.5 Hz, $J_{H3'-H4'}$ = 3.0 Hz, $H_{3'}$), 3.86 (dd, 1H, $J_{H4'-H3'}$ = 3.0 Hz, $J_{H4'-H5'}$ = 2.0 Hz, $H_{4'}$), 3.84–3.78 (m, 2H, $H_{5''a}$, $H_{5''b}$), 3.47 (dd, 1H, $J_{H6'a-H6'b}$ = 14.0 Hz, $J_{H6'a-H5'}$ = 5.0 Hz, $H_{6'a}$), 3.07 (dd, 1H, $J_{H6'b-H6'a}$ = 14.0 Hz, $J_{H6'b-H5'}$ = 10.5 Hz, $H_{6'b}$), 1.71–1.62 (m, 2H, $H_{7''}$), 1.55–1.50 (m, 2H, $H_{7''}$), 0.88 (t, 3H, $J_{H8''-H7''}$ = 7.5 Hz, $H_{8''}$), 0.87 (s, 9H, –C(CH_3)$_3$), 0.84 (s, 9H, –C(CH_3)$_3$), 0.81 (t, 3H, $J_{H8''-H7''}$ = 7.5 Hz, $H_{8''}$), 0.07, 0.07, 0.06, −0.03 (4s, 12H, –Si–*t*-Bu–(CH_3)$_2$); ^{13}C NMR δ 195.6 ($C_{19'}$), 168.2 ($C_{9''}$), 162.9 (C_4), 162.3 ($C_{15'}$), 150.4 (C_2), 143.6 ($C_{7'}$), 139.9 (C_6), 138.3 ($C_{20'}$), 137.1 ($C_{13'}$), 134.8 ($C_{10'}$), 134.4 ($C_{12''}$), 132.7 ($C_{17'}$), 132.1 ($C_{23'}$), 131.9 ($C_{10''}$), 130.7 ($C_{18'}$), 129.9 ($C_{21'}$), 128.4 ($C_{22'}$), 128.3 ($C_{11'}$), 128.3 ($C_{12'}$), 123.9 ($C_{11''}$), 122.3 ($C_{8'}$), 117.7 ($C_{6''}$), 114.9 ($C_{16'}$), 112.5 ($C_{1''}$), 103.2 (C_5), 87.6 ($C_{1'}$), 86.4 ($C_{3''}$), 84.5 ($C_{4''}$), 84.5 ($C_{4'}$), 82.2 ($C_{2''}$), 80.8 ($C_{2'}$), 75.4 ($C_{5'}$), 72.8 ($C_{3'}$), 69.7 ($C_{14'}$), 53.9 ($C_{9'}$), 40.4 ($C_{5''}$), 29.5 ($C_{7''}$), 28.9 ($C_{7''}$), 28.9 ($C_{6'}$), 25.9, 25.8 (–C(*C*H_3)$_3$), 18.1, 18.1 (–*C*(CH$_3$)$_3$), 8.5, 7.5 ($C_{8''}$), −4.2, −4.5, −4.5, −4.5 (–Si–*t*-Bu–(*C*H_3)$_2$); HRMS ESI$^+$ calcd for $C_{63}H_{79}N_6O_{13}Si_2^+$ (M + H)$^+$ 1183.5238, found 1183.5230.

Compound 23h. Triazole **23h** was synthesized according to the general procedure for Cu(I)-catalyzed azide–alkyne cycloaddition from alkyne **5** (108 mg, 0.13 mmol) and azide **7h** (98 mg, 0.26 mmol, 2 equiv.). Flash chromatography (cyclohexane/EtOAc 1/1) afforded **23h** as a white foam (90 mg, 57% yield): R_f 0.27 (cyclohexane/EtOAc 1/1); m.p. 96–102 °C; $[\alpha]_D$ −25 (*c* 1.0, CH_2Cl_2); IR (film) 2930m, 1710s, 1696s, 1256s; ^{1}H NMR δ 8.63–8.60 (m, 1H, NH), 7.89–7.87 (m, 3H, $H_{11''}$, H_6), 7.83–7.80 (m, 2H, $H_{21'}$), 7.77–7.74 (m, 4H, $H_{12''}$, $H_{25'}$), 7.57–7.54 (m, 1H, $H_{27'}$), 7.47 (t, 2H, $J_{H26'-H27'}$ = $J_{H26'-H25'}$ = 8.0 Hz, $H_{26'}$), 7.38 (s, 1H, $H_{8'}$), 6.96–6.93 (m, 2H, $H_{20'}$), 6.20 (dd, 1H, J_{H5-H6} = 8.0 Hz, J_{H5-NH} = 2.0 Hz, H_5), 5.97 (d, 1H, $J_{H1'-H2'}$ = 5.5 Hz, $H_{1'}$), 5.33 (s, 1H, $H_{1''}$), 4.78 (d, 1H, $J_{H2''-H3''}$ = 6.0 Hz, $H_{2''}$), 4.68 (d, 1H, $J_{H3''-H2''}$ = 6.0 Hz, $H_{3''}$), 4.53 (dd, 1H, $J_{H4''-H5''a}$ = 7.0 Hz, $J_{H4''-H5''b}$ = 9.0 Hz, $H_{4''}$), 4.36–4.26 (m, 2H, $H_{9'}$), 4.20–4.18 (m, 2H, $H_{2'}$, $H_{5'}$), 4.03 (t, 1H, $J_{H18'-H19'}$ = 6.5 Hz, $H_{18'}$), 4.00 (t, 1H, $J_{H3'-H2'}$ = $J_{H3'-H4'}$ = 4.5 Hz, $H_{3'}$), 3.92–3.83 (m, 3H, $H_{5''a}$, $H_{5''b}$, $H_{4'}$), 3.52 (dd, 1H, $J_{H6'a-H6'b}$ = 14.0 Hz, $J_{H6'a-H5'}$ = 5.0 Hz, $H_{6'a}$), 3.08 (dd, 1H, $J_{H6'b-H6'a}$ = 14.0 Hz, $J_{H6'b-H5'}$ = 11.0 Hz, $H_{6'b}$), 1.92–1.85 (m, 2H, $H_{10'}$), 1.84–1.78 (m, 2H, $H_{17'}$), 1.73–1.61 (m, 2H, $H_{7''}$), 1.57–1.50 (m, 2H, $H_{7''}$), 1.48–1.44 (m, 2H, $H_{16'}$), 1.38–1.26 (m, 10H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$), 0.88 (t, 3H, $J_{H8''-H7''}$ = 8.0 Hz, $H_{8''}$), 0.86 (s, 9H, –C(CH_3)$_3$), 0.84 (s, 9H, –C(CH_3)$_3$), 0.82 (t, 3H, $J_{H8''-H7''}$ = 8.0 Hz, $H_{8''}$), 0.08, 0.08, 0.07, −0.01 (4s, 12H, –Si–*t*-Bu–(CH_3)$_2$); ^{13}C NMR δ 195.6 ($C_{23'}$), 168.2 ($C_{9''}$), 163.2 (C_4), 162.9 ($C_{19'}$), 150.5 (C_2), 142.9 ($C_{7'}$), 139.9 (C_6), 138.5 ($C_{24'}$), 134.5 ($C_{12''}$), 132.7 ($C_{21'}$), 131.9 ($C_{27'}$), 132.2 ($C_{21'}$), 130.1 ($C_{10''}$), 129.8 ($C_{25'}$), 128.3 ($C_{26'}$), 123.8 ($C_{11''}$), 122.2 ($C_{8'}$), 117.7 ($C_{6''}$), 114.9 ($C_{20'}$), 112.4 ($C_{1''}$), 103.2 (C_5), 87.6 ($C_{1'}$), 86.4 ($C_{4'}$), 84.5 ($C_{2''}$), 84.4 ($C_{4''}$), 82.2 ($C_{2'}$), 80.8 ($C_{3''}$), 75.4 ($C_{3'}$), 72.7 ($C_{5'}$), 68.4 ($C_{18'}$), 50.4 ($C_{9'}$), 40.5 ($C_{5''}$), 30.5 ($C_{17'}$), 29.6, 29.5, 29.4, 29.2, 29.1, 28.9, 26.6, 26.1 ($C_{6'}$, $C_{10'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$, $C_{7''}$), 25.9, 25.8 (–C(*C*H_3)$_3$), 18.1, 18.1 (–*C*(CH$_3$)$_3$), 8.4, 7.4 ($C_{8''}$), −4.2, −4.5, −4.5, −4.6 (–Si–*t*-Bu–(*C*H_3)$_2$); HRMS ESI$^+$ calcd for $C_{65}H_{91}N_6O_{13}Si_2^+$ (M + H)$^+$ 1219.6177, found 1219.6187.

General procedure for the preparation of *N*-triazoles 24a–h

To a solution of azide **6** (1 equiv.) and alkyne partner **8a–h** (1 to 2 equiv.) in *tert*-BuOH/H_2O (1.5 mL/500 μL) were successively added $CuSO_4$ (0.1 equiv.), sodium ascorbate (0.3 equiv.) and *N*-diisopropylethylamine (2.2 equiv.). The suspension was sonicated for 5 min to solubilise all reagents. The mixture was stirred at r.t. for 18 h and diluted with DCM (30 mL) and NH_4Cl (15 mL). The aqueous phase was extracted with DCM (6 × 30 mL) and the combined organic layers were washed with 10^{-3} M solution of tetra-sodium EDTA, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was then purified by flash chromatography to give the corresponding *N*-triazole **24a–h**.

Compound 24a. Triazole **24a** was synthesized according to the general procedure for the preparation of *N*-triazoles from

azide **6** (52 mg, 0.06 mmol) and 1-dodecyne **8a** (25 mg, 0.12 mmol, 2 equiv.). Flash chromatography (cyclohexane/EtOAc 7/3) afforded **24a** as a white foam (35 mg, 55% yield): R_f 0.61 (cyclohexane/EtOAc 1/1); m.p. 102–106 °C; $[\alpha]_D$ −30 (*c* 0.5, CH_2Cl_2); IR (film) 3060m, 2928m, 2856m, 1714s, 1386m; ^{1}H NMR δ 8.63 (br d, 1H, $J_{NH–H5}$ = 1.0 Hz, NH), 7.91–7.88 (m, 2H, $H_{11''}$), 7.85 (d, 1H, $J_{H6–H5}$ = 8.0 Hz, H_6), 7.79–7.76 (m, 2H, $H_{12''}$), 7.33 (s, 1H, $H_{7'}$), 6.16 (dd, 1H, $J_{H5–H6}$ = 8.0 Hz, $J_{H5–NH}$ = 1.0 Hz, H_5), 5.92 (d, 1H, $J_{H1'–H2'}$ = 5.0 Hz, $H_{1'}$), 5.34 (s, 1H, $H_{1''}$), 5.02 (dd, 1H, $J_{H6'a–H6'b}$ = 13.0 Hz, $J_{H6'a–H5'}$ = 5.0 Hz, $H_{6'a}$), 4.77 (d, 1H, $J_{H2''–H3''}$ = 6.0 Hz, $H_{2''}$), 4.68 (d, 1H, $J_{H3''–H2''}$ = 6.0 Hz, $H_{3''}$), 4.58 (dd, 1H, $J_{H4''–H5''a}$ = 5.5 Hz, $J_{H4''–H5''b}$ = 10.0 Hz, $H_{4''}$), 4.44 (dd, 1H, $J_{H6'b–H6'a}$ = 13.0 Hz, $J_{H6'b–H5'}$ = 10.5 Hz, $H_{6'b}$), 4.26 (ddd, 1H, $J_{H5'–H6'a}$ = 5.0 Hz, $J_{H5'–H6'b}$ = 10.5 Hz, $J_{H5'–H4'}$ = 1.0 Hz, $H_{5'}$), 4.17 (t, 1H, $J_{H2'–H1'}$ = $J_{H2'–H3'}$ = 5.0 Hz, $H_{2'}$), 4.02 (t, 1H, $J_{H3'–H2'}$ = $J_{H3'–H4'}$ = 5.0 Hz, $H_{3'}$), 3.84 (dd, 1H, $J_{H5''a–H5''b}$ = 14.0 Hz, $J_{H5''a–H4''}$ = 5.5 Hz, $H_{5''a}$), 3.80 (dd, 1H, $J_{H5''b–H5''a}$ = 14.0 Hz, $J_{H5''b–H4''}$ = 10.0 Hz, $H_{5''b}$), 3.60 (dd, 1H, $J_{H4'–H3'}$ = 5.0 Hz, $J_{H4'–H5'}$ = 1.0 Hz, $H_{4'}$), 2.74–2.64 (m, 2H, $H_{9'}$), 1.74–1.61 (m, 4H, $H_{10'}$, $H_{7''}$), 1.58–1.50 (m, 2H, $H_{7''}$), 1.38–1.25 (m, 14H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16'}$, $H_{17'}$), 0.91–0.86 (m, 6H, $H_{8''}$, $H_{18'}$), 0.87 (s, 9H, –C(CH_3)$_3$), 0.84 (s, 9H, –C(CH_3)$_3$), 0.83–0.82 (m, 3H, $H_{8''}$), 0.11, 0.08, 0.06, −0.01 (4s, 12H, –Si–*t*-Bu–(CH_3)$_2$); ^{13}C NMR δ 168.2 ($C_{9''}$), 163.1 (C_4), 150.4 (C_2), 142.9 ($C_{8'}$), 139.6 (C_6), 134.6 ($C_{12''}$), 131.9 ($C_{10''}$), 123.9 ($C_{11''}$), 122.1 ($C_{7'}$), 118.1 ($C_{6''}$), 112.7 ($C_{1''}$), 103.1 (C_5), 88.3 ($C_{1'}$), 86.3 ($C_{3''}$), 84.6 ($C_{4''}$), 82.4 ($C_{4'}$), 82.1 ($C_{2''}$), 79.0 ($C_{5'}$), 75.4 ($C_{2'}$), 71.7 ($C_{3'}$), 50.5 ($C_{6'}$), 40.5 ($C_{5''}$), 32.9 ($C_{7''}$), 29.8, 29.8, 29.7, 29.7, 29.5, 29.5, 28.9 ($C_{7''}$, $C_{9'}$, $C_{10'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$), 25.8, 25.7 (–C(*C*H$_3$)$_3$), 22.8 ($C_{17'}$), 18.1, 18.0 (–*C*(CH$_3$)$_3$), 14.2 ($C_{18'}$), 8.5, 7.5 ($C_{8''}$), −4.1, −4.4, −4.6, −4.7 (–Si–*t*-Bu–(*C*H$_3$)$_2$); HRMS, ESI$^+$ calcd for $C_{52}H_{83}N_6O_{11}Si_2^+$ (M + H)$^+$ 1023.5653, found 1023.5671.

Compound 24b. Triazole **24b** was synthesized according to the general procedure for the preparation of *N*-triazoles from azide **6** (40 mg, 0.47 mmol) and 12-phenyl-dodec-1-yne **8b** (17 mg, 0.07 mmol, 1.5 equiv.). Flash chromatography (cyclohexane/EtOAc 7/3) afforded **24b** as a white foam (31 mg, 60% yield): R_f 0.11 (cyclohexane/EtOAc 7/3); m.p. 106–110 °C; $[\alpha]_D$ −34 (*c* 0.5, CH_2Cl_2); IR (film) 2928m, 2848w, 2163m, 1693s, 1394m, 1090w, 837m; ^{1}H NMR δ 8.61 (br s, 1H, NH), 7.92–7.88 (m, 2H, $H_{11''}$), 7.85 (d, 1H, $J_{H6–H5}$ = 8.0 Hz, H_6), 7.79–7.76 (m, 2H, $H_{12''}$), 7.32 (s, 1H, $H_{7'}$), 7.28–7.25 (m, 2H, $H_{20'}$), 7.18–7.15 (m, 3H, $H_{21'}$, $H_{22'}$), 6.16 (dd, 1H, $J_{H5–H6}$ = 8.0 Hz, $J_{H5–NH}$ = 2.5 Hz, H_5), 5.92 (d, 1H, $J_{H1'–H2'}$ = 5.0 Hz, $H_{1'}$), 5.35 (s, 1H, $H_{1''}$), 5.03 (dd, 1H, $J_{H6'a–H6'b}$ = 13.0 Hz, $J_{H6'a–H5'}$ = 5.0 Hz, $H_{6'a}$), 4.77 (d, 1H, $J_{H2''–H3''}$ = 6.0 Hz, $H_{2''}$), 4.69 (d, 1H, $J_{H3''–H2''}$ = 6.0 Hz, $H_{3''}$), 4.58 (dd, 1H, $J_{H4''–H5''a}$ = 5.5 Hz, $J_{H4''–H5''b}$ = 10.0 Hz, $H_{4''}$), 4.45–4.41 (m, 1H, $H_{6'b}$), 4.28–4.25 (m, 1H, $H_{5'}$), 4.17 (t, 1H, $J_{H2'–H1'}$ = $J_{H2'–H3'}$ = 5.0 Hz, $H_{2'}$), 4.02 (t, 1H, $J_{H3'–H2'}$ = $J_{H3'–H4'}$ = 5.0 Hz, $H_{3'}$), 3.84 (dd, 1H, $J_{H5''a–H5''b}$ = 13.5 Hz, $J_{H5''a–H4''}$ = 5.5 Hz, $H_{5''a}$), 3.80 (dd, 1H, $J_{H5''b–H5''a}$ = 13.5 Hz, $J_{H5''b–H4''}$ = 10.0 Hz, $H_{5''b}$), 3.60–3.59 (m, 1H, $H_{4'}$), 2.73–2.68 (m, 2H, $H_{9'}$), 2.59 (t, 2H, $J_{H18'–H17'}$ = 7.5 Hz, $H_{18'}$), 1.73–1.58 (m, 6H, $H_{10'}$, $H_{17'}$, $H_{7''}$), 1.57–1.52 (m, 2H, $H_{7''}$), 1.38–1.24 (m, 12H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16'}$), 0.90 (t, 3H, $J_{H8''–H7''}$ = 7.5 Hz, $H_{8''}$), 0.87 (s, 9H, –C(CH_3)$_3$), 0.85–0.82 (m, 12H, –C(CH_3)$_3$, $H_{8''}$), 0.83–0.82 (m, 3H, $H_{8''}$), 0.11, 0.08, 0.06, −0.01 (4s, 12H, –Si–*t*-Bu–(CH_3)$_2$); ^{13}C NMR δ 168.2 ($C_{9''}$), 163.1 (C_4), 150.4 (C_2), 143.1 ($C_{19'}$), 139.5 ($C_{8'}$), 134.6 (C_6), 134.6 ($C_{12''}$), 131.9 ($C_{10''}$), 128.5 ($C_{21'}$), 128.3 ($C_{20'}$), 125.7 ($C_{22'}$), 123.9 ($C_{11''}$), 121.9 ($C_{7'}$), 118.1 ($C_{6''}$), 112.7 ($C_{1''}$), 103.1 (C_5), 88.3 ($C_{1'}$), 86.3 ($C_{3''}$), 84.6 ($C_{4''}$), 82.4 ($C_{4'}$), 82.1 ($C_{2''}$), 79.0 ($C_{2'}$), 75.4 ($C_{5'}$), 71.7 ($C_{3'}$), 49.9 ($C_{9'}$), 40.4 ($C_{5''}$), 36.1 ($C_{18'}$), 31.6 ($C_{10'}$), 29.8, 29.8, 29.7, 29.7, 29.6, 29.5, 29.5 ($C_{7''}$, $C_{6'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$, $C_{17'}$), 25.9, 25.9 (–C(*C*H$_3$)$_3$), 18.1, 18.0 (–*C*(CH$_3$)$_3$), 8.5, 7.5 ($C_{8''}$), −4.1, −4.4, −4.6, −4.7 (–Si–*t*-Bu–(*C*H$_3$)$_2$); HRMS, ESI$^+$ calcd for $C_{58}H_{87}N_6O_{11}Si_2^+$ (M + H)$^+$ 1099.5966, found 1099.5994.

Compound 24c. Triazole **24c** was synthesized according to the general procedure for the preparation of *N*-triazoles from azide **6** (40 mg, 0.047 mmol) and 5-heptyne-1-ol **8c** (8 mg, 0.07 mmol, 1.5 equiv.). Flash chromatography (cyclohexane/EtOAc 3/7) afforded **24c** as a white foam (24 mg, 53% yield): R_f 0.12 (cyclohexane/EtOAc 3/7); m.p. 110–112 °C; $[\alpha]_D$ −22 (*c* 0.5, CH_2Cl_2); IR (film) 2931w, 2857w, 1715s, 1523w, 1256m, 1159m, 838w; ^{1}H NMR δ 8.76–8.66 (br m, 1H, NH), 7.94–7.89 (m, 2H, $H_{11''}$), 7.83 (d, 1H, $J_{H6–H5}$ = 8.5 Hz, H_6), 7.79–7.76 (m, 2H, $H_{12''}$), 7.34 (s, 1H, $H_{7'}$), 6.15 (dd, 1H, $J_{H5–H6}$ = 8.5 Hz, $J_{H5–NH}$ = 2.0 Hz, H_5), 5.92 (d, 1H, $J_{H1'–H2'}$ = 5.0 Hz, $H_{1'}$), 5.34 (s, 1H, $H_{1''}$), 5.02 (dd, 1H, $J_{H6'a–H6'b}$ = 13.5 Hz, $J_{H6'a–H5'}$ = 5.5 Hz, $H_{6'a}$), 4.77 (d, 1H, $J_{H2''–H3''}$ = 6.0 Hz, $H_{2''}$), 4.69 (d, 1H, $J_{H3''–H2''}$ = 6.0 Hz, $H_{3''}$), 4.57 (dd, 1H, $J_{H4''–H5''a}$ = 6.0 Hz, $J_{H4''–H5''b}$ = 10.0 Hz, $H_{4''}$), 4.43 (dd, 1H, $J_{H6'b–H6'a}$ = 13.5 Hz, $J_{H6'b–H5'}$ = 10.0 Hz, $H_{6'b}$), 4.27 (ddd, 1H, $J_{H5'–H6'a}$ = 5.5 Hz, $J_{H5'–H6'b}$ = 10.0 Hz, $J_{H5'–H4'}$ = 1.0 Hz, $H_{5'}$), 4.17 (t, 1H, $J_{H2'–H1'}$ = $J_{H2'–H3'}$ = 5.0 Hz, $H_{2'}$), 4.02 (t, 1H, $J_{H3'–H2'}$ = $J_{H3'–H4'}$ = 5.0 Hz, $H_{3'}$), 3.83 (dd, 1H, $J_{H5''a–H5''b}$ = 13.5 Hz, $J_{H5''a–H4''}$ = 6.0 Hz, $H_{5''a}$), 3.80 (dd, 1H, $J_{H5''b–H5''a}$ = 13.5 Hz, $J_{H5''b–H4''}$ = 10.0 Hz, $H_{5''b}$), 3.65 (t, 2H, $J_{H13'–H12'}$ = 6.5 Hz, $H_{13'}$), 3.59 (dd, 1H, $J_{H4'–H3'}$ = 5.0 Hz, $J_{H4'–H5'}$ = 1.0 Hz, $H_{4'}$), 2.76–2.66 (m, 2H, $H_{9'}$), 1.73–1.66 (m, 4H, $H_{10'}$, $H_{7''}$), 1.61 (qt, 2H, $J_{H12'–H13'}$ = $J_{H12'–H11'}$ = 6.5 Hz, $H_{12'}$), 1.56–1.54 (m, 2H, $H_{7''}$), 1.44 (qt, 2H, $J_{H11'–H12'}$ = $J_{H11'–H10'}$ = 6.5 Hz, $H_{11'}$), 0.89 (t, 3H, $J_{H8''–H7''}$ = 7.0 Hz, $H_{8''}$), 0.86 (s, 9H, –C(CH_3)$_3$), 0.85–0.82 (m, 12H, –C(CH_3)$_3$, $H_{8''}$), 0.10, 0.08, 0.07, −0.01 (4s, 12H, –Si–*t*-Bu–(CH_3)$_2$); ^{13}C NMR δ 168.2 ($C_{9''}$), 163.1 (C_4), 150.4 (C_2), 148.3 ($C_{8'}$), 139.6 (C_6), 134.6 ($C_{12''}$), 131.9 ($C_{10''}$), 123.9 ($C_{11''}$), 122.2 ($C_{7'}$), 118.1 ($C_{6''}$), 112.6 ($C_{1''}$), 103.2 (C_5), 88.2 ($C_{1'}$), 86.3 ($C_{3''}$), 84.6 ($C_{4''}$), 82.6 ($C_{4'}$), 82.1 ($C_{2''}$), 79.0 ($C_{5'}$), 75.3 ($C_{2'}$), 71.2 ($C_{3'}$), 62.8 ($C_{13'}$), 49.9 ($C_{6'}$), 40.4 ($C_{5''}$), 32.5 ($C_{12'}$), 29.5 ($C_{7''}$), 29.3 ($C_{10'}$), 28.9 ($C_{7''}$), 25.8, 25.8 (–C(*C*H$_3$)$_3$), 25.6 ($C_{9'}$), 25.5 ($C_{11'}$), 18.1, 18.1 (–*C*(CH$_3$)$_3$), 8.5, 7.5 ($C_{8''}$), −4.1, −4.4, −4.6, −4.7 (–Si–*t*-Bu–(*C*H$_3$)$_2$); HRMS, ESI$^+$ calcd for $C_{47}H_{73}N_6O_{12}Si_2^+$ (M + H)$^+$ 969.4820, found 969.4824.

Compound 24d. Triazole **24d** was synthesized according to the general procedure for the preparation of *N*-triazoles from azide **6** (50 mg, 0.06 mmol) and 12-dodecyne-1-ol **8d** (20 mg, 0.12 mmol, 2 equiv.). Flash chromatography (cyclohexane/EtOAc 1/1) afforded **24d** as a white foam (43 mg, 66% yield): R_f 0.21 (cyclohexane/EtOAc 1/1); m.p. 110–112 °C; $[\alpha]_D$ −23 (*c* 0.5, CH_2Cl_2); IR (film) 2929br, 2853w, 1712s, 1459w, 1396m; ^{1}H NMR δ 8.70 (br s, 1H, NH), 7.91–7.89 (m, 2H, $H_{11''}$), 7.84 (d, 1H, $J_{H6–H5}$ = 8.5 Hz, H_6), 7.79–7.76 (m, 2H, $H_{12''}$), 7.32 (s, 1H, $H_{7'}$), 6.15 (d, 1H, $J_{H5–H6}$ = 8.5 Hz, H_5), 5.92 (d, 1H, $J_{H1'–H2'}$ = 5.0

Hz, $H_{1'}$), 5.35 (s, 1H, $H_{1''}$), 5.02 (dd, 1H, $J_{H6'a–H6'b}$ = 13.0 Hz, $J_{H6'a–H5'}$ = 5.0 Hz, $H_{6'a}$), 4.77 (d, 1H, $J_{H2''–H3''}$ = 6.0 Hz, $H_{2''}$), 4.68 (d, 1H, $J_{H3''–H2''}$ = 6.0 Hz, $H_{3''}$), 4.58 (dd, 1H, $J_{H4''–H5''a}$ = 6.0 Hz, $J_{H4''–H5''b}$ = 10.0 Hz, $H_{4''}$), 4.43 (dd, 1H, $J_{H6'b–H6'a}$ = 13.0 Hz, $J_{H6'b–H5'}$ = 10.5 Hz, $H_{6'b}$), 4.27 (ddd, 1H, $J_{H5'–H6'a}$ = 5.0 Hz, $J_{H5'–H6'b}$ = 10.5 Hz, $J_{H5'–H4'}$ = 1.0 Hz, $H_{5'}$), 4.17 (t, 1H, $J_{H2'–H1'}$ = $J_{H2'–H3'}$ = 5.0 Hz, $H_{2'}$), 4.02 (t, 1H, $J_{H3'–H2'}$ = $J_{H3'–H4'}$ = 5.0 Hz, $H_{3'}$), 3.85 (dd, 1H, $J_{H5''a–H5''b}$ = 13.5 Hz, $J_{H5''a–H4''}$ = 6.0 Hz, $H_{5''a}$), 3.80 (dd, 1H, $J_{H5''b–H5''a}$ = 13.5 Hz, $J_{H5''b–H4''}$ = 10.0 Hz, $H_{5''b}$), 3.64 (t, 2H, $J_{H18'–H17'}$ = 6.5 Hz, $H_{18'}$), 3.59 (dd, 1H, $J_{H4'–H3'}$ = 5.0 Hz, $J_{H4'–H5'}$ = 1.0 Hz, $H_{4'}$), 2.73–2.64 (m, 2H, $H_{9'}$), 1.74–1.63 (m, 4H, $H_{10'}$, $H_{7''}$), 1.58–1.52 (m, 4H, $H_{17'}$, $H_{7''}$), 1.38–1.25 (m, 13H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16'}$, OH), 0.89 (t, 3H, $J_{H8''–H7''}$ = 7.0 Hz, $H_{8''}$), 0.86 (s, 9H, –C(CH_3)$_3$), 0.85–0.82 (m, 12H, –C(CH_3)$_3$, $H_{8''}$), 0.11, 0.08, 0.06, −0.02 (4s, 12H, –Si–*t*-Bu–(CH_3)$_2$); ^{13}C NMR δ 168.2 ($C_{9''}$), 163.1 (C_4), 150.4 (C_2), 148.6 ($C_{8'}$), 139.5 (C_6), 134.6 ($C_{12''}$), 131.8 ($C_{10''}$), 123.9 ($C_{11''}$), 121.9 ($C_{7'}$), 118.1 ($C_{6''}$), 112.7 ($C_{1''}$), 103.1 (C_5), 88.2 ($C_{1'}$), 86.3 ($C_{3''}$), 84.6 ($C_{4''}$), 82.4 ($C_{4'}$), 82.1 ($C_{2''}$), 79.1 ($C_{5'}$), 75.4 ($C_{2'}$), 71.8 ($C_{3'}$), 63.0 ($C_{18'}$), 49.5 ($C_{6'}$), 40.4 ($C_{5''}$), 32.9 ($C_{7''}$), 29.7, 29.6, 29.5, 29.5, 29.5, 29.4, 29.4, 28.9 ($C_{7''}$, $C_{9'}$, $C_{10'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$), 25.8, 25.8 (–C(*C*H$_3$)$_3$), 25.7 ($C_{17'}$), 18.1, 18.0 (–*C*(CH$_3$)$_3$), 8.5, 7.5 ($C_{8''}$), −4.1, −4.4, −4.6, −4.7 (–Si–*t*-Bu–(*C*H$_3$)$_2$); HRMS, ESI$^+$ calcd for $C_{52}H_{83}N_6O_{12}Si_2^+$ $(M + H)^+$ 1039.5602, found 1039.5624.

Compound 24e. Triazole **24e** was synthesized according to the general procedure for the preparation of *N*-triazoles from azide **6** (40 mg, 0.047 mmol) and alkyne **8e** (7.2 mg, 0.031 mmol, 1 equiv.). Flash chromatography (EtOAc/MeOH 100/0 to 90/10) afforded **24e** as a pale red film (22 mg, 44% yield): R_f 0.10 (EtOAc/MeOH 90/10); $[\alpha]_D$ −22 (*c* 0.5, CH_2Cl_2); IR (film) 3744br, 2677m, 2160s, 1712s, 1096m, 830m; ^{1}H NMR δ 8.31 (br s, 1H, NH), 7.91–7.88 (m, 2H, $H_{11''}$), 7.82 (d, 1H, $J_{H6–H5}$ = 8.0 Hz, H_6), 7.79–7.77 (m, 2H, $H_{12''}$), 7.69 (s, 1H, $H_{8'}$), 6.13 (dd, 1H, $J_{H5–H6}$ = 8.0 Hz, $J_{H5–NH}$ = 1.5 Hz, H_5), 5.91 (d, 1H, $J_{H1'–H2'}$ = 5.0 Hz, $H_{1'}$), 5.35 (s, 1H, $H_{1''}$), 5.00 (dd, 1H, $J_{H6'a–H6'b}$ = 13.5 Hz, $J_{H6'a–H5'}$ = 5.5 Hz, $H_{6'a}$), 4.77 (d, 1H, $J_{H2''–H3''}$ = 6.0 Hz, $H_{2''}$), 4.69–4.66 (m, 3H, $H_{9'}$, $H_{3''}$), 4.57 (dd, 1H, $J_{H4''–H5''a}$ = 6.5 Hz, $J_{H4''–H5''b}$ = 9.5 Hz, $H_{4''}$), 4.51 (d, 1H, $J_{H6'b–H6'a}$ = 13.5 Hz, $J_{H6'b–H5'}$ = 9.5 Hz, $H_{6'b}$), 4.33 (ddd, 1H, $J_{H5'–H6'a}$ = 5.5 Hz, $J_{H5'–H6'b}$ = 9.5 Hz, $J_{H5'–H4'}$ = 1.0 Hz, $H_{5'}$), 4.18 (t, 1H, $J_{H2'–H1'}$ = $J_{H2'–H3'}$ = 5.0 Hz, $H_{2'}$), 4.03 (t, 1H, $J_{H3'–H2'}$ = $J_{H3'–H4'}$ = 5.0 Hz, $H_{3'}$), 3.85 (dd, 1H, $J_{H5''a–H5''b}$ = 13.5 Hz, $J_{H5''a–H4''}$ = 6.0 Hz, $H_{5''a}$), 3.79 (dd, 1H, $J_{H5''b–H5''a}$ = 13.5 Hz, $J_{H5''b–H4''}$ = 10.0 Hz, $H_{5''b}$), 3.72–3.59 (m, 17H, $H_{4'}$, $H_{10'}$, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16'}$, $H_{17'}$), 1.73–1.63 (m, 3H, $H_{7''}$, OH), 1.56–1.51 (m, 2H, $H_{7''}$), 0.89 (t, 3H, $J_{H8''–H7''}$ = 7.0 Hz, $H_{8''}$), 0.87 (s, 9H, –C(CH_3)$_3$), 0.85–0.82 (m, 12H, –C(CH_3)$_3$, $H_{8''}$), 0.10, 0.08, 0.07, −0.01 (4s, 12H, –Si–*t*-Bu–(CH_3)$_2$); ^{13}C NMR δ 168.2 ($C_{9''}$), 162.9 (C_4), 150.3 (C_2), 145.3 ($C_{8'}$), 139.6 (C_6), 134.6 ($C_{12''}$), 131.8 ($C_{10''}$), 124.2 ($C_{7'}$), 123.9 ($C_{11''}$), 118.1 ($C_{6''}$), 112.6 ($C_{1''}$), 103.1 (C_5), 88.2 ($C_{1'}$), 86.3 ($C_{3''}$), 84.6 ($C_{4''}$), 82.7 ($C_{4'}$), 82.1 ($C_{2''}$), 78.9 ($C_{5'}$), 75.3 ($C_{2'}$), 72.6 (CH_{2PEG}), 71.9 ($C_{3'}$),70.6, 70.3, 69.8 (CH_{2PEG}), 64.7 ($C_{9'}$), 61.8 (CH_{2PEG}), 50.5 ($C_{6'}$), 40.5 ($C_{5''}$), 29.5, 28.9 ($C_{7''}$), 25.9, 25.8 (–C(*C*H$_3$)$_3$), 18.1, 18.1 (–*C*(CH$_3$)$_3$), 8.5, 7.5 ($C_{8''}$), −4.1, −4.4, −4.5, −4.6 (–Si–*t*-Bu–(*C*H$_3$)$_2$); HRMS, ESI$^+$ calcd for $C_{51}H_{81}N_6O_{16}Si_2^+$ $(M + H)^+$ 1089.5242, found 1089.5260.

Compound 24f. Triazole **24f** was synthesized according to the general procedure for the preparation of *N*-triazoles from azide **6** (40 mg, 0.047 mmol) and alkyne **8f** (22 mg, 0.07 mmol, 1.5 equiv.). Flash chromatography (cyclohexane/EtOAc 6/4) afforded **24f** as a white foam (37.5 mg, 68% yield): R_f 0.11 (cyclohexane/EtOAc 6/4); m.p. 120–124 °C; $[\alpha]_D$ −21 (*c* 0.5, CH_2Cl_2); IR (film) 2923m, 1713s, 1273m, 1253w, 1075w, 746m; ^{1}H NMR δ 8.57 (brs, 1H, NH), 7.90–7.88 (m, 2H, $H_{11''}$), 7.88–7.81 (m, 3H, $H_{21'}$, H_6), 7.79–7.75 (m, 2H, $H_{22'}$), 7.72–7.69 (m, 2H, $H_{12''}$), 7.32 (s, 1H, $H_{7'}$), 6.16 (dd, 1H, $J_{H5–H6}$ = 8.0 Hz, $J_{H5–NH}$ = 2.0 Hz, H_5), 5.92 (d, 1H, $J_{H1'–H2'}$ = 5.0 Hz, $H_{1'}$), 5.34 (s, 1H, $H_{1''}$), 5.02 (dd, 1H, $J_{H6'a–H6'b}$ = 13.0 Hz, $J_{H6'a–H5'}$ = 5.0 Hz, $H_{6'a}$), 4.77 (d, 1H, $J_{H2''–H3''}$ = 6.5 Hz, $H_{2''}$), 4.68 (d, 1H, $J_{H3''–H2''}$ = 6.5 Hz, $H_{3''}$), 4.58 (dd, 1H, $J_{H4''–H5''a}$ = 5.5 Hz, $J_{H4''–H5''b}$ = 10.5 Hz, $H_{4''}$), 4.43 (dd, 1H, $J_{H6'b–H6'a}$ = 13.0 Hz, $J_{H6'b–H5'}$ = 10.5 Hz, $H_{6'b}$), 4.26 (ddd, 1H, $J_{H5'–H6'a}$ = 5.0 Hz, $J_{H5'–H6'b}$ = 10.5 Hz, $J_{H5'–H4'}$ = 1.0 Hz, $H_{5'}$), 4.16 (t, 1H, $J_{H2'–H1'}$ = $J_{H2'–H3'}$ = 5.0 Hz, $H_{2'}$), 4.01 (t, 1H, $J_{H3'–H2'}$ = $J_{H3'–H4'}$ = 5.0 Hz, $H_{3'}$), 3.84 (dd, 1H, $J_{H5''a–H5''b}$ = 13.5 Hz, $J_{H5''a–H4''}$ = 5.5 Hz, $H_{5''a}$), 3.80 (dd, 1H, $J_{H5''b–H5''a}$ = 13.5 Hz, $J_{H5''b–H4''}$ = 10.5 Hz, $H_{5''b}$), 3.67 (t, 2H, $J_{H18'–H17'}$ = 7.0 Hz, $H_{18'}$), 3.59 (dd, 1H, $J_{H4'–H3'}$ = 5.0 Hz, $J_{H4'–H5'}$ = 1.0 Hz, $H_{4'}$), 2.72–2.63 (m, 2H, $H_{9'}$), 1.69–1.60 (m, 6H, $H_{10'}$, $H_{17'}$, $H_{7''}$), 1.57–1.51 (m, 2H, $H_{7''}$), 1.37–1.23 (m, 12H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16'}$), 0.89 (t, 3H, $J_{H8''–H7''}$ = 7.0 Hz, $H_{8''}$), 0.87 (s, 9H, –C(CH_3)$_3$), 0.85–0.82 (m, 12H, –C(CH_3)$_3$, $H_{8''}$), 0.10, 0.07, 0.05, −0.02 (4s, 12H, –Si–*t*-Bu–(CH_3)$_2$); ^{13}C NMR δ 168.6, 168.2 ($C_{19'}$, $C_{9''}$), 163.1 (C_4), 150.3 (C_2), 148.7 ($C_{8'}$), 139.5 (C_6), 134.6 ($C_{12''}$), 133.9 ($C_{22'}$), 132.4 ($C_{20'}$), 131.2 ($C_{10''}$), 123.8 ($C_{11''}$), 123.3 ($C_{21'}$), 121.9 ($C_{7'}$), 118.1 ($C_{6''}$), 112.7 ($C_{1''}$), 103.1 (C_5), 88.2 ($C_{1'}$), 86.3 ($C_{3''}$), 84.6 ($C_{4''}$), 82.4 ($C_{4'}$), 82.1 ($C_{2''}$), 79.1 ($C_{2'}$), 75.4 ($C_{5'}$), 71.8 ($C_{3'}$), 49.9 ($C_{9'}$), 40.5 ($C_{5''}$), 38.2 ($C_{18'}$), 29.8, 29.6, 29.6, 29.5, 29.4, 29.4, 29.3, 28.9, 28.7, 27.1, 26.9 ($C_{7''}$, $C_{6'}$, $C_{10'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$, $C_{17'}$), 25.8, 25.7 (–C(*C*H$_3$)$_3$), 18.1, 18.0 (–*C*(CH$_3$)$_3$), 8.4, 7.5 ($C_{8''}$), −4.1, −4.1, −4.6, −4.7 (–Si–*t*-Bu–(*C*H$_3$)$_2$); HRMS, ESI$^+$ calcd for $C_{60}H_{86}N_7O_{13}Si_2^+$ $(M + H)^+$ 1168.5817, found 1168.5838.

Compound 24g. Triazole **24g** was synthesized according to the general procedure for the preparation of *N*-triazoles from azide **6** (21 mg, 0.024 mmol) and alkyne **8g** (16.0 mg, 0.049 mmol, 2.0 equiv.). Flash chromatography (cyclohexane/EtOAc 6/4 to 3/7) afforded **24g** as a white foam (19 mg, 64% yield): R_f 0.30 (cyclohexane/EtOAc 3/7); m.p. 112–116 °C; $[\alpha]_D$ −34 (*c* 1.0, CH_2Cl_2); IR (film) 2928br, 2550w, 1718s, 1696s, 1655m, 1463w, 1253m, 839m; ^{1}H NMR δ 8.56 (br s, 1H, NH), 7.92–7.88 (m, 2H, $H_{11''}$), 7.84–7.80 (m, 3H, $H_{17'}$, H_6), 7.78–7.43 (m, 4H, $H_{12''}$, $H_{21'}$), 7.57 (t, 1H, $J_{H23'–H22'}$ = 8.0 Hz, $H_{23'}$), 7.48–7.45 (m, 2H, $H_{22'}$), 7.41–7.39 (br s, 1H, $H_{7'}$), 7.36 (d, 2H, $J_{H11'–H12'}$ = 8.0 Hz, $H_{11'}$), 7.27 (d, 2H, $J_{H12'–H11'}$ = 8.0 Hz, $H_{12'}$), 7.03–7.01 (m, 2H, $H_{16'}$), 6.11 (dd, 1H, $J_{H5–H6}$ = 8.5 Hz, $J_{H5–NH}$ = 1.5 Hz, H_5), 5.88 (d, 1H, $J_{H1'–H2'}$ = 5.0 Hz, $H_{1'}$), 5.32 (s, 1H, $H_{1''}$), 5.14 (m, 2H, $H_{14'}$), 4.96 (dd, 1H, $J_{H6'a–H6'b}$ = 13.5 Hz, $J_{H6'a–H5'}$ = 5.5 Hz, $H_{6'a}$), 4.75 (d, 1H, $J_{H2''–H3''}$ = 6.0 Hz, $H_{2''}$), 4.68 (d, 1H, $J_{H3''–H2''}$ = 6.0 Hz, $H_{3''}$), 4.56 (dd, 1H, $J_{H4''–H5''a}$ = 6.0 Hz, $J_{H4''–H5''b}$ = 9.5 Hz, $H_{4''}$), 4.45 (dd, 1H, $J_{H6'b–H6'a}$ = 13.0 Hz, $J_{H6'b–H5'}$ = 10.0 Hz, $H_{6'b}$), 4.27 (ddd, 1H, $J_{H5'–H6'a}$ = 5.5 Hz, $J_{H5'–H6'b}$ = 10.0 Hz, $J_{H5'–H4'}$ = 1.0 Hz, $H_{5'}$), 4.17 (t, 1H, $J_{H2'–H1'}$ = $J_{H2'–H3'}$ = 5.0 Hz,

$H_{2'}$), 4.13 (d, 1H, $J_{H9'a–H9'b}$ = 16.0 Hz, $H_{9'a}$), 4.06 (d, 1H, $J_{H9'b–H9'a}$ = 16.0 Hz, $H_{9'b}$), 4.02 (t, 1H, $J_{H3'–H2'} = J_{H3'–H4'}$ = 5.0 Hz, $H_{3'}$), 3.80 (dd, 1H, $J_{H5''a–H5''b}$ = 13.5 Hz, $J_{H5''a–H4''}$ = 6.0 Hz, $H_{5''a}$), 3.80 (dd, 1H, $J_{H5''b–H5''a}$ = 13.5 Hz, $J_{H5''b–H4''}$ = 9.5 Hz, $H_{5''b}$), 3.61 (dd, 1H, $J_{H4'–H3'}$ = 5.0 Hz, $J_{H4'–H5'}$ = 1.5 Hz, $H_{4'}$), 1.71–1.62 (m, 2H, $H_{7''}$), 1.57–1.49 (m, 2H, $H_{7''}$), 0.94–0.80 (m, 24H, $H_{8''}$, –C(CH_3)$_3$), 0.10, 0.08, 0.08, −0.02 (4s, 12H, –Si–*t*-Bu–(CH_3)$_2$); ^{13}C NMR δ ^{13}C NMR δ 195.6 ($C_{19'}$), 168.2 ($C_{9''}$), 163.0 (C_4), 162.5 ($C_{15'}$), 150.3 (C_2), 147.4 ($C_{8'}$), 139.5 (C_6), 139.1 ($C_{20'}$), 138.4 ($C_{13'}$), 135.8 ($C_{10'}$), 134.6 ($C_{12''}$), 132.7 ($C_{17'}$), 132.0 ($C_{23'}$), 131.8 ($C_{10''}$), 130.5 ($C_{18'}$), 129.8 ($C_{21'}$), 129.1 ($C_{22'}$), 128.5 ($C_{11'}$), 128.3 ($C_{12'}$), 128.0($C_{11''}$), 123.8 ($C_{7'}$), 118.1 ($C_{6''}$), 114.5 ($C_{16'}$), 112.7 ($C_{1''}$), 103.0 (C_5), 88.3 ($C_{1'}$), 86.2 ($C_{3''}$), 84.6 ($C_{4''}$), 82.6 ($C_{4'}$), 82.0 ($C_{2''}$), 78.9 ($C_{2'}$), 75.3 ($C_{5'}$), 71.8 ($C_{3'}$), 70.1 ($C_{14'}$), 50.2 ($C_{9'}$), 40.4 ($C_{5''}$), 29.5 ($C_{7''}$), 29.5 ($C_{7''}$), 28.9 ($C_{6'}$), 25.9, 25.8 (–C(*C*H$_3$)$_3$), 18.1, 18.0 (–*C*(CH$_3$)$_3$), 8.5, 7.5 ($C_{8''}$), −4.1, −4.4, −4.6, −4.7 (–Si–*t*-Bu–(*C*H$_3$)$_2$); HRMS, ESI$^+$ calcd for $C_{63}H_{79}N_6O_{13}Si_2^+$ (M + H)$^+$ 1183.5238, found 1183.5222.

Compound 24h. Triazole **24h** was synthesized according to the general procedure for the preparation of *N*-triazoles from azide **6** (40 mg, 0.047 mmol) and alkyne **8h** (25.4 mg, 0.07 mmol, 1.5 equiv.). Flash chromatography (cyclohexane/EtOAc 6/4) afforded **24h** as a white foam (33 mg, 58% yield): R_f 0.20 (cyclohexane/EtOAc 6/4); m.p. 102–106 °C; $[\alpha]_D$ −24 (*c* 0.5, CH_2Cl_2); IR (film) 1710s, 1643m, 1602w, 1256m, 835w; ^{1}H NMR δ 8.68 (br d, 1H, $J_{NH–H5}$ = 1.5 Hz, NH), 7.92–7.88 (m, 2H, $H_{11''}$), 7.85 (d, 1H, $J_{H6–H5}$ = 8.0 Hz, H_6), 7.83–7.80 (m, 2H, $H_{21'}$), 7.79–7.74 (m, 4H, $H_{12''}$, $H_{25'}$), 7.57–7.54 (m, 1H, $H_{27'}$), 7.48–7.45 (m, 2H, $H_{26'}$), 7.32 (s, 1H, $H_{7'}$), 6.96–6.93 (m, 2H, $H_{20'}$), 6.16 (dd, 1H, $J_{H5–H6}$ = 8.0 Hz, $J_{H5–NH}$ = 1.5 Hz, H_5), 5.92 (d, 1H, $J_{H1'–H2'}$ = 5.0 Hz, $H_{1'}$), 5.35 (s, 1H, $H_{1''}$), 5.02 (dd, 1H, $J_{H6'a–H6'b}$ = 13.0 Hz, $J_{H6'a–H5'}$ = 5.0 Hz, $H_{6'a}$), 4.77 (d, 1H, $J_{H2''–H3''}$ = 6.0 Hz, $H_{2''}$), 4.68 (d, 1H, $J_{H3''–H2''}$ = 6.5 Hz, $H_{3''}$), 4.57 (dd, 1H, $J_{H4''–H5''a}$ = 5.5 Hz, $J_{H4''–H5''b}$ = 10.0 Hz, $H_{4''}$), 4.43 (dd, 1H, $J_{H6'b–H6'a}$ = 13.0 Hz, $J_{H6'b–H5'}$ = 10.5 Hz, $H_{6'b}$), 4.27 (ddd, 1H, $J_{H5'–H6'a}$ = 5.0 Hz, $J_{H5'–H6'b}$ = 10.5 Hz, $J_{H5'–H4'}$ = 1.5 Hz, $H_{5'}$), 4.16 (t, 1H, $J_{H2'–H1'} = J_{H2'–H3'}$ = 5.0 Hz, $H_{2'}$), 4.04 (t, 1H, $J_{H18'–H17'}$ = 7.0 Hz, $H_{18'}$), 4.02 (t, 1H, $J_{H3'–H2'} = J_{H3'–H4'}$ = 5.0 Hz, $H_{3'}$), 3.84 (dd, 1H, $J_{H5''a–H5''b}$ = 13.5 Hz, $J_{H5''a–H4''}$ = 5.5 Hz, $H_{5''a}$), 3.80 (dd, 1H, $J_{H5''b–H5''a}$ = 13.5 Hz, $J_{H5''b–H4''}$ = 10.0 Hz, $H_{5''b}$), 3.59 (dd, 1H, $J_{H4'–H3'}$ = 5.0 Hz, $J_{H4'–H5'}$ = 1.5 Hz, $H_{4'}$), 2.74–2.64 (m, 2H, $H_{9'}$), 1.81 (qt, 2H, $J_{H17'–H18'} = J_{H17'–H16'}$ = 7.0 Hz, $H_{17'}$), 1.71–1.62 (m, 4H, $H_{10'}$, $H_{7''}$), 1.56–1.52 (m, 2H, $H_{7''}$), 1.50–1.44 (m, 2H, $H_{16'}$), 1.38–1.26 (m, 10H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$), 0.89 (t, 3H, $J_{H8''–H7''}$ = 7.5 Hz, $H_{8''}$), 0.86 (s, 9H, –C(CH_3)$_3$), 0.85–0.82 (m, 12H, –C(CH_3)$_3$, $H_{8''}$), 0.11, 0.08, 0.06, −0.02 (4s, 12H, –Si–*t*-Bu–(CH_3)$_2$); ^{13}C NMR δ 195.8 ($C_{23'}$), 168.3 ($C_{9''}$), 163.2 (C_4), 163.1 ($C_{19'}$), 150.5 (C_2), 148.8 ($C_{8'}$), 139.6 (C_6), 138.6 ($C_{24'}$), 134.7 ($C_{12''}$), 132.8 ($C_{21'}$), 132.0 ($C_{27'}$), 131.9 ($C_{21'}$), 130.1 ($C_{10''}$), 129.9 ($C_{25'}$), 128.4 ($C_{26'}$), 123.9 ($C_{11''}$), 122.1 ($C_{7'}$), 118.2 ($C_{6''}$), 114.3 ($C_{20'}$), 112.8 ($C_{1''}$), 103.2 (C_5), 88.3 ($C_{1'}$), 86.4 ($C_{4'}$), 84.7 ($C_{2''}$), 82.5 ($C_{4''}$), 82.2 ($C_{2'}$), 79.2 ($C_{3''}$), 75.5 ($C_{3'}$), 71.9 ($C_{5'}$), 68.5 ($C_{18'}$), 50.0 ($C_{9'}$), 40.5 ($C_{5''}$), 29.9, 29.8, 29.7, 29.6, 29.4, 29.1, 27.2, 26.2 ($C_{6'}$, $C_{10'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$, $C_{17'}$, $C_{7''}$), 25.9, 25.8 (–C(*C*H$_3$)$_3$), 18.2, 18.2 (–*C*(CH$_3$)$_3$), 8.6, 7.6 ($C_{8''}$), −4.0, −4.3, −4.5, −4.6 (–Si–*t*-Bu–(*C*H$_3$)$_2$); HRMS, ESI$^+$ calcd for $C_{65}H_{91}N_6O_{13}Si_2^+$ (M + H)$^+$ 1219.6177, found 1219.6198.

General procedure for phthalimide, isopentylidene and TBS group cleavage

To a solution of triazole **23a–h** or **24a–h** (1 equiv.), in MeOH (700 μL) was added dropwise an ethanolic solution of methylamine (8.03 M, 400 equiv.). The solution was stirred at r.t. for 5 h and volatiles were removed *in vacuo*. To the crude residue was added pure H_2O (700 μL) and the resulting suspension was cooled to 0 °C. At 0 °C, TFA (2 mL) was added dropwise. The pale yellow resulting solution was stirred at 0 °C for 10 min and then at r.t. for 18 h and then concentrated to dryness. The residue was then purified by semi-preparative reverse phase HPLC to give the corresponding fully deprotected tetrols **25a–h** or **26a–h**. Yields were given after 2 steps and purification by semi-preparative reverse phase HPLC.

Compound 25a. Compound **25a** was synthesized according to the general procedure for phthalimide, isopentylidene and TBS group cleavage from *C*-triazole **23a** (60 mg, 0.059 mmol). After semi-preparative reverse phase HPLC (method A) and lyophilisation, **25a** was obtained as an ammonium trifluoroacetate salt (white powder, 25.8 mg, 62% yield): m.p. 138–140 °C; $[\alpha]_D$ +17 (*c* 0.2, MeOH); IR (film) 2383m, 1715s, 1698s, 1226m; ^{1}H NMR (CD_3OD), δ 7.83 (s, 1H, $H_{8'}$), 7.79 (d, 1H, $J_{H6–H5}$ = 8.0 Hz, H_6), 5.79 (d, 1H, $J_{H1'–H2'}$ = 3.5 Hz, $H_{1'}$), 5.71 (d, 1H, $J_{H5–H6}$ = 8.0 Hz, H_5), 5.16 (s, 1H, $H_{1''}$), 4.37 (t, 2H, $J_{H9'–H10'}$ = 7.0 Hz, $H_{9'}$), 4.16–4.08 (m, 4H, $H_{2'}$, $H_{4'}$, $H_{5'}$, $H_{4''}$), 4.02 (dd, 1H, $J_{H3''–H2''}$ = 5.0 Hz, $J_{H3''–H4''}$ = 7.0 Hz, $H_{3''}$), 3.98 (d, 1H, $J_{H2''–H3''}$ = 5.0 Hz, $H_{2''}$), 3.91 (dd, 1H, $J_{H3'–H2'}$ = 6.0 Hz, $J_{H3'–H4'}$ = 3.5 Hz, $H_{3'}$), 3.29–3.27 (m, 1H, $H_{5''a}$), 3.24 (dd, 1H, $J_{H6'a–H6'b}$ = 14.5 Hz, $J_{H6'a–H5'}$ = 8.0 Hz, $H_{6'a}$), 3.17 (dd, 1H, $J_{H6'b–H6'a}$ = 14.5 Hz, $J_{H6'b–H5'}$ = 5.5 Hz, $H_{6'b}$), 2.98 (dd, 1H, $J_{H5''b–H5''a}$ = 13.5 Hz, $J_{H5''b–H4''}$ = 9.5 Hz, $H_{5''b}$), 1.88 (qt, 2H, $J_{H10'–H9'} = J_{H10'–H11'}$ = 7.0 Hz, $H_{10'}$), 1.34–1.26 (m, 14H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16'}$, $H_{17'}$), 0.89 (t, 3H, $J_{H18'–H17'}$ = 7.0 Hz, $H_{18'}$); ^{13}C NMR (CD_3OD) δ 166.2 (C_4), 152.3 (C_2), 144.8 ($C_{7'}$), 142.3 (C_6), 125.1 ($C_{8'}$), 110.9 ($C_{1''}$), 102.6 (C_5), 91.6 ($C_{1'}$), 85.5 ($C_{3''}$), 80.1 ($C_{4''}$), 79.7 ($C_{4'}$), 76.5 ($C_{2''}$), 75.8 ($C_{2'}$), 73.9 ($C_{5'}$), 71.5 ($C_{3'}$), 51.5 ($C_{9'}$), 44.3 ($C_{5''}$), 33.2, 31.5, 30.8, 30.7, 30.5, 30.2, 29.8, 27.6, 23.9 ($C_{6'}$, $C_{10'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$, $C_{17'}$), 14.6 ($C_{18'}$); HRMS, ESI$^+$ calcd for $C_{27}H_{45}N_6O_9^+$ (M + H)$^+$ 597.3243, found 597.3248; HPLC, method D, t_R = 12.19 min, 98%.

Compound 25b. Compound **25b** was synthesized according to the general procedure for phthalimide, isopentylidene and TBS group cleavage from *C*-triazole **23b** (25.6 mg, 0.023 mmol). After semi-preparative reverse phase HPLC (method A) and lyophilisation, **25b** was obtained as an ammonium trifluoroacetate salt (white foam, 9.7 mg, 53% yield): m.p. 129–132 °C; $[\alpha]_D$ +14 (*c* 0.1, MeOH); IR (film) 2923br, 2852br, 2301w, 1699s, 1592m; ^{1}H NMR (CD_3OD), δ 7.83 (s, 1H, $H_{8'}$), 7.79 (d, 1H, $J_{H6–H5}$ = 8.0 Hz, H_6),7.24–7.22 (m, 2H, $H_{20'}$), 7.16–7.11 (m, 3H, $H_{21'}$, $H_{22'}$), 5.78 (d, 1H, $J_{H1'–H2'}$ = 3.0 Hz, $H_{1'}$), 5.70 (d, 1H, $J_{H5–H6}$ = 8.0 Hz, H_5), 5.16 (s, 1H, $H_{1''}$), 4.37 (t, 2H, $J_{H9'–H10'}$ = 7.0 Hz, $H_{9'}$), 4.15–4.08 (m, 4H, $H_{2'}$, $H_{4'}$, $H_{5'}$, $H_{4''}$), 4.01 (dd, 1H, $J_{H3''–H2''}$ = 4.5 Hz, $J_{H3''–H4''}$ = 7.0 Hz, $H_{3''}$), 3.97 (d, 1H, $J_{H2''–H3''}$ = 4.5 Hz, $H_{2''}$), 3.91 (dd, 1H, $J_{H3'–H2'}$ = 6.0 Hz, $J_{H3'–H4'}$ = 3.0 Hz, $H_{3'}$), 3.30–3.25 (m, 1H, $H_{5''a}$), 3.25 (dd,

1H, $J_{H6'a-H6'b}$ = 14.5 Hz, $J_{H6'a-H5'}$ = 8.0 Hz, $H_{6'a}$), 3.16 (dd, 1H, $J_{H6'b-H6'a}$ = 14.5 Hz, $J_{H6'b-H5'}$ = 5.5 Hz, $H_{6'b}$), 2.98 (dd, 1H, $J_{H5''b-H5''a}$ = 13.0 Hz, $J_{H5''b-H4''}$ = 9.5 Hz, $H_{5''b}$), 2.59 (t, 2H, $J_{H18'-H17'}$ = 7.5 Hz, $H_{18'}$), 1.87 (qt, 2H, $J_{H10'-H9'}$ = $J_{H10'-H11'}$ = 7.0 Hz, $H_{10'}$), 1.63–1.57 (m, 2H, $H_{17'}$), 1.35–1.25 (m, 12H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16'}$); ^{13}C NMR (CD_3OD) δ 166.2 (C_4), 152.3 (C_2), 144.8 ($C_{7'}$), 144.1 ($C_{19'}$), 142.3 (C_6), 129.5 ($C_{21'}$), 129.4 ($C_{20'}$), 126.8 ($C_{22'}$), 125.1 ($C_{8'}$), 111.0 ($C_{1''}$), 102.6 (C_5), 91.7 ($C_{1'}$), 85.5 ($C_{3''}$), 80.2 ($C_{4''}$), 79.7 ($C_{4'}$), 76.5 ($C_{2''}$), 75.8 ($C_{2'}$), 73.9 ($C_{5'}$), 71.5 ($C_{3'}$), 51.5 ($C_{9'}$), 44.3 ($C_{5''}$), 37.1 ($C_{18'}$), 32.9 ($C_{17'}$), 31.4 ($C_{10'}$), 30.7, 30.6, 30.6, 30.6, 30.4, 30.2, 29.8, 27.6 ($C_{6'}$, $C_{10'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$); HRMS, ESI$^+$ calcd for $C_{33}H_{49}N_6O_9^+$ $(M + H)^+$ 673.3556, found 673.3544; HPLC, method D, t_R = 13.80 min, 98%.

Compound 25c. Compound **25c** was synthesized according to the general procedure for phthalimide, isopentylidene and TBS group cleavage from *C*-triazole **23c** (35.4 mg, 0.036 mmol). After semi-preparative reverse phase HPLC (flow rate: 15 mL min^{-1}, H_2O–TFA 0.1%/MeOH (100/0 to 40/60% v/v in 25 min)) and lyophilisation, **25c** was obtained as an ammonium trifluoroacetate salt (white foam, 9.2 mg, 38% yield): m.p. 121–125 °C; $[\alpha]_D$ +16 (*c* 0.2, MeOH); IR (film) 2911br, 2842br, 2319w, 1699s, 1552w; ^{1}H NMR (CD_3OD), δ 7.84 (s, 1H, $H_{8'}$), 7.79 (d, 1H, J_{H6-H5} = 8.0 Hz, H_6), 5.79 (d, 1H, $J_{H1'-H2'}$ = 3.5 Hz, $H_{1'}$), 5.71 (d, 1H, J_{H5-H6} = 8.0 Hz, H_5), 5.15 (s, 1H, $H_{1''}$), 4.41–4.36 (m, 2H, $H_{9'}$), 4.16–4.07 (m, 4H, $H_{2'}$, $H_{4'}$, $H_{5'}$, $H_{4''}$), 4.02–3.99 (m, 1H, $H_{3''}$), 3.98–3.97 (m, 1H, $H_{2''}$), 3.91 (dd, 1H, $J_{H3'-H2'}$ = 6.0 Hz, $J_{H3'-H4'}$ = 3.0 Hz, $H_{3'}$), 3.54 (t, 2H, $J_{H13'-H12'}$ = 6.5 Hz, $H_{13'}$), 3.29–3.27 (m, 1H, $H_{5''a}$), 3.24 (dd, 1H, $J_{H6'a-H6'b}$ = 14.5 Hz, $J_{H6'a-H5'}$ = 8.0 Hz, $H_{6'a}$), 3.16 (dd, 1H, $J_{H6'b-H6'a}$ = 14.5 Hz, $J_{H6'b-H5'}$ = 6.0 Hz, $H_{6'b}$), 3.02–2.94 (m, 1H, $H_{5''b}$), 1.96–1.88 (m, 2H, $H_{10'}$), 1.82–1.76 (m, 1H, $H_{11'a}$), 1.58–1.52 (m, 1H, $H_{11'b}$), 1.42–1.33 (m, 2H, $H_{12'}$); ^{13}C NMR (CD_3OD) δ 166.3 (C_4), 152.3 (C_2), 144.9 ($C_{7'}$), 142.3 (C_6), 125.2 ($C_{8'}$), 110.9 ($C_{1''}$), 102.6 (C_5), 91.7 ($C_{1'}$), 85.4 ($C_{3''}$), 80.1 ($C_{4''}$), 79.7 ($C_{4'}$), 76.5 ($C_{2''}$), 75.8 ($C_{2'}$), 73.9 ($C_{5'}$), 71.5 ($C_{3'}$), 62.7 ($C_{13'}$), 51.5 ($C_{9'}$), 44.3 ($C_{5''}$), 33.0 ($C_{12'}$), 31.2 ($C_{11'}$), 29.8 ($C_{6'}$), 24.0 ($C_{10'}$); HRMS, ESI$^+$ calcd for $C_{22}H_{35}N_6O_{10}^+$ $(M + H)^+$ 543.2409, found 543.2396; HPLC, method D, t_R = 13.80 min, 98%.

Compound 25d. Compound **25d** was synthesized according to the general procedure for phthalimide, isopentylidene and TBS group cleavage from *C*-triazole **23d** (40.3 mg, 0.039 mmol). After semi-preparative reverse phase HPLC (method B) and lyophilisation, **25d** was obtained as an ammonium trifluoroacetate salt (white foam, 18.3 mg, 65% yield): m.p. 127–132 °C; $[\alpha]_D$ +14 (*c* 0.1, MeOH); IR (film) 2919br, 2301br, 1699s, 1697s, 1540m; ^{1}H NMR (CD_3OD), δ 7.83 (s, 1H, $H_{8'}$), 7.78 (d, 1H, J_{H6-H5} = 8.5 Hz, H_6), 5.79 (d, 1H, $J_{H1'-H2'}$ = 3.0 Hz, $H_{1'}$), 5.70 (d, 1H, J_{H5-H6} = 8.5 Hz, H_5), 5.16 (s, 1H, $H_{1''}$), 4.37 (t, 2H, $J_{H9'-H10'}$ = 7.0 Hz, $H_{9'}$), 4.16–4.08 (m, 4H, $H_{2'}$, $H_{4'}$, $H_{5'}$, $H_{4''}$), 4.02 (dd, 1H, $J_{H3''-H2''}$ = 4.5 Hz, $J_{H3''-H4''}$ = 7.0 Hz, $H_{3''}$), 3.97 (d, 1H, $J_{H2''-H3''}$ = 4.5 Hz, $H_{2''}$), 3.91 (dd, 1H, $J_{H3'-H2'}$ = 6.0 Hz, $J_{H3'-H4'}$ = 3.0 Hz, $H_{3'}$), 3.54 (t, 2H, $J_{H18'-H17'}$ = 7.0 Hz, $H_{18'}$), 3.29–3.27 (m, 1H, $H_{5''a}$), 3.24 (dd, 1H, $J_{H6'a-H6'b}$ = 14.5 Hz, $J_{H6'a-H5'}$ = 7.5 Hz, $H_{6'a}$), 3.16 (dd, 1H, $J_{H6'b-H6'a}$ = 14.5 Hz, $J_{H6'b-H5'}$ = 5.0 Hz, $H_{6'b}$), 2.98 (dd, 1H, $J_{H5''b-H5''a}$ = 13.0 Hz, $J_{H5''b-H4''}$ = 10.0 Hz, $H_{5''b}$), 1.88 (qt, 2H, $J_{H10'-H9'}$ = $J_{H10'-H11'}$ = 7.0 Hz, $H_{10'}$), 1.52 (qt, 2H, $J_{H17'-H18'}$ = $J_{H17'-H16'}$ = 7.0 Hz, $H_{17'}$), 1.38–1.26 (m, 12H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16'}$); ^{13}C NMR (CD_3OD) δ 166.2 (C_4), 152.3 (C_2), 144.8 ($C_{7'}$), 142.3 (C_6), 125.2 ($C_{8'}$), 111.0 ($C_{1''}$), 102.6 (C_5), 91.7 ($C_{1'}$), 85.5 ($C_{3''}$), 80.1 ($C_{4''}$), 79.7 ($C_{4'}$), 76.5 ($C_{2''}$), 75.8 ($C_{2'}$), 73.9 ($C_{5'}$), 71.5 ($C_{3'}$), 63.1 ($C_{18'}$), 51.5 ($C_{9'}$), 44.3 ($C_{5''}$), 33.8, 31.4, 30.7, 30.6, 30.6, 30.2, 29.8, 27.6, 27.1 ($C_{6'}$, $C_{10'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$, $C_{17'}$); HRMS, ESI$^+$ calcd for $C_{27}H_{45}N_6O_{10}^+$ $(M + H)^+$ 613.3192, found 613.3178; HPLC, method D, t_R = 9.82 min, 98%.

Compound 25e. Compound **25e** was synthesized according to the general procedure for phthalimide, isopentylidene and TBS group cleavage from *C*-triazole **23e** (21.2 mg, 0.019 mmol). After semi-preparative reverse phase HPLC (flow rate: 15 mL min^{-1}, H_2O–TFA 0.1%/MeOH 100/0 to 40/60 in 60 min) and lyophilisation, **25e** was obtained as an ammonium ditrifluoroacetate salt (white foam, 7.9 mg, 52% yield): $[\alpha]_D$ +19 (*c* 0.1, H_2O); IR (film) 3384br, 2951br, 1685s, 1258m; ^{1}H NMR (D_2O + 50 μL CD_3OD, 500 MHz), δ 7.96 (s, 1H, $H_{8'}$), 7.78 (d, 1H, J_{H6-H5} = 8.0 Hz, H_6), 5.88 (d, 1H, J_{H5-H6} = 8.0 Hz, H_5), 5.79 (d, 1H, $J_{H1'-H2'}$ = 3.5 Hz, $H_{1'}$), 5.21 (s, 1H, $H_{1''}$), 4.61 (t, 2H, $J_{H9'-H10'}$ = 5.0 Hz, $H_{9'}$), 4.31 (t, 1H, $J_{H2'-H1'}$ = $J_{H2'-H3'}$ = 3.5 Hz, $H_{2'}$), 4.25 (t, 1H, $J_{H3'-H2'}$ = $J_{H3'-H4'}$ = 3.5 Hz, $H_{3'}$), 4.21 (ddd, 1H, $J_{H5'-H4'}$ = 5.5 Hz, $J_{H5'-H6'a}$ = 7.0 Hz, $J_{H5'-H6'b}$ = 6.0 Hz, $H_{5'}$), 4.14–4.72 (m, 3H, $H_{2''}$, $H_{3''}$, $H_{4''}$), 3.98 (dd, 1H, $J_{H4'-H5'}$ = 5.5 Hz, $J_{H4'-H3'}$ = 3.5 Hz, $H_{4'}$), 3.95 (t, 2H, $J_{H10'-H9'}$ = 5.0 Hz, $H_{10'}$), 3.72–3.61 (m, 16H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16'}$, $H_{17'}$, $H_{18'}$), 3.36–3.34 (m, 1H, $H_{5''a}$), 3.22 (dd, 1H, $J_{H6'a-H6'b}$ = 14.5 Hz, $J_{H6'a-H5'}$ = 7.0 Hz, $H_{6'a}$), 3.21 (dd, 1H, $J_{H6'b-H6'a}$ = 14.5 Hz, $J_{H6'b-H5'}$ = 6.0 Hz, $H_{6'b}$), 2.93 (dd, 1H, $J_{H5''b-H5''a}$ = 13.0 Hz, $J_{H5''b-H4''}$ = 8.5 Hz, $H_{5''b}$); ^{13}C NMR (D_2O + 50 μL CD_3OD) δ 167.2 (C_4), 164.0 (*C*O-TFA), 152.5 (C_2), 140.1 ($C_{7'}$), 142.9 (C_6), 126.4 ($C_{8'}$), 109.8 ($C_{1''}$), 102.9 (C_5), 91.1 ($C_{1'}$), 84.9 ($C_{4'}$), 79.3 ($C_{2''}$), 78.9 ($C_{5'}$), 75.6 ($C_{3''}$), 74.8 ($C_{2'}$), 73.2 ($C_{4''}$), 72.8, 70.8, 70.8, 70.7, 70.7, 70.7, 70.6, 70.6 (C_{PEG}, $C_{3'}$), 69.9 ($C_{10'}$), 61.5 ($C_{9'}$), 43.9 ($C_{5''}$), 29.1 ($C_{6'}$); HRMS, ESI$^+$ calcd for $C_{27}H_{45}N_6O_{14}^+$ $(M + H)^+$ 677.2988, found 677.2999; HPLC, method D, t_R = 3.15 min, 96%.

Compound 25f. Compound **25f** was synthesized according to the general procedure for phthalimide, isopentylidene and TBS group cleavage from *C*-triazole **23f** (37.5 mg, 0.032 mmol). After semi-preparative reverse phase HPLC (method: 15 mL min^{-1}, H_2O–TFA 0.1%/MeOH 90/10 to 40/60 in 60 min) and lyophilisation, **25f** was obtained as an ammonium ditrifluoroacetate salt (white foam, 11.1 mg, 41% yield): $[\alpha]_D$ +8 (*c* 0.1, H_2O); IR (film) 3265br, 2942br, 1683s, 1487m, 1273m, 1138s; ^{1}H NMR (D_2O/CD_3OD = 1/1), δ 7.84 (s, 1H, $H_{8'}$), 7.76 (d, 1H, J_{H6-H5} = 8.0 Hz, H_6), 5.82 (d, 1H, J_{H5-H6} = 8.0 Hz, H_5), 5.76 (d, 1H, $J_{H1'-H2'}$ = 2.0 Hz, $H_{1'}$), 5.20 (s, 1H, $H_{1''}$), 4.37 (t, 2H, $J_{H9'-H10'}$ = 7.5 Hz, $H_{9'}$), 4.21–4.13 (m, 4H, $H_{2'}$, $H_{4'}$, $H_{5'}$, $H_{4''}$), 4.09–4.02 (m, 2H, $H_{2''}$, $H_{3''}$), 3.97–3.93 (m, 1H, $H_{3'}$), 3.37–3.34 (m, 1H, $H_{5''a}$), 3.25–3.17 (m, 2H, $H_{6'a}$, $H_{6'b}$), 3.02–2.98 (m, 1H, $H_{5''b}$), 2.95 (t, 2H, $J_{H18'-H17'}$ = 7.0 Hz, $H_{18'}$), 1.87–1.80 (m, 2H, $H_{10'}$), 1.65–1.62 (m, 2H, $H_{17'}$), 1.39–1.12 (m, 12H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16'}$); ^{13}C NMR (D_2O/CD_3OD = 1/1) δ 166.7 (C_4), 163.5 (*C*O-TFA), 152.3 (C_2), 144.5 ($C_{7'}$), 142.5 (C_6), 125.5 ($C_{8'}$), 111.4 ($C_{1''}$), 102.9 (C_5), 91.1 ($C_{1'}$), 85.4 ($C_{3''}$), 79.6 ($C_{4''}$), 79.2 ($C_{4'}$), 76.0 ($C_{2''}$), 75.2 ($C_{2'}$), 73.5

($C_{5'}$), 71.1 ($C_{3'}$), 51.4 ($C_{9'}$), 43.9 ($C_{5''}$), 40.8 ($C_{17'}$), 30.8, 30.0, 29.9, 29.7, 29.6, 29.5, 28.2, 27.1, 27.0 ($C_{6'}$, $C_{10'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$, $C_{17'}$); HRMS, ESI^+ calcd for $C_{27}H_{46}N_7O_9^+$ $(M + H)^+$ 612.3352, found 612.3357; HPLC, method D, t_R = 4.56 min, 98%.

Compound 25g. Compound **25g** was synthesized according to the general procedure for phthalimide, isopentylidene and TBS group cleavage from *C*-triazole **23g** (56 mg, 0.047 mmol). After semi-preparative reverse phase HPLC (method A) and lyophilisation, **25g** was obtained as an ammonium trifluoroacetate salt (white powder, 26 mg, 64% yield): m.p. 137–140 °C; $[\alpha]_D$ +21 (*c* 0.2, MeOH); IR (film) 2922br, 1714s, 1276m, 1260m, 830w; ^{1}H NMR (CD_3OD), 7.88 (s, 1H, $H_{8'}$), 7.79–7.77 (m, 2H, $H_{17'}$), 7.71–7.62 (m, 3H, H_6, $H_{21'}$), 7.64 (t, 1H, $J_{H23'–H22'}$ = 7.5 Hz, $H_{23'}$), 7.53 (t, 2H, $J_{H22'–H23'}$ = $J_{H22'–H21'}$ = 7.5 Hz, $H_{22'}$), 7.46 (d, 2H, $J_{H11'–H12'}$ = 8.0 Hz, $H_{11'}$), 7.34 (d, 2H, $J_{H12'–H11'}$ = 8.0 Hz, $H_{12'}$), 7.13–7.10 (m, 2H, $H_{16'}$), 5.71–5.69 (m, 2H, H_5, $H_{1'}$), 5.60 (d, 1H, $J_{H9'a–H9'b}$ = 15.0 Hz, $H_{9'a}$), 5.57 (d, 1H, $J_{H9'b–H9'a}$ = 15.0 Hz, $H_{9'b}$), 5.20 (s, 2H, $H_{14'}$), 5.16 (s, 1H, $H_{1''}$), 4.15–4.09 (m, 4H, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{4''}$), 4.00–3.93 (m, 3H, $H_{2''}$, $H_{3''}$, $H_{4'}$), 3.27–3.23 (m, 2H, $H_{5''a}$, $H_{6'a}$), 3.16 (dd, 1H, $J_{H5''b–H5''a}$ = 14.5 Hz, $J_{H5''b–H4''}$ = 5.0 Hz, $H_{5''b}$), 2.92 (dd, 1H, $J_{H6'b–H6'a}$ = 13.5 Hz, $J_{H6'b–H5'}$ = 9.5 Hz, $H_{6'b}$); ^{13}C NMR (CD_3OD) δ 198.4 ($C_{19'}$), 166.4 (C_4), 164.2 ($C_{15'}$), 152.3 (C_2), 145.3 ($C_{7'}$), 142.3 (C_6), 139.3 ($C_{20'}$), 138.6 ($C_{13'}$), 136.7 ($C_{10'}$), 133.9 ($C_{17'}$), 133.7 ($C_{23'}$), 131.4 ($C_{18'}$), 130.8 ($C_{21'}$), 129.7 ($C_{22'}$), 129.5 ($C_{11'}$), 129.4 ($C_{12'}$), 125.6 ($C_{8'}$), 115.6 ($C_{16'}$), 110.8 ($C_{1''}$), 102.6 (C_5), 91.6 ($C_{1'}$), 85.7 ($C_{3''}$), 80.0 ($C_{4''}$), 79.4 ($C_{4'}$), 79.4 ($C_{2''}$), 75.6 ($C_{2'}$), 73.7 ($C_{5'}$), 71.4 ($C_{3'}$), 70.9 ($C_{14'}$), 54.8 ($C_{9'}$), 44.1 ($C_{5''}$), 29.9 ($C_{6'}$); HRMS ESI^+ calcd for $C_{38}H_{41}N_6O_{11}^+$ $(M + H)^+$ 757.2828, found 758.2808; HPLC, method C, t_R = 12.09 min, 99%.

Compound 25h. Compound **25h** was synthesized according to the general procedure for phthalimide, isopentylidene and TBS group cleavage from *C*-triazole **23h** (47 mg, 0.039 mmol). After semi-preparative reverse phase HPLC (method A) and lyophilisation, **25h** was obtained as an ammonium trifluoroacetate salt (white powder, 24 mg, 69% yield): m.p. 132–136 °C; $[\alpha]_D$ +8 (*c* 0.2, MeOH); IR (film) 2741w, 2383m, 1698s, 1598m; ^{1}H NMR (CD_3OD), 7.83 (s, 1H, $H_{8'}$), 7.79–7.76 (m, 3H, $H_{21'}$, H_6), 7.72–7.69 (m, 2H, $H_{25'}$), 7.63–7.59 (m, 1H, $H_{27'}$), 7.53–7.49 (m, 2H, $H_{26'}$), 7.04–7.01 (m, 2H, $H_{20'}$), 5.79 (d, 1H, $J_{H1'–H2'}$ = 3.0 Hz, $H_{1'}$), 5.70 (d, 1H, $J_{H5–H6}$ = 8.0 Hz, H_5), 5.16 (s, 1H, $H_{1''}$), 4.36 (t, 2H, $J_{H9'–H10'}$ = 7.0 Hz, $H_{9'}$), 4.15–4.06 (m, 6H, $H_{2'}$, $H_{4'}$, $H_{5'}$, $H_{18'}$, $H_{4''}$), 4.02 (dd, 1H, $J_{H3''–H2''}$ = 5.5 Hz, $J_{H3''–H4''}$ = 7.0 Hz, $H_{3''}$), 3.97 (d, 1H, $J_{H2''–H3''}$ = 5.5 Hz, $H_{2''}$), 3.91 (dd, 1H, $J_{H3'–H2'}$ = 6.0 Hz, $J_{H3'–H4'}$ = 3.5 Hz, $H_{3'}$), 3.29–3.27 (m, 1H, $H_{5''a}$), 3.24 (dd, 1H, $J_{H6'a–H6'b}$ = 14.5 Hz, $J_{H6'a–H5'}$ = 8.0 Hz, $H_{6'a}$), 3.16 (dd, 1H, $J_{H6'b–H6'a}$ = 14.5 Hz, $J_{H6'b–H5'}$ = 5.5 Hz, $H_{6'b}$), 2.99 (dd, 1H, $J_{H5''b–H5''a}$ = 13.5 Hz, $J_{H5''b–H4''}$ = 9.5 Hz, $H_{5''b}$), 1.87 (qt, 2H, $J_{H10'–H9'}$ = $J_{H10'–H11'}$ = 7.0 Hz, $H_{10'}$), 1.80 (qt, 2H, $J_{H17'–H18'}$ = $J_{H17'–H16'}$ = 7.0 Hz, $H_{17'}$), 1.52–1.46 (m, 2H, $H_{16'}$), 1.40–1.25 (m, 10H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$); ^{13}C NMR (CD_3OD) δ 197.8 ($C_{23'}$), 166.2 (C_4), 164.8 ($C_{19'}$), 152.3 (C_2), 144.8 ($C_{7'}$), 142.3 (C_6), 139.7 ($C_{24'}$), 133.8 ($C_{21'}$), 133.4 ($C_{27'}$), 131.0 ($C_{22'}$), 130.8 ($C_{25'}$), 129.6 ($C_{26'}$), 125.2 ($C_{8'}$), 115.4 ($C_{20'}$), 111.0 ($C_{1''}$), 102.6 (C_5), 91.6 ($C_{1'}$), 85.5 ($C_{4'}$), 80.5 ($C_{2''}$), 79.7 ($C_{4''}$), 76.5 ($C_{2'}$), 75.8 ($C_{3''}$), 73.9 ($C_{3'}$), 71.5 ($C_{5'}$), 69.6 ($C_{18'}$), 50.4 ($C_{9'}$), 44.3 ($C_{5''}$), 31.4, 30.6, 30.6, 30.5, 30.3, 30.2, 29.9, 27.6, 27.2 ($C_{6'}$, $C_{10'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$, $C_{17'}$); HRMS ESI^+ calcd for $C_{40}H_{53}N_6O_{11}^+$ $(M + H)^+$ 793.3767, found 793.3768; HPLC, method C, t_R = 15.19 min, 98%.

Compound 26a. Compound **26a** was synthesized according to the general procedure for phthalimide, isopentylidene and TBS group cleavage from *N*-triazole **24a** (35.2 mg, 0.034 mmol). After semi-preparative reverse phase HPLC (method A) and lyophilisation, **26a** was obtained as an ammonium trifluoroacetate salt (white powder, 13.3 mg, 56% yield): m.p. 142–146 °C; $[\alpha]_D$ +21 (*c* 0.4, MeOH); IR (film) 2926m, 1677s, 1465w, 1202m, 1134m, 801w; ^{1}H NMR (CD_3OD), δ 7.79 (s, 1H, $H_{7'}$), 7.65 (d, 1H, $J_{H6–H5}$ = 8.0 Hz, H_6), 5.74 (d, 1H, $J_{H1'–H2'}$ = 2.5 Hz, $H_{1'}$), 5.69 (d, 1H, $J_{H5–H6}$ = 8.0 Hz, H_5), 5.14 (s, 1H, $H_{1''}$), 4.80 (dd, 1H, $J_{H6'a–H6'b}$ = 14.5 Hz, $J_{H6'a–H5'}$ = 6.0 Hz, $H_{6'a}$), 4.70 (dd, 1H, $J_{H6'b–H6'a}$ = 14.5 Hz, $J_{H6'b–H5'}$ = 6.0 Hz, $H_{6'b}$), 4.32 (dt, 1H, $J_{H5'–H6'a}$ = 6.0 Hz, $J_{H5'–H6'b}$ = 6.0 Hz, $J_{H5'–H4'}$ = 3.5 Hz, $H_{5'}$), 4.18–4.15 (m, 2H, $H_{2'}$, $H_{3'}$), 4.06 (ddd, 1H, $J_{H4''–H5''a}$ = 2.5 Hz, $J_{H4''–H5''b}$ = 9.5 Hz, $J_{H4''–H3''}$ = 7.0 Hz, $H_{4''}$), 3.96–3.91 (m, 3H, $H_{4'}$, $H_{2''}$, $H_{3''}$), 3.23 (dd, 1H, $J_{H5''a–H5''b}$ = 13.0 Hz, $J_{H5''a–H4''}$ = 2.5 Hz, $H_{5''a}$), 2.98 (dd, 1H, $J_{H5''b–H5''a}$ = 13.0 Hz, $J_{H5''b–H4''}$ = 9.5 Hz, $H_{5''b}$), 2.69 (t, 2H, $J_{H9'–H10'}$ = 7.5 Hz, $H_{9'}$), 1.68–1.62 (m, 2H, $H_{10'}$), 1.37–1.26 (m, 14H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16'}$, $H_{17'}$), 0.89 (t, 3H, $J_{H18'–H7'}$ = 6.5 Hz, $H_{18'}$); ^{13}C NMR (CD_3OD) δ 166.2 (C_4), 162.5 (*C*O-TFA), 152.2 (C_2), 149.5 ($C_{8'}$), 142.4 (C_6), 125.1 ($C_{7'}$), 110.9 ($C_{1''}$), 102.7 (C_5), 92.5 ($C_{1'}$), 84.7 ($C_{4'}$), 80.2 ($C_{4''}$), 78.4 ($C_{5'}$), 76.4 ($C_{2''}$), 75.4 ($C_{2'}$), 73.9 ($C_{3''}$), 71.4 ($C_{3'}$), 52.6 ($C_{6'}$), 44.3 ($C_{5''}$), 33.2, 30.9, 30.8, 30.8, 30.6, 30.4, 26.4, 23.9 ($C_{9'}$, $C_{10'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$, $C_{17'}$), 14.6 ($C_{18'}$); HRMS, ESI^+ calcd for $C_{27}H_{45}N_6O_9^+$ $(M + H)^+$ 597.3243, found 597.3254; HPLC, method C, t_R = 12.09 min, 99%.

Compound 26b. Compound **26b** was synthesized according to the general procedure for phthalimide, isopentylidene and TBS group cleavage from *N*-triazole **24b** (30.0 mg, 0.027 mmol). After semi-preparative reverse phase HPLC (method A) and lyophilisation, **26b** was obtained as an ammonium trifluoroacetate salt (white foam, 11.2 mg, 52% yield): m.p. 132–135 °C; $[\alpha]_D$ +14 (*c* 0.1, MeOH); IR (film) 2926br, 2855br, 2303w, 1697s, 1594m; ^{1}H NMR (CD_3OD) δ 7.79 (s, 1H, $H_{7'}$), 7.65 (d, 1H, $J_{H6–H5}$ = 8.0 Hz, H_6), 7.24–7.22 (m, 2H, $H_{20'}$), 7.16–7.11 (m, 3H, $H_{21'}$, $H_{22'}$), 5.74 (d, 1H, $J_{H1'–H2'}$ = 2.0 Hz, $H_{1'}$), 5.69 (d, 1H, $J_{H5–H6}$ = 8.0 Hz, H_5), 5.14 (s, 1H, $H_{1''}$), 4.80 (dd, 1H, $J_{H6'a–H6'b}$ = 14.0 Hz, $J_{H6'a–H5'}$ = 5.5 Hz, $H_{6'a}$), 4.70 (dd, 1H, $J_{H6'b–H6'a}$ = 14.0 Hz, $J_{H6'b–H5'}$ = 5.5 Hz, $H_{6'b}$), 4.32 (dt, 1H, $J_{H5'–H6'a}$ = 5.5 Hz, $J_{H5'–H6'b}$ = 5.5 Hz, $J_{H5'–H4'}$ = 3.5 Hz, $H_{5'}$), 4.18–4.15 (m, 2H, $H_{2'}$, $H_{3'}$), 4.06 (ddd, 1H, $J_{H4''–H5''a}$ = 3.0 Hz, $J_{H4''–H5''b}$ = 9.5 Hz, $J_{H4''–H3''}$ = 7.0 Hz, $H_{4''}$), 3.96–3.92 (m, 3H, $H_{4'}$, $H_{2''}$, $H_{3''}$), 3.23 (dd, 1H, $J_{H5''a–H5''b}$ = 13.0 Hz, $J_{H5''a–H4''}$ = 3.0 Hz, $H_{5''a}$), 2.99 (dd, 1H, $J_{H5''b–H5''a}$ = 13.0 Hz, $J_{H5''b–H4''}$ = 9.5 Hz, $H_{5''b}$), 2.69 (t, 2H, $J_{H9'–H10'}$ = 7.5 Hz, $H_{9'}$), 2.59 (t, 2H, $J_{H18'–H17'}$ = 7.5 Hz, $H_{18'}$), 1.67–1.57 (m, 4H, $H_{10'}$, $H_{17'}$), 1.37–1.23 (m, 12H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16'}$); ^{13}C NMR (CD_3OD) δ 166.2 (C_4), 152.2 (C_2), 149.5 ($C_{8'}$), 144.1 ($C_{19'}$), 142.4 (C_6), 129.5 ($C_{21'}$), 129.4 ($C_{20'}$), 126.8 ($C_{22'}$), 125.1 ($C_{7'}$), 110.9 ($C_{1''}$), 102.7 (C_5), 92.4 ($C_{1'}$), 84.8 ($C_{4'}$), 80.2 ($C_{4''}$), 78.4 ($C_{5'}$), 76.4 ($C_{2''}$), 75.4 ($C_{2'}$), 73.9 ($C_{3''}$), 71.4 ($C_{3'}$), 52.6 ($C_{6'}$), 44.3 ($C_{5''}$), 37.1 ($C_{18'}$), 32.9 ($C_{17'}$),

30.8, 30.8, 30.7, 30.7, 30.6, 30.5, 30.3, 26.4 ($C_{9'}$, $C_{10'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$); HRMS, ESI$^+$ calcd for $C_{33}H_{49}N_6O_9^+$ $(M + H)^+$ 673.3556, found 673.3552; HPLC, method D, t_R = 13.29 min, 99%.

Compound 26c. Compound **26c** was synthesized according to the general procedure for phthalimide, isopentylidene and TBS group cleavage from *N*-triazole **24c** (35.1 mg, 0.036 mmol). After semi-preparative reverse phase HPLC (method B) and lyophilisation, **26c** was obtained as an ammonium trifluoroacetate salt (white foam, 8.0 mg, 34% yield): m.p. 130–134 °C; $[\alpha]_D$ +13 (*c* 0.2, MeOH); IR (film) 2914br, 2843br, 2317w, 1692s, 1552w; ^{1}H NMR (CD_3OD), δ 7.81 (s, 1H, $H_{7'}$), 7.66 (d, 1H, J_{H6-H5} = 8.0 Hz, H_6), 5.76 (d, 1H, $J_{H1'-H2'}$ = 2.0 Hz, $H_{1'}$), 5.69 (d, 1H, J_{H5-H6} = 8.0 Hz, H_5), 5.14 (s, 1H, $H_{1''}$), 4.78 (dd, 1H, $J_{H6'a-H6'b}$ = 14.0 Hz, $J_{H6'a-H5'}$ = 6.0 Hz, $H_{6'a}$), 4.70 (dd, 1H, $J_{H6'b-H6'a}$ = 14.0 Hz, $J_{H6'b-H5'}$ = 8.5 Hz, $H_{6'b}$), 4.34–4.31 (m, 1H, $H_{5'}$), 4.18–4.16 (m, 2H, $H_{2'}$, $H_{3'}$), 4.05 (ddd, 1H, $J_{H4''-H5''a}$ = 3.0 Hz, $J_{H4''-H5''b}$ = 9.5 Hz, $J_{H4''-H3''}$ = 7.0 Hz, $H_{4''}$), 3.96–3.91 (m, 3H, $H_{4'}$, $H_{2''}$, $H_{3''}$), 3.55 (t, 2H, $J_{H13'-H12'}$ = 6.5 Hz, $H_{13'}$), 3.23 (dd, 1H, $J_{H5''a-H5''b}$ = 13.5 Hz, $J_{H5''a-H4''}$ = 3.0 Hz, $H_{5''a}$), 2.97 (dd, 1H, $J_{H5''b-H5''a}$ = 13.5 Hz, $J_{H5''b-H4''}$ = 9.5 Hz, $H_{5''b}$), 2.71 (t, 2H, $J_{H9'-H10'}$ = 7.5 Hz, $H_{9'}$), 1.68 (qt, 2H, $J_{H10'-H9'}$ = $J_{H10'-H11'}$ = 7.5 Hz, $H_{10'}$), 1.56 (qt, 2H, $J_{H12'-H13'}$ = $J_{H12'-H11'}$ = 6.5 Hz, $H_{12'}$), 1.45–1.39 (m, 2H, $H_{11'}$); ^{13}C NMR (CD_3OD) δ 166.2 (C_4), 152.2 (C_2), 149.4 ($C_{8'}$), 142.4 (C_6), 125.2 ($C_{7'}$), 110.8 ($C_{1''}$), 102.8 (C_5), 92.4 ($C_{1'}$), 84.7 ($C_{4'}$), 80.2 ($C_{4''}$), 78.4 ($C_{5'}$), 76.4 ($C_{2''}$), 75.4 ($C_{2'}$), 73.9 ($C_{3''}$), 71.4 ($C_{3'}$), 63.2 ($C_{13'}$), 52.6 ($C_{6'}$), 44.3 ($C_{5''}$), 33.4 ($C_{12'}$), 30.5 ($C_{10'}$), 26.6 ($C_{11'}$), 26.4 ($C_{9'}$); HRMS, ESI$^+$ calcd for $C_{22}H_{35}N_6O_{10}^+$ $(M + H)^+$ 543.2409, found 543.2399; HPLC, method D, t_R = 2.66 min, 98%.

Compound 26d. Compound **26d** was synthesized according to the general procedure for phthalimide, isopentylidene and TBS group cleavage from *N*-triazole **24d** (34.1 mg, 0.033 mmol). After semi-preparative reverse phase HPLC (method A) and lyophilisation, **26d** was obtained as an ammonium trifluoroacetate salt (white foam, 10.0 mg, 42% yield): m.p. 126–129 °C; $[\alpha]_D$ +15 (*c* 0.1, MeOH); IR (film) 2914br, 2851br, 2300m, 1731s, 1259m; ^{1}H NMR (CD_3OD), δ 7.79 (s, 1H, $H_{7'}$), 7.65 (d, 1H, J_{H6-H5} = 8.0 Hz, H_6), 5.75 (d, 1H, $J_{H1'-H2'}$ = 2.0 Hz, $H_{1'}$), 5.69 (d, 1H, J_{H5-H6} = 8.0 Hz, H_5), 5.14 (s, 1H, $H_{1''}$), 4.79 (dd, 1H, $J_{H6'a-H6'b}$ = 14.0 Hz, $J_{H6'a-H5'}$ = 5.5 Hz, $H_{6'a}$), 4.70 (dd, 1H, $J_{H6'b-H6'a}$ = 14.0 Hz, $J_{H6'b-H5'}$ = 5.5 Hz, $H_{6'b}$), 4.32 (dt, 1H, $J_{H5'-H6'a}$ = 5.5 Hz, $J_{H5'-H6'b}$ = 5.5 Hz, $J_{H5'-H4'}$ = 3.5 Hz, $H_{5'}$), 4.18–4.15 (m, 2H, $H_{2'}$, $H_{3'}$), 4.06 (ddd, 1H, $J_{H4''-H5''a}$ = 3.0 Hz, $J_{H4''-H5''b}$ = 10.0 Hz, $J_{H4''-H3''}$ = 6.5 Hz, $H_{4''}$), 3.96–3.92 (m, 3H, $H_{4'}$, $H_{2''}$, $H_{3''}$), 3.53 (t, 2H, $J_{H18'b-H17'}$ = 6.5 Hz, $H_{18'}$), 3.24 (dd, 1H, $J_{H5''a-H5''b}$ = 13.0 Hz, $J_{H5''a-H4''}$ = 3.0 Hz, $H_{5''a}$), 3.00 (dd, 1H, $J_{H5''b-H5''a}$ = 13.0 Hz, $J_{H5''b-H4''}$ = 10.0 Hz, $H_{5''b}$), 2.69 (t, 2H, $J_{H9'-H10'}$ = 7.5 Hz, $H_{9'}$), 1.68–1.62 (m, 2H, $H_{10'}$), 1.52 (qt, 2H, $J_{H17'-H18'}$ = $J_{H17'-H16'}$ = 6.5 Hz, $H_{17'}$), 1.38–1.26 (m, 12H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16''}$); ^{13}C NMR (CD_3OD) δ 166.2 (C_4), 152.2 (C_2), 149.5 ($C_{8'}$), 142.4 (C_6), 125.1 ($C_{7'}$), 110.9 ($C_{1''}$), 102.7 (C_5), 92.4 ($C_{1'}$), 84.7 ($C_{4'}$), 80.2 ($C_{4''}$), 78.4 ($C_{5'}$), 76.4 ($C_{2''}$), 75.4 ($C_{2'}$), 73.9 ($C_{3''}$), 71.4 ($C_{3'}$), 63.2 ($C_{18'}$), 52.6 ($C_{6'}$), 44.3 ($C_{5''}$), 33.8 ($C_{17'}$), 30.9, 30.7, 30.7, 30.6, 30.3, 27.1, 26.4 ($C_{9'}$, $C_{10'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$); HRMS, ESI$^+$ calcd for $C_{27}H_{45}N_6O_{10}^+$ $(M + H)^+$ 613.3192, found 613.3181; HPLC, method D, t_R = 11.10 min, 97%.

Compound 26e. Compound **26e** was synthesized according to the general procedure for phthalimide, isopentylidene and TBS group cleavage from *N*-triazole **24e** (19.7 mg, 0.018 mmol). After semi-preparative reverse phase HPLC (method: 15 mL min^{-1}, H_2O–TFA 0.1%/MeOH 100/0 to 60/40 in 50 min) and lyophilisation, **26e** was obtained as an ammonium trifluoroacetate salt (white foam, 9.7 mg, 69% yield): $[\alpha]_D$ +12 (*c* 0.1, MeOH); IR (film) 3058br, 2931br, 1687s, 1462m; ^{1}H NMR (D_2O + 50 μL CD_3OD), δ 8.12 (s, 1H, $H_{8'}$), 7.66 (d, 1H, J_{H6-H5} = 8.5 Hz, H_6), 5.85 (d, 1H, J_{H5-H6} = 8.5 Hz, H_5), 5.75 (d, 1H, $J_{H1'-H2'}$ = 3.0 Hz, $H_{1'}$), 5.16 (s, 1H, $H_{1''}$), 4.84 (dd, 1H, $J_{H6'a-H6'b}$ = 15.0 Hz, $J_{H6'a-H5'}$ = 5.0 Hz, $H_{6'a}$), 4.70–4.69–4.64 (m, 3H, $H_{6'b}$, $H_{9'}$), 4.45–4.42 (m, 1H, $H_{5'}$), 4.30 (dd, 1H, $J_{H2'-H1'}$ = 3.0 Hz, $J_{H2'-H3'}$ = 5.5 Hz), 4.27 (dd, 1H, $J_{H3'-H2'}$ = 5.5 Hz, $J_{H3'-H4'}$ = 4.5 Hz), 4.11–4.02 (m, 4H, $H_{4'}$, $H_{2''}$, $H_{3''}$, $H_{4''}$), 3.72–3.61 (m, 14H, $H_{10'}$, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16'}$), 3.30–3.29 (m, 3H, $H_{5''a}$, $H_{17'}$), 2.91 (dd, 1H, $J_{H5''b-H5''a}$ = 13.0 Hz, $J_{H5''b-H4''}$ = 9.0 Hz, $H_{5''b}$); ^{13}C NMR (CD_3OD) δ 167.2 (C_4), 152.3 (C_2), 145.0 ($C_{8'}$), 142.7 (C_6), 127.5 ($C_{7'}$), 110.1 ($C_{1''}$), 102.9 (C_5), 91.5 ($C_{1'}$), 84.4 ($C_{4'}$), 79.4 ($C_{4''}$), 77.9 ($C_{5'}$), 75.7 ($C_{2''}$), 74.6 ($C_{2'}$), 73.0 ($C_{3''}$), 72.9 (CH_{2PEG}), 70.9 ($C_{3'}$), 70.8, 70.7, 70.7, 70.6, 70.6, 70.2 (CH_{2PEG}), 64.2 ($C_{9'}$), 61.5 (CH_{2PEG}), 52.7 ($C_{6'}$), 43.8 ($C_{5''}$); HRMS, ESI$^+$ calcd for $C_{26}H_{43}N_6O_{14}^+$ $(M + H)^+$ 663.2832, found 663.2842; HPLC, method D, t_R = 3.21 min, 96%.

Compound 26f. Compound **26f** was synthesized according to the general procedure for phthalimide, isopentylidene and TBS group cleavage from *N*-triazole **24f** (37.5 mg, 0.032 mmol). After semi-preparative reverse phase HPLC (method: 15 mL min^{-1}, H_2O–TFA 0.1%/MeOH 100/0 to 60/40 in 50 min) and lyophilisation, **26f** was obtained as an ammonium ditrifluoroacetate salt (white foam, 12.2 mg, 45% yield): $[\alpha]_D$ +9 (*c* 0.1, H_2O); IR (film) 3384br, 2951br, 1685s, 1258m; ^{1}H NMR (D_2O : CD_3OD = 1 : 1), δ 7.79 (s, 1H, $H_{7'}$), 7.55 (d, 1H, J_{H6-H5} = 7.5 Hz, H_6), 5.78 (d, 1H, J_{H5-H6} = 7.5 Hz, H_5), 5.72 (sl, 1H, $H_{1'}$), 5.19 (s, 1H, $H_{1''}$), 4.87–4.83 (m, 2H, $H_{6'a}$, $H_{6'b}$), 4.37–4.32 (m, 1H, $H_{5'}$), 4.24–4.11 (m, 3H, $H_{2'}$, $H_{3'}$, $H_{4''}$), 4.08–3.98 (m, 3H, $H_{4'}$, $H_{2''}$, $H_{3''}$), 3.37–3.34 (m, 1H, $H_{5''a}$), 3.14–3.11 (m, 1H, $H_{5''b}$), 2.95 (t, 2H, $J_{H9'-H10'}$ = 6.5 Hz, $H_{9'}$), 2.66 (t, 2H, $J_{H18'-H17'}$ = 6.5 Hz, $H_{18'}$), 1.68–1.62 (m, 2H, $H_{10'}$), 1.59–1.54 (m, 2H, $H_{17'}$), 1.41–1.24 (m, 12H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$, $H_{16''}$); ^{13}C NMR (D_2O : CD_3OD = 1 : 1) δ 166.7 (C_4), 163.5 (*C*O-TFA), 152.2 (C_2), 149.2 ($C_{8'}$), 142.3 (C_6), 125.7 ($C_{7'}$), 110.6 ($C_{1''}$), 102.8 (C_5), 91.4 ($C_{1'}$), 84.9 ($C_{4'}$), 79.8 ($C_{4''}$), 77.9 ($C_{5'}$), 76.0 ($C_{2''}$), 74.9 ($C_{2'}$), 73.3 ($C_{3''}$), 71.3 ($C_{3'}$), 52.9 ($C_{6'}$), 43.7 ($C_{5''}$), 40.7 ($C_{18'}$), 30.1, 30.1, 30.0, 29.9, 29.7, 29.5, 28.2, 27.1, 25.7 ($C_{9'}$, $C_{10'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$, $C_{17'}$); HRMS, ESI$^+$ calcd for $C_{27}H_{45}N_7O_9^+$ $(M + H)^+$ 612.3352, found 612.3361; HPLC, method D, t_R = 4.47 min, 96%.

Compound 26g. Compound **26g** was synthesized according to the general procedure for phthalimide, isopentylidene and TBS group cleavage from *N*-triazole **24g** (21.0 mg, 0.018 mmol). After semi-preparative reverse phase HPLC (method A) and lyophilisation, **26g** was obtained as an ammonium trifluoroacetate salt (white foam, 11.3 mg, 72% yield): m.p. 156–158 °C; $[\alpha]_D$ +13 (*c* 0.1, MeOH); IR (film) 2925br, 2301br, 1731s, 1691s, 1542m; ^{1}H NMR (CD_3OD) δ 7.67

(s, 1H, $H_{7'}$), 7.54–7.46 (m, 4H, $H_{17'}$, $H_{21'}$), 7.39–7.33 (m, 2H, H_6, $H_{23'}$), 7.20–7.06 (m, 6H, $H_{11'}$, $H_{12'}$, $H_{22'}$), 6.87–6.80 (m, 2H, $H_{16'}$), 5.57 (d, 1H, J_{H5-H6} = 7.0 Hz, H_5), 5.50 (br s, 1H, $H_{1'}$), 5.18 (s, 1H, $H_{1''}$), 4.99–4.92 (m, 2H, $H_{9'}$), 4.89–4.85 (m, 1H, $H_{6'a}$), 4.69–4.62 (m, 3H, $H_{6'b}$, $H_{14'}$), 4.33–4.30 (m, 1H, $H_{5'}$), 4.16–4.11 (m, 3H, $H_{2'}$, $H_{3'}$, $H_{4''}$), 4.04–4.92 (m, 1H, $H_{3''}$), 3.99–3.97 (m, 1H, $H_{2''}$), 3.91–3.87 (m, 1H, $H_{4'}$), 3.35–3.32 (m, 1H, $H_{5''}$), 3.12 (dd, 1H, $J_{H5''b-H5''a}$ = 13.0 Hz, $J_{H5''b-H4''}$ = 10.0 Hz, $H_{5''b}$); ^{13}C NMR (CD_3OD) δ 190.9 ($C_{19'}$), 166.7 (C_4), 164.0 ($C_{15'}$), 163.5 (*C*O-TFA), 151.9 (C_2), 147.6 ($C_{8'}$), 141.6 (C_6), 140.1 ($C_{20'}$), 138.3 ($C_{13'}$), 135.6 ($C_{10'}$), 135.2 ($C_{17'}$), 133.6 ($C_{23'}$), 130.5 ($C_{18'}$), 130.4 ($C_{21'}$), 129.7 ($C_{22'}$), 129.3 ($C_{11'}$), 128.8 ($C_{12'}$), 120.9 ($C_{7'}$), 116.3 ($C_{16'}$), 110.3 ($C_{1''}$), 102.5 (C_5), 90.9 ($C_{1'}$), 84.9 ($C_{3''}$), 79.6 ($C_{4''}$), 77.2 ($C_{4'}$), 75.7 ($C_{2''}$), 74.9 ($C_{2'}$), 73.0 ($C_{5'}$), 71.0 ($C_{3'}$), 70.6 ($C_{14'}$), 52.3 ($C_{6'}$), 43.6 ($C_{5''}$), 31.3 ($C_{9'}$); HRMS, ESI^+ calcd for $C_{38}H_{41}N_6O_{11}^+$ $(M + H)^+$ 757.2828, found 757.2839; HPLC, method C, t_R = 11.99 min, 99%.

Compound 26h. Compound **26h** was synthesized according to the general procedure for phthalimide, isopentylidene and TBS group cleavage from *N*-triazole **24h** (30.0 mg, 0.025 mmol). After semi-preparative reverse phase HPLC (method A) and lyophilisation, **26h** was obtained as an ammonium trifluoroacetate salt (white foam, 14.3 mg, 64% yield): m.p. 135–138 °C; $[\alpha]_D$ +10 (*c* 0.2, MeOH); IR (film) 2921br, 2304br, 1731s, 1699s, 1540m; ^{1}H NMR (CD_3OD) δ 7.79–7.77 (m, 3H, $H_{7'}$, $H_{21'}$), 7.73–7.70 (m, 2H, $H_{25'}$), 7.65 (d, 1H, J_{H6-H5} = 8.0 Hz, H_6), 7.63–7.60 (m, 1H, $H_{27'}$), 7.53–7.50 (m, 2H, $H_{26'}$), 7.05–7.02 (m, 2H, $H_{20'}$), 5.75 (d, 1H, $J_{H1'-H2'}$ = 2.0 Hz, $H_{1'}$), 5.68 (dd, 1H, J_{H5-H6} = 8.0 Hz, H_5), 5.15 (s, 1H, $H_{1''}$), 4.79 (dd, 1H, $J_{H6'a-H6'b}$ = 14.5 Hz, $J_{H6'a-H5'}$ = 5.5 Hz, $H_{6'a}$), 4.70 (dd, 1H, $J_{H6'b-H6'a}$ = 14.5 Hz, $J_{H6'b-H5'}$ = 5.5 Hz, $H_{6'b}$), 4.32 (dt, 1H, $J_{H5'-H6'a}$ = 5.5 Hz, $J_{H5'-H6'b}$ = 5.5 Hz, $J_{H5'-H4'}$ = 3.5 Hz, $H_{5'}$), 4.18–4.15 (m, 2H, $H_{2'}$, $H_{3'}$), 4.98–4.05 (m, 3H, $H_{18'}$, $H_{4''}$), 3.96–3.90 (m, 3H, $H_{4'}$, $H_{2''}$, $H_{3''}$), 3.24 (dd, 1H, $J_{H5''a-H5''b}$ = 13.0 Hz, $J_{H5''a-H4''}$ = 2.5 Hz, $H_{5''a}$), 3.01 (dd, 1H, $J_{H5''b-H5''a}$ = 13.0 Hz, $J_{H5''b-H4''}$ = 10.0 Hz, $H_{5''b}$), 2.69 (t, 2H, $J_{H9'-H10'}$ = 7.5 Hz, $H_{9'}$), 1.81 (qt, 2H, $J_{H17'-H18'}$ = $J_{H17'-H16'}$ = 7.5 Hz, $H_{17'}$), 1.68–1.62 (m, 2H, $H_{10'}$), 1.49 (qt, 2H, $J_{H16'-H17'}$ = $J_{H16'-H15'}$ = 7.5 Hz, $H_{16'}$), 1.37–1.23 (m, 10H, $H_{11'}$, $H_{12'}$, $H_{13'}$, $H_{14'}$, $H_{15'}$); ^{13}C NMR (CD_3OD) δ 197.9 ($C_{23'}$), 166.2 (C_4), 164.8 ($C_{19'}$), 152.2 (C_2), 149.4 ($C_{8'}$), 142.4 (C_6), 139.7 ($C_{24'}$), 133.8 ($C_{21'}$), 133.4 ($C_{27'}$), 131.1 ($C_{21'}$), 130.8 ($C_{25'}$), 129.6 ($C_{26'}$), 125.1 ($C_{7'}$), 115.4 ($C_{20'}$), 110.9 ($C_{1''}$), 102.7 (C_5), 92.4 ($C_{1'}$), 84.8 ($C_{4'}$), 80.2 ($C_{4''}$), 78.4 ($C_{5'}$), 76.4 ($C_{2''}$), 75.4 ($C_{2'}$), 73.9 ($C_{3''}$), 71.4 ($C_{3'}$), 69.6 ($C_{18'}$), 52.6 ($C_{6'}$), 44.3 ($C_{5''}$), 30.8, 30.8, 30.7, 30.7, 30.7, 30.5, 30.4, 30.3, 27.2, 26.4 ($C_{9'}$, $C_{10'}$, $C_{11'}$, $C_{12'}$, $C_{13'}$, $C_{14'}$, $C_{15'}$, $C_{16'}$, $C_{17'}$); HRMS, ESI^+ calcd for $C_{40}H_{53}N_6O_{11}^+$ $(M + H)^+$ 793.3767, found 793.3750; HPLC, method D, t_R = 13.25 min, 99%.

Compounds 27a–n. Compounds **27a–n** have been synthesised and fully characterized.[24] The corresponding purity has been determined by analytical HPLC and data have been included in the ESI.†

Trifluoroacetate salt of 1″,5″-dideoxy-5″-amino-1″-[5′(*S*)-acetylenylmethyl-uridinyl]-β-D-ribofuranose 28. Compound **28** was synthesized according to the general procedure for phthalimide, isopentylidene and TBS group cleavage from alkyne **5** (50.0 mg, 0.06 mmol). After semi-preparative reverse phase HPLC (method: 15 mL min^{-1}, H_2O–TFA 0.1%/MeOH 100/0 to 60/40 in 50 min) and lyophilisation, **28** was obtained as an ammonium ditrifluoroacetate salt (white foam, 16.3 mg, 52% yield): m.p. 147–154 °C; $[\alpha]_D$ +19 (*c* 0.2, H_2O); IR (film) 2925br, 2300w, 1643s, 1436m, 1270s; ^{1}H NMR (D_2O + 50 μL CD_3OD), δ 7.82 (d, 1H, J_{H6-H5} = 8.0 Hz, H_6), 5.86 (d, 1H, J_{H5-H6} = 8.0 Hz, H_5), 5.81 (d, 1H, $J_{H1'-H2'}$ = 4.0 Hz, $H_{1'}$), 5.20 (s, 1H, $H_{1''}$), 4.28 (dd, 1H, $J_{H2'-H1'}$ = 4.0 Hz, $J_{H2'-H3'}$ = 5.0 Hz, $H_{2'}$), 4.26 (dd, 1H, $J_{H4'-H3'}$ = 5.0 Hz, $J_{H4'-H5'}$ = 3.5 Hz, $H_{4'}$), 4.20 (t, 1H, $J_{H3'-H2'}$ = $J_{H3'-H4'}$ = 5.0 Hz, $H_{3'}$), 4.17–4.11 (m, 2H, $H_{2''}$, $H_{4''}$), 4.08–4.03 (m, 2H, $H_{3''}$, $H_{5'}$), 3.39 (dd, 1H, $J_{H5''a-H5''b}$ = 13.5 Hz, $J_{H5''a-H4''}$ = 2.0 Hz, $H_{5''a}$), 3.20 (dd, 1H, $J_{H5''b-H5''a}$ = 13.5 Hz, $J_{H5''b-H4''}$ = 8.5 Hz, $H_{5''b}$), 2.81–2.70 (m, 2H, $H_{6'a}$, $H_{6'b}$), 2.48–2.47 (m, 1H, $H_{8'}$); ^{13}C NMR (CD_3OD) δ 167.1 (C_4), 152.4 (C_2), 142.8 (C_6), 125.2 ($C_{7'}$), 110.8 ($C_{1''}$), 102.8 (C_5), 91.2 ($C_{1'}$), 85.4 ($C_{4'}$), 81.7 ($C_{7'}$), 79.4 ($C_{4''}$), 77.9 ($C_{5'}$), 75.7 ($C_{2''}$), 74.8 ($C_{2'}$), 73.6 ($C_{3''}$), 72.9 ($C_{8'}$), 70.9 ($C_{3'}$), 44.4 ($C_{5''}$), 23.2 ($C_{6'}$); HRMS, ESI^+ calcd for $C_{17}H_{24}N_3O_9^+$ $(M + H)^+$ 414.1507, found 414.1513; HPLC, method D, t_R = 3.32 min, 95%.

Trifluoroacetate salt of 1″,5″-dideoxy-5″-amino-1″-[5′(*S*)-azidomethyl-uridinyl]-β-D-ribofuranose 29. Compound **29** was synthesized according to the general procedure for phthalimide, isopentylidene and TBS group cleavage from azide **6** (10.0 mg, 0.012 mmol). After semi-preparative reverse phase HPLC (method: 15 mL min^{-1}, H_2O–TFA 0.1%/MeOH 95/5 to 60/40 in 40 min) and lyophilisation, **29** was obtained as an ammonium trifluoroacetate salt (white powder, 2.0 mg, 31% yield): m.p. 142–146 °C; $[\alpha]_D$ +14 (*c* 0.1, MeOH); IR (film) 2926m, 2100m, 1610s, 1462w, 1202m, 1133m,; ^{1}H NMR (D_2O + 50 μL CD_3OD), δ 7.79 (d, 1H, J_{H6-H5} = 8.0 Hz, H_6), 5.87 (d, 1H, J_{H5-H6} = 8.0 Hz, H_5), 5.78 (d, 1H, $J_{H1'-H2'}$ = 3.0 Hz, $H_{1'}$), 5.19 (s, 1H, $H_{1''}$), 4.30 (dd, 1H, $J_{H2'-H3'}$ = 5.0 Hz, $J_{H2'-H1'}$ = 3.0 Hz, $H_{2'}$), 4.208 (t, 1H, $J_{H3'-H2'}$ = $J_{H3'-H4'}$ = 5.0 Hz, $H_{3'}$), 4.17–4.07 (m, 4H, $H_{4'}$, $H_{5'}$, $H_{2''}$, $H_{3''}$, $H_{4''}$), 3.76 (dd, 1H, $J_{H6'a-H6'b}$ = 13.5 Hz, $J_{H6'a-H5'}$ = 4.5 Hz, $H_{6'a}$), 3.61 (dd, 1H, $J_{H6'b-H6'a}$ = 13.5 Hz, $J_{H6'b-H5'}$ = 5.5 Hz, $H_{6'b}$), 3.40 (dd, 1H, $J_{H5''a-H5''b}$ = 13.5 Hz, $J_{H5''a-H4''}$ = 1.5 Hz, $H_{5''a}$), 3.18 (dd, 1H, $J_{H5''b-H5''a}$ = 13.5 Hz, $J_{H5''b-H4''}$ = 8.5 Hz, $H_{5''b}$); ^{13}C NMR (D_2O + 50 μL CD_3OD) δ 167.0 (C_4), 152.3 (C_2), 142.8 (C_6), 110.1 ($C_{1''}$), 102.9 (C_5), 91.8 ($C_{1'}$), 84.5 ($C_{4'}$), 79.5 ($C_{4''}$), 78.4 ($C_{5'}$), 75.8 ($C_{2''}$), 74.7 ($C_{2'}$), 73.4 ($C_{3''}$), 70.7 ($C_{3'}$), 53.0 ($C_{6'}$), 44.1 ($C_{5''}$); HRMS, ESI^+ calcd for $C_{15}H_{23}N_6O_9^+$ $(M + H)^+$ 431.1521, found 431.1515; HPLC, method D, t_R = 4.07 min, 99%.

1″,5″-Dideoxy-2″,3″-*O*-isopentylidene-5″-azido-1″-[2′,3′-*O*-isopropylidene-5′(*S*)-ethynyl-uridinyl]-β-D-ribofuranose 32. The fluororibosyl derivative **30** (1.51 g, 6.17 mmol, 2 equiv.) and propargyl alcohol **31** (951 mg, 3.09 mmol, 1 equiv.) were dried together by co-evaporation with toluene (3 × 10 mL) and dissolved in DCM (80 mL). The flask was flushed with argon and molecular sieves 4 Å was added (7 g) in one portion. The suspension was stirred at r.t. for 1 h and then cooled to −78 °C. Boron trifluoride diethyletherate (775 μL, 6.17 mmol, 2 equiv.) was added at −78 °C and the reaction medium was stirred at this temperature for 10 min and was then allowed to warm to r.t. for 16 h. The reaction mixture was filtered on a celite pad

and the cake was washed with DCM (50 mL). The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (50 mL) and the aqueous phase was extracted with DCM (5 × 60 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting white foam was purified by flash chromatography (toluene/acetone 85/15) to give azido alkyne **32** as a β/α mixture (β/α = 13/1) and as a white foam (1.23 g, 75% combined yield). The major diastereoisomer was isolated with 45% yield: R_f 0.30 (toluene/acetone 7/3); m.p. 136–140 °C; $[\alpha]_D$ −32 (*c* 0.5, CH_2Cl_2); IR (film) 3246br, 3070w, 2105s, 1693s, 1458m, 1090s; ^{1}H NMR δ 9.86 (br s, 1H, NH), 7.32 (d, 1H, J_{H6-H5} = 7.5 Hz, H_6), 5.71 (d, 1H, J_{H5-H6} = 7.5 Hz, H_5), 5.64 (d, 1H, $J_{H1'-H2'}$ = 2.0 Hz, $H_{1'}$), 5.26 (s, 1H, $H_{1''}$), 4.96 (dd, 1H, $J_{H2'-H3'}$ = 7.0 Hz, $J_{H2'-H1'}$ = 2.0 Hz, $H_{2'}$), 4.93 (dd, 1H, $J_{H3'-H2'}$ = 7.0 Hz, $J_{H3'-H4'}$ = 4.0 Hz, $H_{3'}$), 4.64 (dd, 1H, $J_{H5'-H4'}$ = 7.5 Hz, $J_{H5'-H7'}$ = 2.5 Hz, $H_{5'}$), 4.60 (d, 1H, $J_{H2''-H3''}$ = 6.5 Hz, $H_{2''}$), 4.59 (d, 1H, $J_{H3''-H2''}$ = 6.5 Hz, $H_{3''}$), 4.47 (dd, 1H, $J_{H4''-H5''a}$ = 10.0 Hz, $J_{H4''-H5''b}$ = 4.5 Hz, $H_{4''}$), 4.34 (dd, 1H, $J_{H4'-H5'}$ = 6.5 Hz, $J_{H4'-H3'}$ = 2.5 Hz, $H_{4'}$), 3.96 (dd, 1H, $J_{H5''a-H5''b}$ = 14.0 Hz, $J_{H5''a-H4''}$ = 10.0 Hz, $H_{5''a}$), 3.90 (dd, 1H, $J_{H5''b-H5''a}$ = 14.0 Hz, $J_{H5''b-H4''}$ = 4.5 Hz, $H_{5''b}$), 2.60 (d, 1H, $J_{H7'-H5'}$ = 2.0 Hz, $H_{7'}$), 1.65–1.61 (m, 2H, $H_{7''}$), 1.59 (s, 3H, $H_{9'}$), 1.52 (q, 2H, $J_{H7''-H8''}$ = 7.5 Hz, $H_{7''}$), 1.39 (s, 3H, $H_{9'}$), 0.85 (t, 3H, $J_{H8''-H7''}$ = 7.5 Hz, $H_{8''}$), 0.82 (t, 3H, $J_{H8''-H7''}$ = 7.5 Hz, $H_{8''}$); ^{13}C NMR δ 168.3 ($C_{9''}$), 162.9 (C_4), 150.1 (C_2), 142.1 (C_6), 134.3 ($C_{12''}$), 132.1 ($C_{10''}$), 123.6 ($C_{11''}$), 117.2 ($C_{6''}$), 114.7 ($C_{8'}$), 109.4 ($C_{1''}$), 102.9 (C_5), 94.8 ($C_{1'}$), 88.6 ($C_{4'}$), 85.9 ($C_{2''}$), 84.9 ($C_{4''}$), 84.2 ($C_{2'}$), 82.6 ($C_{3''}$), 81.5 ($C_{3'}$), 79.7 ($C_{6'}$), 76.5 ($C_{7'}$), 68.6 ($C_{5'}$), 40.7 ($C_{5''}$), 29.6, 28.9 ($C_{7''}$), 27.2, 25.4 ($C_{9'}$), 8.4, 7.4 ($C_{8''}$); HRMS ESI$^+$ calcd for $C_{24}H_{32}N_5O_9^+$ $(M + H)^+$ 534.2195, found 534.2195.

1″,5″-Dideoxy-2″,3″-*O*-isopentylidene-5″-amino-1″-[2′,3′-*O*-isopropylidene-5′(*S*)-ethynyl-uridinyl]-β-D-ribofuranose 33. To a solution of azide **32** (609 mg, 1.14 mmol, 1 equiv.) in THF (12 mL) and water (2 mL) was added triphenylphosphine (598 mg, 2.28 mmol, 2 equiv.). The mixture was stirred at r.t. for 16 h and volatiles were removed *in vacuo*. Flash chromatography of the residue afforded **33** as a white foam (498 mg, 86% yield); m.p. 116–120 °C; $[\alpha]_D$ −15 (*c* 0.5, MeOH); IR (film) 2976w, 2938w, 1694s, 1455m, 1272s; ^{1}H NMR (CD_3OD) δ 7.64 (d, 1H, J_{H6-H5} = 8.5 Hz, H_6), 5.72 (d, 1H, $J_{H1'-H2'}$ = 2.0 Hz, $H_{1'}$), 5.65 (d, 1H, J_{H5-H6} = 8.5 Hz, H_5), 5.17 (s, 1H, $H_{1''}$), 5.08 (dd, 1H, $J_{H2'-H3'}$ = 6.5 Hz, $J_{H2'-H1'}$ = 2.0 Hz, $H_{2'}$), 4.89 (dd, 1H, $J_{H3'-H2'}$ = 6.5 Hz, $J_{H3'-H4'}$ = 3.0 Hz, $H_{3'}$), 4.69 (d, 1H, $J_{H5'-H4'}$ = 8.0 Hz, $H_{5'}$), 4.59 (d, 1H, $J_{H2''-H3''}$ = 6.0 Hz, $H_{2''}$), 4.57 (d, 1H, $J_{H3''-H2''}$ = 6.0 Hz, $H_{3''}$), 4.19 (dd, 1H, $J_{H4'-H5'}$ = 8.0 Hz, $J_{H4'-H3'}$ = 3.0 Hz, $H_{4'}$), 4.15 (dd, 1H, $J_{H4''-H5''a}$ = 9.0 Hz, $J_{H4''-H5''b}$ = 5.0 Hz, $H_{4''}$), 3.27 (sl, 1H, $H_{7'}$), 2.77 (dd, 1H, $J_{H5''a-H5''b}$ = 13.0 Hz, $J_{H5''a-H4''}$ = 9.0 Hz, $H_{5''a}$), 2.69 (dd, 1H, $J_{H5''b-H5''a}$ = 13.0 Hz, $J_{H5''b-H4''}$ = 5.0 Hz, $H_{5''b}$), 1.60 (q, 2H, $J_{H7''-H8'''}$ = 7.5 Hz, $H_{7''}$), 1.52 (q, 2H, $J_{H7''-H8'''}$ = 7.5 Hz, $H_{7''}$), 1.50 (s, 3H, $H_{9'}$), 1.31 (s, 3H, $H_{9'}$), 0.82 (t, 3H, $J_{H8''-H7''}$ = 7.5 Hz, $H_{8''}$), 0.81 (t, 3H, $J_{H8''-H7''}$ = 7.5 Hz, $H_{8''}$); ^{13}C NMR (CD_3OD) δ 166.4 (C_4), 152.4 (C_2), 142.1 (C_6), 117.9 ($C_{6''}$), 115.3 ($C_{8'}$), 111.4 ($C_{1''}$), 103.1 (C_5), 97.8 ($C_{1'}$), 91.4 ($C_{4'}$), 90.5 ($C_{2''}$), 87.3 ($C_{4''}$), 85.6 ($C_{2'}$), 83.8 ($C_{3''}$), 83.5 ($C_{3'}$), 80.2 ($C_{7'}$, $C_{6'}$), 70.1 ($C_{5'}$), 45.8 ($C_{5''}$), 30.5, 30.0 ($C_{7''}$), 27.5, 25.5 ($C_{9'}$), 8.8, 7.9 ($C_{8''}$); HRMS ESI$^+$ calcd for $C_{24}H_{34}N_3O_9^+$ $(M + H)^+$ 508.2290, found 508.2301.

Trifluoroacetate salt of 1″,5″-dideoxy-5″-amino-1″-[5′(*S*)-ethynyl-uridinyl]-β-D-ribofuranose 34. At 0 °C, to a suspension of amine **33** (40 mg, 0.078 mmol, 1 equiv.), in pure water (600 μL), was dropwise added trifluoroacetic acid (2.4 mL). The mixture was stirred at 0 °C for 10 min then at r.t. for 90 min. Trifluoroacetic acid was then removed *in vacuo* without heating. The residue was dissolved in water and lyophilised. The crude foam was recrystallized in dry Et_2O to furnish the corresponding deprotected compound **34** as a trifluoroacetate salt (white powder, 39.6 mg, 99% yield); m.p. 180–186 °C; $[\alpha]_D$ +15 (*c* 0.5, MeOH); IR (film) 3250br, 2925w, 2320w, 1678s, 1519w, 1467w, 1275m; ^{1}H NMR (CD_3OD) δ 7.73 (d, 1H, J_{H6-H5} = 8.5 Hz, H_6), 5.88 (d, 1H, $J_{H1'-H2'}$ = 6.0 Hz, $H_{1'}$), 5.74 (d, 1H, J_{H5-H6} = 8.5 Hz, H_5), 5.21 (s, 1H, $H_{1''}$), 4.65 (dd, 1H, $J_{H5'-H4'}$ = 5.5 Hz, $J_{H5'-H7'}$ = 2.0 Hz, $H_{5'}$), 4.28 (t, 1H, $J_{H2'-H3'}$ = 6.0 Hz, $J_{H2'-H1'}$ = 6.0 Hz, $H_{2'}$), 4.20 (dd, 1H, $J_{H3'-H2'}$ = 6.0 Hz, $J_{H3'-H4'}$ = 3.0 Hz, $H_{3'}$), 4.14–4.09 (m, 3H, $H_{2''}$, $H_{3''}$, $H_{4''}$), 3.99–3.96 (m, 1H, $H_{4'}$), 3.31–3.28 (m, 1H, $H_{5''a}$), 3.17 (dd, 1H, $J_{H5''b-H5''a}$ = 13.0 Hz, $J_{H5''b-H4''}$ = 4.0 Hz, $H_{5''b}$), 3.14 (d, 1H, $J_{H7'-H5'}$ = 2.0 Hz, $H_{7'}$).; ^{13}C NMR (CD_3OD) δ 166.1 (C_4), 152.5 (C_2), 142.5 (C_6), 109.0 ($C_{1''}$), 103.2 (C_5), 90.8 ($C_{1'}$), 87.1 ($C_{4''}$), 81.3 ($C_{6'}$), 80.5 ($C_{3''}$), 77.9 ($C_{7'}$), 76.0 ($C_{4'}$), 74.6 ($C_{2'}$), 74.3 ($C_{2''}$), 71.7 ($C_{3'}$), 69.2 ($C_{5'}$), 44.5 ($C_{5''}$); HRMS ESI$^+$ calcd for $C_{16}H_{22}N_3O_9^+$ $(M + H)^+$ 400.1351, found 400.1351; HPLC, method C, t_R = 2.31 min, 98%.

Enzymatic assays

The activities of the compounds against MraY from *Bacillus subtilis* were tested as previously described.[14b] The assay was performed in a reaction mixture of 10 μL containing, in final concentrations, 100 mM Tris-HCl, pH 7.5, 40 mM $MgCl_2$, 1.1 mM C_{55}-P, 250 mM NaCl, 0.25 mM UDP-Mur*N*Ac-[^{14}C]-pentapeptide (337 Bq), and 8.4 mM *N*-lauroyl sarcosine. The reaction was initiated by the addition of MraY enzyme (50 ng) and the mixture was incubated for 30 min at 37 °C under shaking with a thermomixer (Eppendorf). The reaction was stopped by heating at 100 °C for 1 min and the radiolabeled substrate (UDP-Mur*N*Ac-pentapeptide) and reaction product (lipid I) were separated by TLC on silica gel plates using 2-propanol/ammonium hydroxide/water (6 : 3 : 1; v/v/v) as the mobile phase. The radioactive spots were located and quantified with a radioactivity scanner.

Antibacterial activity

Determination of antibacterial activity was done on microtitric plates, in 200 μL (final volume) of Müeller–Hinton broth (MHB), following the EUCAST (European Committee on Antimicrobial Susceptibility testing)/CLSI (Clinical and Laboratory Standard Institute) recommended procedure.[42]

Compounds were solubilized in DMSO and then diluted in MHB just before utilization. Inocula were prepared for each strain, resuspending isolated colonies from 18 h cultured plates. Equivalents of 0.5 Mac Farland turbidity standard (approximately 1×10^8 CFU ml^{-1}) were prepared in saline solu-

tion (NaCl 0.085%) and then diluted 200 fold in MHB. MIC values were determined as the lowest dilution of product showing no visual turbidity.

Molecular docking

All calculations were performed in Discovery Studio 4.0. MraY structure (PDB code: 4J72) was prepared by the use of the Prepare Protein protocol of DS 4.0 including the cleaning of the protein, the optimization of side-chain conformation for residues with inserted atoms, the removal of water molecules present in the PDB structure, the modeling of missing loop regions based on SEQRES information, and the prediction of titration site *p*Ks and protonation state of the structure at the specified pH. Flexible ligand/rigid protein docking was performed using CDOCKER.[33] Ligands were prepared using the Prepared Ligand protocol of DS 4.0 including the generation of canonical tautomers, keeping only largest fragments, the set of standard formal charges of common functional groups, the generation of kekule structures, enumeration of ionization states at a given pH range, enumeration of tautomers and the generation of a reasonable 3D conformation using Catalyst. Random ligand conformations were generated from the initial ligand structure through high-temperature molecular dynamics. Due to the high flexibility of the MraY ligand, we docked for each ligand several conformations previously generated with the BEST algorithm[43] to cover the full range of conformers. The poses showing the lowest energy were retained and clustered according to their binding mode. Three-dimensional snapshots of the docked ligands were generated using Accelrys DS Visualizer.

Acknowledgements

We thank the "Centre National de la Recherche Scientifique" and the "Ministère de l'Enseignement Supérieur et de la Recherche" for financial support of this work and for awarding M. J. F. a PhD grant. This work has benefited from the facilities and expertise of the Small Molecule Mass Spectrometry platform of IMAGIF (Centre de Recherche de Gif – http://www.imagif.cnrs.fr). Assia Hessani (Université Paris Descartes) is gratefully acknowledged for assistance with low resolution and high resolution mass spectra analyses. The NMR experiments were performed at the NMR platform of the Interdisciplinary Center for Chemistry and Biology, Paris.

References

1 (*a*) S. B. Levy and B. Marshall, *Nat. Med.*, 2004, **10**, S122–S129; (*b*) M. N. Alekshun and S. B. Levy, *Cell*, 2007, **128**, 1037–1050; (*c*) C. T. Walsh and G. Wright, *Chem. Rev.*, 2005, 391–393 and all references of this volume are dedicated to antibiotic resistance.

2 B. Lechartier, J. Rybniker, A. Zumla and S. T. Cole, *EMBO Mol. Med.*, 2014, **6**, 158–168.

3 D. J. Payne, M. N. Gwynn, D. J. Holmes and D. L. Pompliano, *Nat. Rev. Drug Discovery*, 2007, **6**, 29–40.

4 (*a*) K. M. Fisch, A. F. Gillaspy, M. Gipson, J. C. Henrikson, A. R. Hoover, L. Jackson, F. Z. Najar, H. Wägele and R. H. Cichewicz, *J. Ind. Microbiol. Biotechnol.*, 2009, **36**, 1199–1213; (*b*) C. Zhao, J. M. Coughlin, J. Ju, D. Zhu, E. Wendt-Pienkowski, X. Zhou, Z. Wang, B. Shen and Z. Deng, *J. Biol. Chem.*, 2010, **285**, 20097–20108.

5 J. Swarbrick, P. Iliades, J. Simpson and I. Macreadie, *Open Enzyme Inhib. J.*, 2008, **1**, 12–33.

6 J. W. Campbell and J. E. Cronan, *Annu. Rev. Microbiol.*, 2001, **55**, 305–332.

7 A. Boularot, C. Giglione, I. Artaud and T. Meinnel, *Curr. Opin. Invest. Drugs*, 2004, **5**, 809–822.

8 J. G. Hurdle, A. J. O'Neill and I. Chopra, *Antimicrob. Agents Chemother.*, 2005, **49**, 4821–4833.

9 J. van Heijenoort, *Nat. Prod. Rep.*, 2001, **8**, 503–519.

10 S. Jovetic, Y. Zhu, G. L. Marcone, F. Marinelli and J. Tramper, *Trends Biotechnol.*, 2010, **28**, 596–604.

11 B. C. Chung, J. Zhao, R. Gillespie, D.-Y. Kwon, Z. Guan, J. Hong, P. Zhou and S.-Y. Lee, *Science*, 2013, **341**, 1012–1016.

12 A. Bouhss, D. Mengin-Lecreulx, D. Le Beller and J. van Heijenoort, *Mol. Microbiol.*, 1999, **34**, 576–585.

13 B. Al-Dabbagh, X. Henry, M. El Ghachi, G. Auger, D. Blanot, C. Parquet, D. Mengin-Lecreulx and A. Bouhss, *Biochemistry*, 2008, **47**, 8919–8928.

14 (*a*) A. Bouhss, A. E. Trunkfield, T. D. H. Bugg and D. Mengin-Lecreulx, *FEMS Microbiol. Rev.*, 2008, **32**, 208–233; (*b*) A. Bouhss, M. Crouvoisier, D. Blanot and D. Mengin-Lecreulx, *J. Biol. Chem.*, 2004, **279**, 29974–29980.

15 (*a*) S. Tanaka and W. M. Clemons Jr., *Mol. Microbiol.*, 2012, **85**, 975–985; (*b*) M. T. Rodolis, A. Mihalyi, A. O'Reilly, J. Slikas, D. I. Roper, R. E. W. Hankock and T. D. H. Bugg, *ChemBioChem*, 2014, **15**, 1300–1308; (*c*) A. Mihalyi, S. Jamshidi, J. Slikas and T. D. H. Bugg, *Bioorg. Med. Chem.*, 2014, **22**, 4566–4571.

16 (*a*) K. Ochi, M. Ezaki, M. Iwani, T. Komori and M. Kohsaka, EP-333177, Fujisawa Pharmaceutical Co., Ltd, Japan, 1989; (*b*) Y. Yoshida, H. Yamanaka and K. Sakane, JP H05-78385, 1993.

17 (*a*) M. Ubukata and K. Isono, *J. Am. Chem. Soc.*, 1988, 4416–4417; (*b*) M. Ubukata, K. Kimura, K. Isono, C. C. Nelson, J. M. Gregson and J. McCloskey, *J. Org. Chem.*, 1992, **57**, 6392–6403; (*c*) P. E. Brandish, K. I. Kimura, M. Inukai, R. Southgate, J. T. Lonsdale and T. D. H. Bugg, *Antimicrob. Agents Chemother.*, 1996, **40**, 1640–1644; (*d*) Y. Esumi, Y. Suzuki, K. Kimura, M. Yoshihama, T. Ichikawa and M. Uramoto, *J. Antibiot.*, 1999, **52**, 281–287.

18 (*a*) M. Igarashi, N. Nakagawa, S. Doi, N. Hattori, H. Naganawa and M. Hamada, *J. Antibiot.*, 2003, **56**, 580–583; (*b*) M. Igarashi, Y. Takahashi, T. Shitara, H. Nakamura, H. Naganawa, T. Miyake and Y. Akamatsu, *J. Antibiot.*, 2005, **58**, 327–337.

19 L. A. McDonald, L. R. Barbieri, G. T. Carter, E. Lenoy, J. Lotvin, P. J. Petersen, M. M. Siegel, G. Singh and R. T. Williamson, *J. Am. Chem. Soc.*, 2002, **124**, 10260–10261.

20 (*a*) M. Winn, R. J. M. Goss, K. Kimura and T. D. H. Bugg, *Nat. Prod. Rep.*, 2010, **27**, 279–304; (*b*) C. Dini, *Curr. Top. Med. Chem.*, 2005, **5**, 1221–1236; (*c*) T. D. H. Bugg, A. J. Lloyd and D. I. Roper, *Infect. Disord.: Drug Targets*, 2006, **6**, 85–106.

21 For recent and selected synthetic approaches toward FR-900493 and muraymycins: (*a*) Y. I. Lin, Z. Li, G. D. Francisco, L. A. McDonald, R. A. Davis, G. Singh, Y. Yang and T. S. Mansour, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2341–2344; (*b*) A. Yamashita, E. Norton, P. J. Peterson, B. A. Rasmussen, G. Singh, Y. Yang, T. S. Mansour and D. M. Ho, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3345–3350; (*c*) F. Sarabia and L. Martin-Ortiz, *Tetrahedron*, 2005, **61**, 11850–11865; (*d*) S. Hirano, S. Ichikawa and A. Matsuda, *Tetrahedron*, 2007, **63**, 2798–2804; (*e*) A. Clouet, C. Gravier-Pelletier, B. Al-Dabbagh, A. Bouhss and Y. Le Merrer, *Tetrahedron: Asymmetry*, 2008, **19**, 397–400; (*f*) T. Tanino, S. Hirano, S. Ichikawa and A. Matsuda, *Nucleic Acids Symp. Ser.*, 2008, **52**, 557–558; (*g*) M. Kurosu and K. Li, *J. Org. Chem.*, 2008, **73**, 9767–9770; (*h*) A. P. Spork, S. Koppermann and C. Ducho, *Synlett*, 2009, 2503–2507; (*i*) D. Lecerclé, A. Clouet, B. Al-Dabbagh, A. Bouhss, C. Gravier-Pelletier and Y. Le Merrer, *Bioorg. Med. Chem.*, 2010, **18**, 4560–4569; (*j*) T. Tanino, S. Ichikawa, M. Shiro and A. Matsuda, *J. Org. Chem.*, 2010, **75**, 1366–1377; (*k*) T. Tanino, S. Ichikawa, B. Al-Dabbagh, A. Bouhss, H. Oyama and A. Matsuda, *ACS Med. Chem. Lett.*, 2010, **1**, 258–262; (*l*) A. P. Spork and C. Ducho, *Org. Biomol. Chem.*, 2010, **8**, 2323–2326; (*m*) A. P. Spork, S. Koppermann, B. Dittrich, R. Herbst-Irmer and C. Ducho, *Tetrahedron: Asymmetry*, 2010, **21**, 763–766; (*n*) A. P. Spork, D. Wiegmann, M. Granitzka, D. Stalke and C. Ducho, *J. Org. Chem.*, 2011, **76**, 10083–10098; (*o*) B. A. Aleiwi and M. Kurosu, *Tetrahedron Lett.*, 2012, **53**, 3758–3762; (*p*) A. P. Spork and C. Ducho, *Synlett*, 2013, 343–346; (*q*) A. P. Spork, M. Bueschleb, O. Ries, D. Wiegmann, S. Boettcher, A. Mihalyi, T. D. H. Bugg and C. Ducho, *Chem. – Eur. J.*, 2014, **20**, 15292–15297.

22 For recent and selected synthetic approaches toward liposidomycins and caprazamycins: (*a*) S. Knapp, G. J. Moriello and G. A. Doss, *Org. Lett.*, 2002, **4**, 603–606; (*b*) F. Sarabia, L. Martín-Ortiz and F. J. López-Herrera, *Org. Lett.*, 2003, **5**, 3927–3930; (*c*) S. Ichikawa and A. Matsuda, *Nucleosides, Nucleotides Nucleic Acids*, 2005, **24**, 319–329; (*d*) S. Hirano, S. Ichikawa and A. Matsuda, *Angew. Chem., Int. Ed.*, 2005, **44**, 1854–1856; (*e*) Y. Bourdreux, B. Drouillat and C. Greck, *Lett. Org. Chem.*, 2006, **3**, 368–370; (*f*) O. Monasson, M. Ginisty, G. Bertho, C. Gravier-Pelletier and Y. Le Merrer, *Tetrahedron Lett.*, 2007, **48**, 8149–8152; (*g*) B. Drouillat, Y. Bourdreux, D. Perdon and C. Greck, *Tetrahedron: Asymmetry*, 2007, **18**, 1955–1963; (*h*) S. Hirano, S. Ichikawa and A. Matsuda, *J. Org. Chem.*, 2007, **72**, 9936–9946; (*i*) X. H. Xu, A. E. Trunkfield, T. D. H. Bugg and F.-L. Quing, *Org. Biomol. Chem.*, 2008, **6**, 157–161; (*j*) S. Hirano, S. Ichikawa and A. Matsuda, *J. Org. Chem.*, 2008, **73**, 569–577; (*k*) S. Hirano, S. Ichikawa and A. Matsuda, *Bioorg. Med. Chem.*, 2008, **16**, 428–436; (*l*) S. Hirano, S. Ichikawa and A. Matsuda, *Bioorg. Med. Chem.*, 2008, **16**, 5123–5133; (*m*) J. Mravljak, O. Monasson, B. Al-Dabbagh, M. Crouvoisier, A. Bouhss, C. Gravier-Pelletier and Y. Le Merrer, *Eur. J. Med. Chem.*, 2011, **46**, 1582–1592; (*n*) F. Sarabia, C. Vivar-García, C. García-Ruiz, L. Martín-Ortiz and A. Romero-Carrasco, *J. Org. Chem.*, 2012, **77**, 1328–1339; (*o*) P. Gopinath, L. Wang, H. Abe, G. Ravi, T. Masuda, T. Watanabe and M. Shibasaki, *Org. Lett.*, 2014, **16**, 3364–3367; (*p*) H. Nakamura, C. Tsukano, M. Yasui, S. Yokouchi, M. Igarashi and Y. Takemoto, *Angew. Chem., Int. Ed.*, 2015, **54**, 3136–3139.

23 (*a*) C. Dini, P. Collette, N. Drochon, J. C. Guillot, G. Lemoine, P. Mauvais and J. Aszodi, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1839–1843; (*b*) C. Dini, N. Drochon, S. Feteanu, J. C. Guillot, C. Peixoto and J. Aszodi, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 529–531; (*c*) C. Dini, N. Drochon, J. C. Guillot, P. Mauvais, P. Walter and J. Aszodi, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 533–536.

24 M. J. Fer, S. Olatunji, A. Bouhss, S. Calvet-Vitale and C. Gravier-Pelletier, *J. Org. Chem.*, 2013, **78**, 10088–10105.

25 For the correlation of molecular flexibility and inhibitory activities, see for example: (*a*) A. Mai, S. Massa, R. Ragno, I. Cerbara, F. Jesacher, P. Loidl and G. Brosch, *J. Med. Chem.*, 2003, **46**, 512–524; (*b*) T. Narsinghani and S. C. Chaturvedi, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 461–468.

26 V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596–2599.

27 M. J. Fer, P. Doan, T. Prangé, S. Calvet-Vitale and C. Gravier-Pelletier, *J. Org. Chem.*, 2014, **79**, 7758–7765.

28 S. Hirano, S. Ichikawa and A. Matsuda, *Angew. Chem., Int. Ed.*, 2005, **44**, 1854–1856.

29 M. W. Hosseini and J.-M. Lehn, *Helv. Chim. Acta*, 1986, **69**, 587–603.

30 K. A. Davies, R. C. Abel and J. E. Wulff, *J. Org. Chem.*, 2009, **74**, 3997–4000.

31 X. Zhang, B. Bernet and A. Vasella, *Helv. Chim. Acta*, 2006, **89**, 2861–2917.

32 J. Li, T. Ehlers, J. Sutter, S. Varma-O'Brien and J. Kirchmair, *J. Chem. Inf. Model.*, 2007, **47**, 1923–1932.

33 G. Wu, D. H. Robertson, C. L. Brooks and M. Vieth, *J. Comput. Chem.*, 2003, **24**, 1549–1562.

34 C. Dini, S. Didier-Laurent, N. Drochon, S. Feteanu, J. C. Guillot, F. Monti, E. Uridat, J. Zhang and J. Aszodi, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1209–1213.

35 T. Tanino, B. Al-Dabbagh, D. Mengin-Lecreulx, A. Bouhss, H. Oyama, S. Ichikawa and A. Matsuda, *J. Med. Chem.*, 2011, **54**, 8421–8439.

36 G. Gorgen, W. Boland, U. Preiss and H. Simon, *Helv. Chim. Acta*, 1989, **72**, 917–928.

37 C. D. Perchonock, I. Uzinskas, M. E. McCarthy, K. F. Erhard, J. G. Gleason, M. A. Wasserman,

R. M. Muccitelli, J. F. DeVan, S. S. Tucker and L. M. Vickery, *J. Med. Chem.*, 1986, **29**, 1442–1452.
38 O. Vechorkin, A. Godinat, R. Scopelliti and X. Hu, *Angew. Chem., Int. Ed.*, 2011, **50**, 11777–11781.
39 M. Camail, A. Margaillan, I. Martin, A. L. Papailhou and J. L. Vernet, *Eur. Polym. J.*, 2000, **36**, 1853–1863.
40 M. S. Newman and J. H. Wotiz, *J. Am. Chem. Soc.*, 1949, **71**, 1292–1297.
41 (*a*) W. W. Christie and R. T. Holman, *Chem. Phys. Lipids*, 1967, **1**, 407–423; (*b*) R. Rossi and A. Carpita, *Tetrahedron*, 1983, **39**, 287–290.
42 (*a*) Clinical and Laboratory Standards Institute (CLSI). Methods for dilution Antimicrobial Susceptibility Tests for Bacteria that growth aerobically; Approved standard, 8th edn, 2009, M7 A8, vol. **29**, no. 2; (*b*) European Committee for Antimicrobial Susceptibility Testing (EUCAST) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). Determination of minimum inhibitory concentrations (MICs) of antibacterial agents by broth dilution, 2003, E. Dis. 5.1.
43 J. Kirchmair, C. Laggner, G. Wolber and T. Langer, *J. Chem. Inf. Model.*, 2005, **45**, 422–430.