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Aglycone Mimics for Tuning of Glycosidase Inhibition: Design, Synthesis and Biological Evaluation of Bicyclic Pyrrolidotriazole Iminosugars.

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Various *fuco*-configured bicyclic pyrrolidotriazole aglycone mimics were synthesised using copper-catalysed coupling of allyl bromides with terminal alkynes and Sonogashira-Hagihara reaction followed by intramolecular azide-alkyne 'click' reaction. The mimicry of the aglycone segment tends to bring about switching of activity amongst α-glucosidases and a 10 to 14-fold enhancement in potency for α-fucosidase inhibition.

Introduction

Iminosugars are monosaccharide mimics with a nitrogen atom in place of the ring oxygen atom.[1] The significant biological activities of iminosugars have certainly made them the most prominent amongst diverse glycomimetics reported till date.[2] Iminosugars have found implication in the treatment of a range of diseases like cancer, diabetes, tuberculosis, lysosomal storage disorders, cystic fibriosis and various viral infections including HIV and HCV.[3] The theraupetic relevance of iminosugars is attributed to their ability to act as glycosidase inhibitors.[4] However, the major drawback associated with the use of iminosugars is their lack of selectivity towards a particular glycosidase which may lead to detrimental side effects thereby limiting their clinical applications.[2a,5] In most cases, these small organic molecules inhibit glycosidases by mimicking the glycone moiety of the presumed substrate or acting as transition state analogues.[6] The glycone moiety of the presumed substrate for a particular glycosidase is akin to that of substrate for other glycosidases of the same family which accounts for the promiscuous binding and hence the non-specific behaviour associated with iminosugar based glycosidase inhibitors.

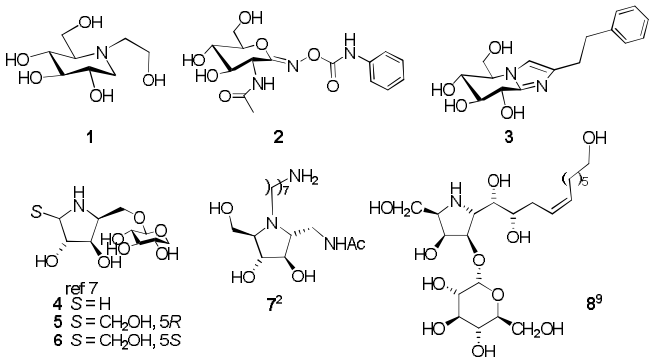

Fig. 1 Examples of Iminosugar Aglycone Mimics.

An aglycone is a substituent incorporated in the inhibitor that tends to interact with the subsite of the enzyme that normally binds the leaving group. The incorporation of hydrophobic aglycones in an inhibitor helps to capture the binding energy thereby enhancing the affinity.[5,10] As in case of a charge mimic *N*-hydroxyethyl deoxynojirimycin (Miglitol **1**, an approved piperidine iminosugar drug for the treatment of type II diabetes), the *N*-alkyl chain occupies the leaving group binding site (Fig. 1).[11] *O*-(2-acetamido-2-deoxy-D-glucopyranosylidene) amino *N*-phenyl carbamate (PUGNAc **2**) which is a shape mimic and a nanomolar inhibitor of both α- and β-*N*-acetylhexosaminidases[12] presents another example of aglycone with a pendant aromatic group. Glycoimidazoles of type **3** with a phenethyl substituent are among the most potent glycosyl hydrolase inhibitors.[13,14] Compounds **4-8** represent pyrrolidine iminosugar based aglycone mimics. Glycosides **4**, **5** and **6** contributed to the early advances in the design of aglycone mimics. Lipophilic compound **7** was found to be a potent human β-hexosaminidase inhibitor with a K_i value of 2.6 nM. Naturally

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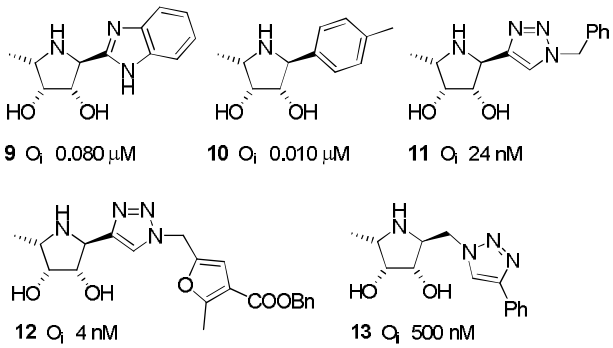


Fig. 2 Pyrrolidine Iminosugar Based Aglycone Mimics as Fucosidase Inhibitors.

occurring iminosugar **8** with a long side chain strongly inhibited α-galactosidase.

It has been demonstrated in several cases[10,15-17] that the active site of the enzyme is occupied by the glycone segment and simultaneously the aglycone makes additional interactions with the amino acids in the allosteric sites of the enzyme thus augmenting the binding affinity for the formation of enzyme-inhibitor complex. Alternatively, the interactions made by the aglycone with the allosteric site might bring about an induced fit of the glycone into the active site. An interesting case where aglycone based interactions are used as a tool for tuning the glycosidase inhibition came up with the efforts of Mellet, Fernandez and Suzuki who fruitfully obtained competitive inhibitors of either α-galactosidase or β-galactosidase from conformationally locked iminosugars.[18] Their previous explorations revealed that the aglycone interactions control the configurational-conformational switch mechanism which brings about selectivity in enzyme inhibition.[19] The concept of aglycone mimicry for inhibition of carbohydrate processing enzymes has recently shown much success for AFU (α-L-fucosidase) inhibition[17,20] and has attracted the interest of various groups towards synthesising fucosidase inhibitors with aglycones having variable functionalities and spatial dispositions with respect to the glycone part. These results are suggestive of further exploiting the favourable aglycone interactions to bring about a higher affinity and/or selectivity in enzyme inhibition.

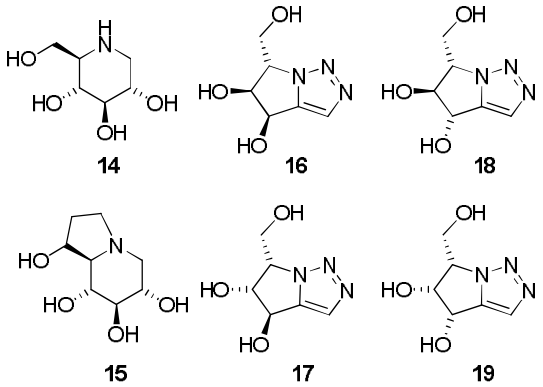


Fig. 3 Structures of DNJ **14**, Castanospermine **15** and Bicyclic Pyrrolidotriazoles **16** to **19**.

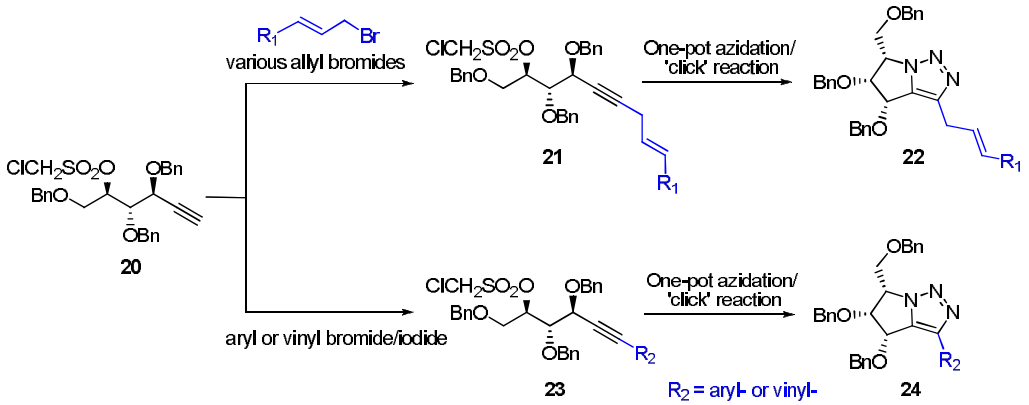
Bicyclic iminosugar frameworks are more rigid and conformationally constrained than their monocyclic counterparts, a feature that has significantly contributed to achieve an improved selectivity in glycosidase inhibition. For example, Castanospermine **15**, a bicyclic analogue of deoxynojirimycin (DNJ) **14** displays a relatively selective inhibition profile over parent molecule DNJ which is both α- and β-glucosidase inhibitor. [21] Consequently, a large number of bicyclic iminosugars have been synthesised and evaluated.[22] Various iminosugars with an appended functionality have also demonstrated their utility in enzyme inhibition studies.[10,17,19b,23]

In our earlier efforts we have succeeded in addressing the selectivity issues encountered by pyrrolidine iminosugars by constructing bicyclic pyrrolidotriazoles **16-19** (Fig. 3) which proved to be selective α-glucosidase inhibitors owing to the conformational restriction imposed by the planar triazole ring on the mobility of the polyhydroxylated pyrrolidine core.[24a] While the bicyclic triazoles **16**, **17** and **18** were completely specific for *α*-glucosidases, the *fuco*-configured isomer **19** was active against both *α*-glucosidase and *α*-fucosidase. Encouraged by these results and as a part of our continuing efforts aimed at developing new potent and selective glycosidase inhibitors, we herein describe the extension of our previously reported work. In order to study the cumulative effect of mobility restriction and aglycone mimicry in fine tuning the selectivity between *α*-glucosidase and *α*-fucosidase inhibition, we planned the syntheses of analogues of *fuco*-configured pyrrolidotriazole **19** with variations in the aglycone segment that comprised of linear or branched alkyl chains, substituents with polar or non-polar distal ends and arylated analogues.

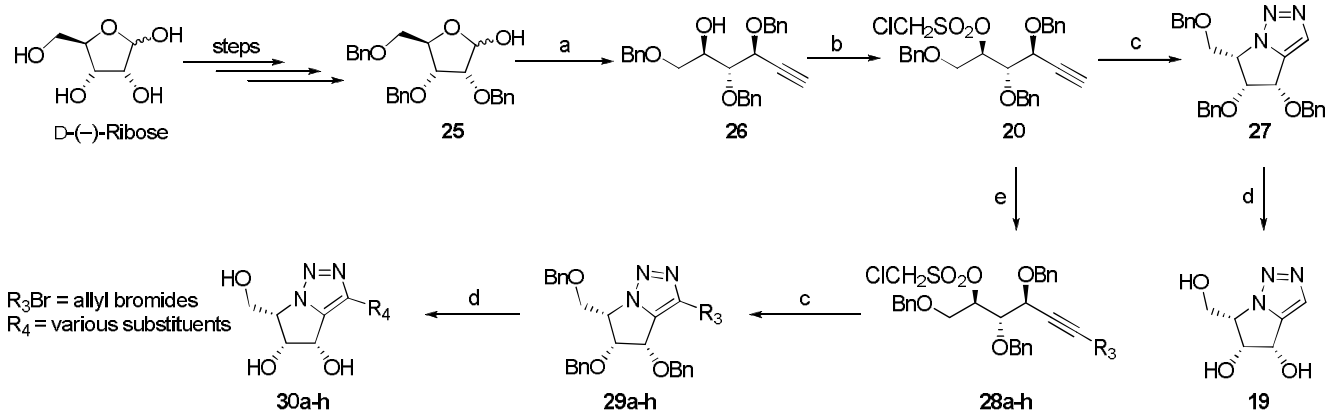
Results and Discussion

Two different strategies for the construction of aglycone mimics were intended as delineated in Scheme 1. First method would involve coupling of allyl bromides with chloromesylated alkyne **20** to form coupled product **21** followed by its one-pot azidation/intramolecular 1,3 dipolar cycloaddition to form bicyclic triazoles of type **22** and their subsequent debenzylation. Second method would comprise of Sonogashira-Hagihara reaction of vinyl or aryl halide with chloromesylated alkyne **20** to furnish internal alkyne **23**. It would then be subjected to one-pot azidation/intramolecular 'click' reaction to furnish the desired triazoles of type **24** followed by their deprotection. For the synthesis of pyrrolidotriazoles, a few reports from synthetic and structure elucidation point of view have been published earlier.[24b-e]

Thus proceeding to prepare the starting chiral building block **20**, D-ribose was first converted to its *O*-benzyl protected hemiacetal **25** according to the literature precedence.[25a,b] The hemiacetal **25** on treating with Bestmann-Ohira reagent and K_2CO_3 as a base in MeOH furnished enantiopure terminal alkyne **26** (Scheme 2).[25c] The free hydroxyl functionality of alkyne **26** was then esterified with chloromethanesulphonyl chloride to provide chloromesylate **20** in 88% yield. It was then subjected to one-pot azidation/intramolecular azide-alkyne cycloaddition by refluxing with NaN_3 in DMF at 120 °C under inert conditions to yield unsubstituted condensed bicyclic triazole **27**. This was followed by



Scheme 1. Strategies for the synthesis of antennated bicyclic triazoles with general structures **22** and **24**.



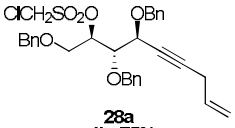
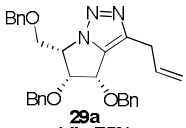
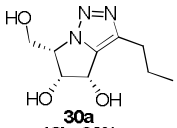
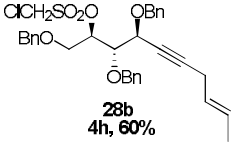
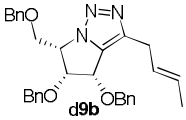
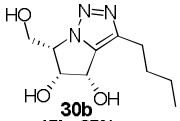
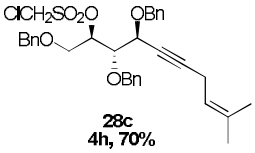
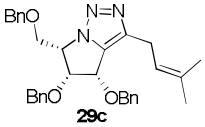
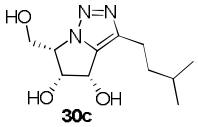
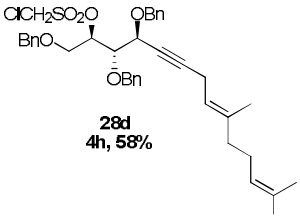
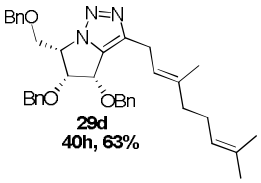
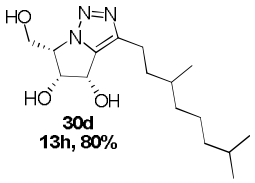
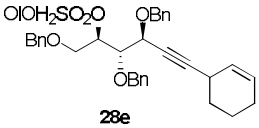
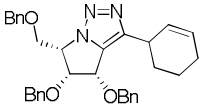
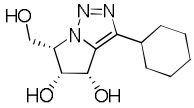
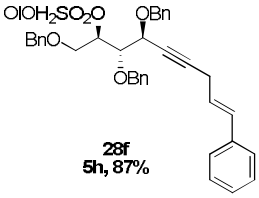
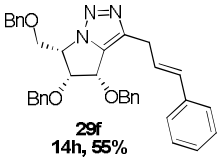
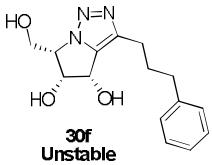
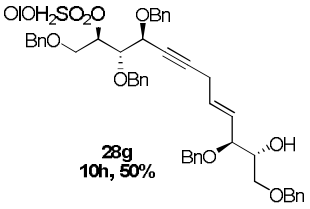
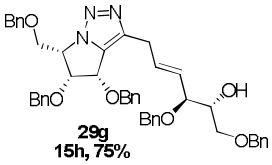
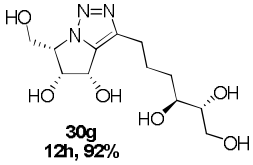
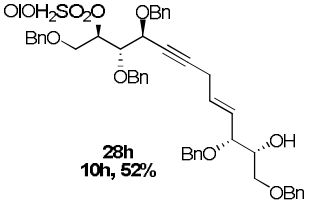
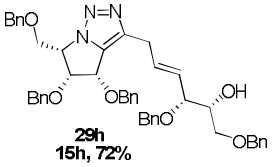
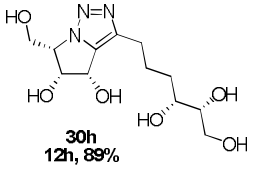
[a]**Scheme 2.** (a) Ohira-Bestmann Reagent [$CH_3COC(N_2)P(O)(OMe)_2$], K_2CO_3, MeOH rt, 8-12 h, 60%; (b) $ClCH_2SO_2Cl$, Py, rt, 10 min, 89%; (c) NaN_3, DMF, 120 °C, 4-6h, 89%; (d) H_2, $Pd(OH)_2/C$, MeOH, rt, 10h quant.; (e) CuI, Na_2SO_3, K_2CO_3, DBU, DMF, R_3Br, rt.

its debenzylation with $Pd(OH)_2/C$ in MeOH to furnish trihydroxylated bicyclic triazole **19** which tends to inhibit α-fucosidase along with α-glucosidase as demonstrated earlier.[24a]

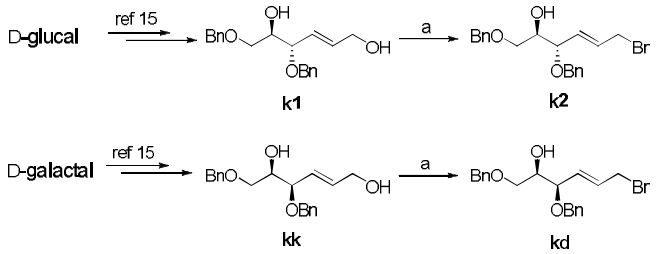
For the synthesis of substituted bicyclic triazoles, chloromesylated acetylene **20** was coupled with different allyl bromides in the presence of Na_2SO_3, K_2CO_3 and a catalytic amount of copper (I) iodide in DMF under inert conditions. This was followed by addition of a drop of DBU (1,8-diazabicycloundec-7-ene) and the reaction mixture was allowed to stir at room temperature (Scheme 2).[26] Complete consumption of the chloromesylate on TLC took place in more or less 4h. The different allyl bromides employed, corresponding yields of the coupled products **28** and time required for coupling with various allyl bromides are detailed in Table 1. For the synthesis of straight chain analogues, allyl bromide and crotyl bromide were used (entry 1 and 2). For branched chain analogues, 3,3 dimethyl allyl bromide (prenyl bromide) and geranyl bromide were employed (entry 3 and 4). To append a lipophilic group at the distal end, we utilized cinnamyl bromide (entry 5). In addition, the attachment of a lipophilic substituent in close vicinity was obtained by employing cyclohexenyl bromide (entry 6). Analogues with polar terminals were also synthesized (entry 7 and 8) by exploiting sugar derived allylic bromides as coupling partners.

To synthesize the aglycone mimics possessing polar hydroxyl groups at distal end of the aglycone chain, we used allylic alcohols **31** and **33** (Scheme 3) which were synthesised from D-glucal and D-galactal derived Perlin aldehydes respectively according to our previously reported protocol.[27] The primary hydroxyl group of allylic alcohols **31** and **33** were brominated under Appel reaction conditions by treating each of them with CBr_4 and PPh_3 in DCM at room temperature under inert conditions for 4 h. Next, the allylic bromides **32** (95% yield from **31**) and **34** (93% yield from **33**) were coupled with activated acetylene precursor **20** under similar conditions as stated earlier to obtain enynes **28g** and **28h** respectively. All the enynes (**28a-h**) were subsequently subjected to intramolecular azide-alkyne 'click' reaction[28,29] by refluxing with sodium azide in DMF at 120°C under inert conditions to yield

Table 1. Coupling products **28a-h** of alkyne **20** with various allyl bromides RBr, their subsequent cycloaddition products **29a-h** and deprotected antennated bicyclic triazoles **30a-h**.

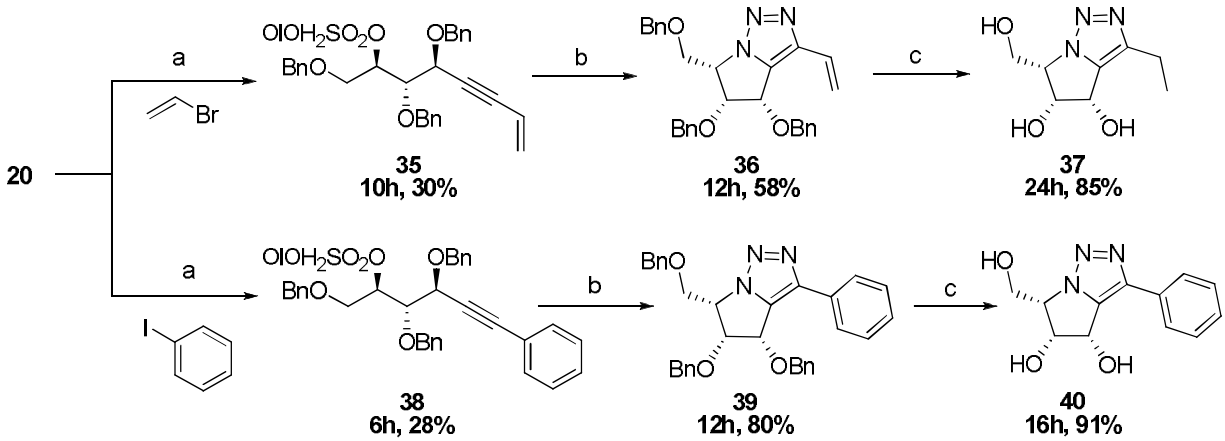
Entry	RBr Allyl Bromides	08 Coupling Products	09 Bicyclic Triazoles	30 Deprotected Triazoles
1	R = allyl	 **28a** **4h, 75%**	 **29a** **14h, 75%**	 **30a** **12h, 90%**
2	R = crotyl	 **28b** **4h, 60%**	 **d9b** **20h, 72%**	 **30b** **15h, 85%**
3	R = prenyl	 **28c** **4h, 70%**	 **29c** **36h, 71%**	 **30c** **16h, 95%**
4	R = geranyl	 **28d** **4h, 58%**	 **29d** **40h, 63%**	 **30d** **13h, 80%**
5	R = cyclohexenyl	 **28e** **3h, 71%**	 **29e** **34h, 59%**	 **30e** **10h, 97%**
6	R = cinnamyl	 **28f** **5h, 87%**	 **29f** **14h, 55%**	 **30f** **Unstable**
7	RBr = **3d**	 **28g** **10h, 50%**	 **29g** **15h, 75%**	 **30g** **12h, 92%**
8	RBr = **34**	 **28h** **10h, 52%**	 **29h** **15h, 72%**	 **30h** **12h, 89%**

condensed bicyclic triazoles (**29a-h**) in fair yields (Table 1). Finally, this was followed by hydrogenolysis of benzyl ether of **29a-h** with $Pd(OH)_2/C$ in MeOH to yield the deprotected analogues of the *fuco*-configured bicyclic pyrrolidinoses with diverse aglycone segments **30a-h**.



Scheme 3. (a) CBr_4, PPh_3, DCM, rt, 4h, 93% for **32** and 90% for **34.**

Another method that was applied to attach vinyl or aryl halides to acetylene precursor involved coupling under the Sonogashira-Hagihara conditions.[30] For this, vinyl bromide (or iodobenzene) was slowly added to a solution containing the terminal alkyne **20**, copper (I) iodide and bis(triphenylphosphine)palladium (II) dichloride, $Pd(PPh_3)_2Cl_2$ in Et_2NH under N_2 atmosphere to form the coupled products **35** (from vinyl bromide) and **38** (from iodobenzene) (Scheme 4). However, this coupling process proceeded with poor yields and was not a method of choice for further analogue synthesis. Each of the coupled products **35** and **38** was refluxed with NaN_3 in DMF at 120 °C under N_2 environment to furnish substituted condensed bicyclic triazoles **36** and **39** respectively followed by their *O*-benzyl deprotection using $Pd(OH)_2/C$ in MeOH to afford the desired aglycone mimics **37** and **40**.



Scheme 4. (a) CuI, $Pd(PPh_3)_2Cl_2$, diethylamine, rt; (b) NaN_3, DMF, 120 °C; (c) H_2, $Pd(OH)_2/C$, MeOH, rt.

Evaluation of Glycosidase Inhibitory Activity

The synthesised compounds were screened against carbohydrate processing enzymes and their inhibition results are summarised in Table 2. For linear alkyl substituents, analogues with ethyl or propyl chain (**37** and **30a**) did not show any activity whereas analogue with *n*-butyl chain **30b** *emerged as a potent and selective α-glucosidase inhibitor*. Long alkyl chain in 30d and cyclic substituent in **30e** do not seem to be accommodated in the hydrophobic pocket of any of the glycosidases. To our surprise, the activity against α-glucosidase from rice and *A. niger* was completely lost for all the tested molecules as compared to the parent molecule **19**. Instead α-glucosidase activity against yeast was now observed for *n*-butyl substituted (**30b**), isopentyl substituted (**30c**) compounds and compounds with polar distal ends (**30g** and **30h**). This feature was not observed earlier with the unsubstituted bicyclic triazole **19** which tends to inhibit α-glucosidases from rice and *A. niger* only. *It is interesting to observe that these molecules show a switching of inhibition between α-glucosidases from various sources merely by the presence or absence of an alkyl chain of suitable length.*

Noteworthy, the presence of hydroxyl functionalities at distal ends of linear alkyl chains as in **30g** and **30h** lead to enzyme inhibition probably due to fortuitous hydrogen-bonding interactions. Analogues with polar distal ends **30g** and **30h** proved to be potent α-glucosidase inhibitors although they also exhibited moderate inhibition of β-galactosidase which was less significant (See Fig. 5 and Fig. 7 in ESI). In addition to α-glucosidase inhibition, 30h retained potent α-fucosidase inhibition with K_i value of~14 μM and is non-specific for either of the targets. The activity data of **30c** and **30h** when compared with that of parent compound **19** indicates that *α-fucosidase inhibition becomes more pronounced on appending the aglycone segment to the parent bicyclic triazole*. Although the fucosidase inhibition by these compounds was not as good as those of the known AFU inhibitors (Fig. 2), the observed 10 to 14-fold enhancement in fucosidase inhibition over parent molecule could provide significant insight into the structure and activity relationship.

The comparison of activity of the promising analogues realised from this study with known monocyclic inhibitors (**A**, **B**, **C**) and parent bicyclic triazole **19** are represented in Table 3. Two selective α-glucosidase inhibitors **30b** and **30g** were obtained. *A shift of*

inhibition from α-glucosidases (in parent molecule **19***) to α-fucosidase was observed for* **30c** *and* **30h**.

Table 2. Concentration of substituted pyrrolidotriazoles giving 50% inhibition[a] (IC_{50}) of various glycosidases.

IC_{50} in μM									
Enzyme	**19**	**30a**	**30b**	**30c**	**30d**	**30e**	**30g**	**30h**	**37**
α-glucosidase									
Yeast	NI[b]	NI	86.21 **[34.97]**[c]	32.99 **[13.97]**	NI	NI	71.04 **[23.15]**	46.19 **[14.13]**	NI
Rice	13.75 **[15.75]**	NI	NI	NI	NI	NI	NI	NI	NI
Aspergillus niger	8 **[22.63]**	NI	NI	NI	NI	NI	NI	NI	NI
β-glucosidase									
Almond	NI	NI	NI	NI	NI	NI	NI	NI	NI
α-galactosidase									
Green coffee beans	NI	NI	NI	NI	NI	NI	NI	NI	NI
β-galactosidase									
Bovine liver	NI	NI	NI	NI	NI	NI	187.14 **[82.94]**	217.1 **[100.6]**	NI
α-mannosidase									
Jack bean	NI	NI	NI	NI	NI	NI	NI	NI	NI
α-L-Fucosidase									
Bovine kidney	96.8 **[138]**	NI	NI	25.12 **[9.67]**	NI	NI	NI	48.57 **[13.78]**	NI

[a]Inhibition was competitive in all cases. [b]NI: No inhibition (less than 50% inhibition) at 1000 μM [c]K_i values are given in square brackets

Conclusions

In our previous study we found that the *fuco*-configured bicyclic pyrrolidotriazole was a non-specific glycosidase inhibitor as it inhibited α-glucosidase (from rice and *A. niger*) more strongly than α-fucosidase. In order to bring about selectivity in favour of any one of the enzymes, various aglycone mimics were synthesised by appending different substituents using copper-catalysed coupling of allyl bromides with terminal alkynes or Sonogashira-Hagihara reaction and intramolecular azide-alkyne 'click' reaction as the key steps. These substituted triazoles were subjected to the glycosidase inhibition assays. To our surprise, the α-glucosidase activity against rice and *A. niger* is completely lost for all the tested molecules. Instead α-glucosidase activity against yeast is now observed for various compounds. These observations are in contrast to the activity of the parent triazole. Thus, mimicry of the aglycone segment tends to bring about switching of activity amongst different glycosidases. The values for α-fucosidase inhibition by **30c** and **30h** suggest a 10 to 14 fold enhanced potency over parent molecule **19** due to the incorporation of aglycone segments. These results substantiate that aglycone interactions can be implemented as an important tool to modulate the potency and specificity of carbohydrate processing enzyme inhibitors. Further efforts in this direction to obtain selective fucosidase inhibitors by synthesising and evaluating more diverse iminosugar analogues and their relevance to anti-cancer activity are currently underway.

Experimental section

General methods Organic solvents used in the present study were dried by standard methods. All the products were characterized by ^{1}H, ^{13}C, two-dimensional heteronuclear single quantum coherence (HSQC), IR and ESI-MS. NMR spectra of the synthesized compounds were recorded in $CDCl_3$ at 25 ° at 300, 400 MHz (^{1}H) and 50, 75 and 100 MHz (^{13}C) respectively. Chemical shifts are given on the δ scale and are referenced to the TMS at 0.00 ppm for proton and 0.00 ppm for carbon. Reference $CDCl_3$ for ^{13}C NMR appeared at 77.20 ppm. Optical rotations were determined using a 1 dm cell at 28 °C in methanol as solvent; concentrations mentioned are in g/100 mL. Analytical TLC was performed on 2.5 × 5 cm plates coated with a 0.25 mm thickness of silica gel (60F-254), and the spots were visualized with $CeSO_4$ (1 % in 2 N H_2SO_4) followed by charring over hot plate. Silica gel (100-200 and 230-400 mesh) was used for column chromatography. Low-temperature reactions were performed by using immersion cooler with ethanol as the cooling agent.

General Procedure for Enzyme Inhibition Assay. All glycosidase enzymes, substrates and other chemicals used in this enzyme inhibition studies were purchased from Sigma-Aldrich Chemical Co. The compounds were tested for inhibition of α-glucosidase (yeast), α-glucosidase (rice), α-glucosidase (*A. niger*), β-glucosidase (almonds), α-galactosidase (green coffee beans), β-galactosidase (bovine liver), α-mannosidase (jack beans), α-L-fucosidase (bovine kidney), spectrophotometrically, as previously described.[24] The stocks of substrates were prepared following the manufacturer's protocol in 50 mM concentration. Briefly, enzyme was pre-incubated with test compound (12.5 µM to 1000 µM) in an appropriate buffer solution at optimal reaction condition for 1 h in 96 well flat bottom microplate (Becton Dickinson), 100 µL of the substrate solution was added to reaction mixture and incubated 1.5 h more. The optimum temperature, buffer and substrate for an enzyme are given in Table S1. Finally, the enzymatic reaction was stopped by adding 1 M Na_2CO_3. Control experiments were carried out without adding test compounds, simultaneously. A series of blank experiments were also carried out in respective buffer without enzyme or test compounds. The absorbance of *p*-nitrophenol released from *p*-nitrophenol glycopyranoside which corresponds to the enzymatic activity was measured at 405 nm in each reaction. Each experiment was done in triplicate. The IC_{50} value was defined as the concentration of the test compound to inhibit 50% of enzyme activity under the assay condition.[31,32] K_i value of test compound was determined by non-linear regression using data to a competitive inhibition model using Graph Pad Prism (version 6.01 for Windows, Graph Pad Software, San Diego California (USA).

(2R,3R,4S)-1,3,4-tris(Benzyloxy)hex-5-yn-2-ol (26). To a stirred solution of hemiacetal **25** (500 mg, 1.19 mmol) in dry methanol (3 mL) was added a solution of freshly prepared Bestmann-Ohira reagent[33] (686 mg, 3.57 mmol) in dry methanol (3 mL) at room temperature. After stirring for 10 min at rt, anhydrous K_2CO_3 (500 mg, 3.62 mmol) was added in three portions and the reaction mixture was allowed to stir for 8h to 12h. On completion (TLC), the reaction mixture was quenched using NH_4Cl solution followed by removal of solvent under reduced pressure. The reaction mixture was then extracted with $CHCl_3$, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography to give **26** (300 mg, 60 % from **25**) as a thick, colourless oil. **Analytical data of 26:** Colorless oil, eluent for column chromatography: EtOAc/Hexane (1/19, v/v); $[\alpha]_D^{28}$ = +60.73 (*c* 0.40, CH_3OH); R_f 0.31 (3/17, EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.55 (d, *J* = 1.9 Hz, 1H), 3.54-3.66 (m, 2H), 3.77-3.85 (m, 1H), 3.94 (s, 1H), 4.42-4.92 (m, 7H), 7.23-7.35 (m, 10H); ^{13}CNMR (75 MHz, $CDCl_3$): δ 70.7 (CH), 70.9 (CH_2), 71.3 (CH), 71.4 (CH_2), 73.5 (CH_2), 74.3 (CH_2), 76.9 (CH), 80.0 (C_q), 80.3 (CH), 127.8-128.5 (ArC), 137.7 (ArC_q), 138.1 (ArC_q), 138.4 (ArC_q); IR(neat,cm^{-1}) 3020, 2923, 2853, 1217, 770; ESI-HRMS m/z $[M + H]^+$: calcd for $C_{27}H_{28}O_4$ 417.2065, measured 417.2064.

(2R,3S,4S)-1,3,4-tris(Benzyloxy)hex-5-yn-2-yl chloromethanesulfonate (20). A solution of compound **26** (178 mg, 0.42 mmol) and chloromethanesulphonyl chloride (0.04 mL, 0.44 mmol) in pyridine (3 mL) was stirred at room temperature for 10 minutes. After completion of the reaction, the mixture was diluted with ethyl acetate and washed with water and brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue on purification by column chromatography yielded **20** as a light orange oil (200 mg, 89 % from **26**). **Analytical data of 20:** Orange oil, eluent for column chromatography: EtOAc/Hexane (1/49, v/v); $[\alpha]_D^{28}$ = +73.77 (*c* 1.24 $CHCl_3$) R_f 0.46 (3/17, EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 2.57 (d, *J* = 2.1, 1H), 3.70-3.80 (m,2H), 4.02 (dd, *J* = 3.6 Hz, 1H), 4.25 (dd, *J* = 2.1 Hz, 1H), 4.45-4.54 (m, 4H), 4.63-4.71 (m, 2H), 4.76-4.84 (m,2H), 5.19-5.23 (m,1H), 7.23-7.33 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.3 (CH_2), 68.6 (CH), 68.8 (CH_2), 71.0 (CH_2), 73.6 (CH_2), 74.8 (CH_2), 76.4 (CH), 79.7 (C_q), 80.4 (CH), 84.2 (CH), 128.0-128.7 (ArC), 136.9 (ArC_q), 137.4 (ArC_q), 137.4 (ArC_q). IR (neat, cm^{-1}) 2853, 1606, 1461, 1217, 763; ESI-HRMS m/z $[M + H]^+$: calcd for $C_{28}H_{30}ClO_6S$ 530.1524, measured 530.1529.

(4S,5R,6S)-4,5-bis(Benzyloxy)-6-(benzyloxymethyl)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3] triazole (27). To a two necked oven dried round bottom flask fitted with a reflux condenser was added sodium azide (20mg, 0.304 mmol), sealed with septum and flushed with nitrogen. To this was added a solution of compound **20** (82 mg, 0.15 mmol) dissolved in dry DMF (3 mL) through a syringe under nitrogen atmosphere. The reaction mixture was refluxed for 4 to 6 h. After completion, the reaction mixture was cooled to room temperature and diluted with water. The aqueous layer was extracted with ethyl acetate, dried with Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography to furnish **27** as a clear oil (68 mg, 89 % from **20**). **Analytical data of 27:** Colorless oil, eluent for column chromatography: EtOAc/Hexane (3/7, v/v); $[\alpha]_D^{28}$ = +12.88 (*c* 0.07 CH_3OH) R_f 0.19 (2/3, EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (dd, *J* = 8.3, 10.4 Hz, 1H), 4.11 (dd, *J* = 4.4, 10.5 Hz, 1H), 4.50-4.79 (m, 8H), 4.91-4.98 (m, 1H), 7.25-7.36 (m, 15H), 7.56 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 60.6 (CH), 69.1 (CH_2), 69.2 (CH), 71.6 (CH_2) , 72.8 (CH_2), 73.5 (CH_2), 81.2 (CH), 125.2 (CH), 127.8-128.8 (ArC), 136.87-137.96 (C_q); IR (neat, cm^{-1}) 3436, 1635, 772; ESI-HRMS m/z $[M + Na]^+$: calcd for $C_{27}H_{27}N_3O_3$ 464.1945, measured 464.1917.

(4S,5R,6S)-6-(Hydroxymethyl)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole-4,5-diol (19). Conventional catalytic hydrogenation of **27** was carried out with $Pd(OH)_2$ in MeOH for 10 hrs at room temperature. Then, the catalyst was filtered over celite and the solvent removed under reduced pressure and residue was purified by silica gel column chromatography to give **19** as a colorless oil (37 mg from 100 mg **27**, quantitative). **Analytical data of 19:** Colorless oil, eluent for column chromatography: MeOH/$CHCl_3$ (3/7, v/v); $[\alpha]_D^{28}$ = +12.84 (*c* 0.14 CH_3OH) R_f 0.5 (3/7, MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD): δ 8.37 (s, 1H), 5.22 (s, 1H), 5.04 (s, 2H), 4.12 (dd, *J* = 18.4, 12.6 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD): 143.4 (C_q), 129.0 (CH), 76.3 (CH), 65.3 (CH), 64.3 (CH), 59.6 (CH_2). ESI-HRMS m/z $[M + H]^+$: calcd for $C_6H_9N_3O_3$ 172.07222, measured 172.07287.

General procedure for the synthesis of 28: To a solution of alkyne **20** (1.0 mmol) in DMF (1 ml) was added sodium sulphite

(0.5 mmol), copper iodide (0.02 mmol) and potassium carbonate (1.0 mmol) under inert atmosphere. This was followed by addition of allylic bromides (1.5 mmol) and a drop of DBU and was allowed to stir at room temperature for 4 hours or until complete disappearance of alkyne **20** on TLC. After completion, the reaction mixture was extracted with DCM and the extracted organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure to obtain clear oil which on column purification yielded **28** (% yields and time taken for various enynes are mentioned in Table1).

General procedure for the synthesis of 29: To a two-necked oven dried round bottom flask fitted with a reflux condenser was added sodium azide (2.0 mmol) sealed with septum and flushed with nitrogen. To this was added a solution of compound **28** (1.0 mmol) dissolved in dry DMF (2 mL) through a syringe under nitrogen atmosphere. The reaction mixture was refluxed for the indicated time (Table 1). After completion, the reaction mixture was cooled to room temperature and diluted with water. The aqueous layer was extracted with ethyl acetate, dried with Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography to furnish **29** (% yields for various bicyclic triazoles are mentioned in Table1).

General procedure for the synthesis of 30: Conventional catalytic hydrogenation of **29** was carried out with $Pd(OH)_2$ in MeOH for 10-15h (Table 1) at room temperature. Then the catalyst was filtered over celite and the solvent was removed under reduced pressure. The filtered compounds did not need any further purification and were as such submitted for chemical analysis and biological assays.

Synthesis of allyl bromide 32: To a two-necked oven dried round bottom flask was added, triphenylphosphine (630 mg, 2.4 mmol), carbon tetrabromide (684 mg, 2.0 mmol) and allylic alcohol **31** (564 mg, 1.7 mmol) dissolved in dry DCM (9 mL) under N_2 environment. The reaction mixture was allowed to stir at room temperature for 4 hours. The reaction mixture was then extracted with DCM and the organic layer was dried with Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography to furnish **32** as a clear viscous oil (93% from **31**).

Synthesis of allyl bromide 34: Compound **34** was synthesized from allylic alcohol **33** following a similar experimental procedure (90% from **33**).

General procedure for the synthesis of 35 and 38: To a two necked RB containing bis(triphenylphosphine)palladium (II) dichloride (0.05 mmol) and cuprous iodide (0.1 mmol), was added a solution of alkyne **20** (20 mmol) in diethylamine under inert environment. To this was added a solution of vinyl bromide (30 mmol) dropwise and the reaction mixture was allowed to stir at room temperature for 10 hours. After completion, diethylamine was evaporated to dryness and the reaction mixture was extracted with DCM. The organic layer was dried with Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography to furnish **35** as a clear oil (30% from **20**). Coupled product **38** was synthesized from alkyne **20** following a similar experimental procedure (28% from **20**).

General procedure for synthesis of 36 and 39: The synthesis of compounds **36** and **39** was carried out following same procedure as mentioned earlier for compounds **29a-h**.

General procedure for synthesis of 37 and 40: The synthesis of compounds **37** and **40** was carried out following same procedure as mentioned earlier for compounds **30a-h.**

(2R,3S,4S)-1,3,4-tris(Benzyloxy)non-8-en-5-yn-2-yl chloromethanesulfonate (28a). Colorless oil, eluent for column chromatography: EtOAc/Hexane (1/19, v/v); $[\alpha]_D^{28}$ = +83.68 (*c* 1.26 CH_3OH); R_f 0.32 (1/19 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.04 (m, 2H), 3.73-3.82 (m, 2H) , 4.00 (dd, *J* = 3.2, 6.0 Hz, 1H), 4.26-4.28 (m, 1H), 4.43-4.55 (m, 4H), 4.65-4.83 (m,4H), 5.12-5.16 (m,1H), 5.24-5.28 (m,1H), 5.32-5.37 (m, 1H), 5.78-5.87 (m, 1H), 7.28-7.33 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.3 (CH_2), 54.4 (CH_2), 69.0 (CH), 69.0 (CH_2), 70.9 (CH_2), 73.6 (CH_2), 74.6 (CH_2), 78.2 (C_q), 81.1 (CH), 84.7 (CH), 85.6 (C_q), 116.7 (CH_2), 128.0-128.7 (ArC), 132.1 (CH), 137.3 (ArC_q), 137.5 (ArC_q), 137.6 (ArC_q). IR (neat, cm^{-1}) 3409, 1642, 1216, 699, 668; ESI-HRMS m/z $[M + H]^+$: calcd for $C_{31}H_{33}ClO_6S$, 569.1757, measured 569.1757.

(2R,3S,4S,E)-1,3,4-tris(Benzyloxy)dec-8-en-5-yn-2-yl chloromethanesulfonate (28b). Colorless oil, eluent for column chromatography : EtOAc/Hexane (1/19, v/v); $[\alpha]_D^{28}$ = +36.54 (*c* 0.26 CH_3OH); R_f 0.48 (1/9 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.66-1.69 (m, 3H), 2.96-2.99 (m, 2H), 3.73-3.82 (m, 2H), 4.00 (dd, *J* = 3.1, 6.0 Hz, 1H), 4.24-4.27 (m, 1H), 4.43-4.47 (m, 2H), 4.50-4.56 (m, 2H), 4.65-4.71 (m, 2H), 4.75-4.82 (m, 2H), 5.24-5.28 (m, 1H), 5.38-5.46 (m, 1H), 5.65-5.75 (m, 1H), 7.25-7.33 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 17.8 (CH_3), 22.2 (CH_2), 54.4 (CH_2), 69.0 (CH) , 69.0 (CH_2), 70.8 (CH_2), 73.6 (CH_2), 74.6 (CH_2), 77.5 (C_q), 81.2 (CH), 84.8 (CH), 86.7 (C_q), 124.7 (CH), 127.5 (CH), 128.0-128.7 (ArC), 137.4 (ArC_q), 137.6 (ArC_q), 137.7 (ArC_q). IR (neat, cm^{-1}) 3396, 1633, 1403, 1219, 1155, 772; ESI-HRMS m/z $[M + H]^+$: calcd for $C_{32}H_{35}ClO_6S$, 583.1817, measured 583.1825.

(2R,3S,4S)-1,3,4-tris(Benzyloxy)-9-methyldec-8-en-5-yn-2-ylchloromethanesulfonate (28c). Colorless oil, eluent for column chromatography: EtOAc/Hexane (3/47, v/v); $[\alpha]_D^{28}$ = +38.18 (*c* 1.86 $CHCl_3$); R_f 0.50 (1/9 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.56 (s, 3H), 1.63 (s,3H), 2.89 (d, *J* = 6.8, 2H), 3.65-3.74 (m, 2H), 3.91 (dd, *J* = 3.0, 6.1 Hz, 1H), 4.15 (d, *J* = 6.1, 1H), 4.35-4.48 (m, 4H), 4.57-4.73 (m, 4H), 5.12 (t, *J* = 6.8 Hz, 1H), 5.17-5.21 (m, 1H), 7.17-7.28 (m, 15H) . ^{13}C NMR (100 MHz, $CDCl_3$) : δ 17.9 (CH_3), 18.1 (CH_2), 25.6 (CH_3), 54.3 (CH_2), 68.9 (CH), 69.0 (CH_2), 70.7 (CH_2), 73.6 (CH_2), 74.6 (CH_2), 75.4 (C_q), 81.2 (CH), 84.8 (CH), 87.8 (C_q), 118.6 (CH), 128.0-128.6 (ArC), 134.4 (C_q), 137.4 (ArC_q), 137.6 ArC_q), 137.7 (ArC_q). IR (neat, cm^{-1}) 3385, 1609, 1421, 1198, 1156, 770; ESI-HRMS m/z $[M + H]^+$: calcd for $C_{33}H_{37}ClO_6S$ 597.2072, measured 597.2073.

(2R,3S,4S,E)-1,3,4-tris(Benzyloxy)-9,13-dimethyltetradeca-8,12-dien-5-yn-2-yl chloromethanesulfonate (28d). Colorless oil, eluent for column chromatography : EtOAc/Hexane (1/49, v/v); R_f 0.20 (1/9 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.15-1.26 (m, 4H), 1.50-1.63 (m, 6H), 1.90-2.00 (m, 4H), 2.90 (d, *J* = 6.8 Hz, 1H), 3.62-3.74 (m, 2H), 3.89-3.92 (m, 1H), 4.13-4.24 (m, 1H), 4.31-4.46 (m, 4H), 4.53-4.84 (m, 4H), 4.99-5.32 (m, 2H), 7.14-7.25 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 16.3, 17.8 (CH_3), 17.9, 18.2 (CH_2), 21.2 (CH_3), 25.8 (CH_3), 26.6 (CH_2), 39.5 (CH_2), 54.3 (CH_2), 68.3, 68.9 (CH_2), 70.7, 70.9 (CH_2), 73.2, 73.5 (CH_2), 74.4, 74.5 (CH_2), 75.4, 75.9 (C_q), 79.0 (CH), 81.1 (CH), 84.7 (CH), 87.8 (C_q), 118.3 (CH), 124.1 (CH), 127.7-128.6 (ArC), 131.7 (C_q), 137.4-138.2 (ArC_q), 170.1 (C_q). IR (neat, cm^{-1}) 3401, 1633, 1357, 1221, 1250, 727; ESI-HRMS m/z [M + H] $^+$: calcd for $C_{38}H_{45}ClO_6S$ 665.2614, measured 665.2656.

(2R,3S,4S)-1,3,4-tris(Benzyloxy)-6-(cyclohex-2-enyl)hex-5-yn-2-yl chloromethanesulfonate (28e). Colorless oil, eluent for column chromatography : EtOAc/Hexane (1/3, v/v); $[\alpha]_D^{28}$ = +93.90 (*c* 2.70 $CHCl_3$); R_f 0.64 (1/4 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.49-1.94 (m, 6H), 3.09 (s, 1H), 3.66-3.75 (m, 2H), 3.91-3.93 (m, 1H), 4.15-4.17 (m, 1H), 4.36-4.49 (m, 4H), 4.57-4.73 (m, 4H), 5.19-5.21 (m, 1H), 5.56-5.59 (m, 1H), 5.68-5.70 (m,1H), 7.17-7.25 (m,15H) ^{13}C NMR (100 MHz, $CDCl_3$) : δ 20.7 (CH_2), 20.7 (CH_2), 24.8 (CH_2), 27.6 (CH), 54.3 (CH_2), 68.8 (CH), 69.0 (CH_2), 70.7 (CH_2), 73.6 (CH_2), 74.6 (CH_2), 75.7 (C_q), 75.8 (C_q), 81.3 (CH), 84.9 (CH), 91.8 (C_q), 126.7 (CH), 126.7 (CH) , 128.0-128.7 (ArC), 137.4 (ArC_q), 137.6 (ArC_q) , 137.7 (ArC_q). IR (neat, cm^{-1}) 3398, 3019, 2927, 1217, 1070, 699, 667; ESI-HRMS m/z [M + H] $^+$: calcd for $C_{34}H_{37}ClO_6S$ 609.2079, measured 609.2069.

(2R,3S,4S,E)-1,3,4-tris(Benzyloxy)-9-phenylnon-8-en-5-yn-2-yl chloromethanesulfonate (28f). Dark brown oil, eluent for column chromatography : EtOAc/Hexane (2/23, v/v); R_f 0.42 (1/9 EtOAc/Hexane); R_f 0.6 (1/4 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.13-3.15 (m, 2H), 3.71-3.74 (m, 2H), 3.94-3.97 (m, 1H), 4.23-4.25 (m, 1h), 4.38-4.40 (m, 2H), 4.43-4.48 (m, 2H), 4.56-4.66 (m, 2H), 4.69-4.79 (m, 2H), 5.19-5.23 (m, 1H), 6.06-6.14 (m, 1H), 6.56-6.60 (m, 1H), 7.16-7.25 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 22.6 (CH_2), 54.3(CH_2), 69.0 (CH_2), 69.0 (CH), 70.9 (CH_2), 73.6 (CH_2), 74.6 (CH_2), 78.2 (C_q), 81.0 (CH), 84.6 (CH), 85.8 (C_q), 123.8 (CH), 126.4-128.7 (ArC), 131.9 (CH), 137.1 (ArC_q), 137.3 (ArC_q), 137.5 (ArC_q), 137.6 (ArC_q). IR (neat, cm^{-1}) 3397, 1630, 1218, 669; ESI-HRMS m/z [M + NH_4] $^+$: calcd for $C_{37}H_{37}ClO_6S$ 662.2338, measured 662.2336.

(2R,3S,E)-1,3-bis(Benzyloxy)-6-bromohex-4-en-2-ol (32). Clear viscous oil, eluent for column chromatography : EtOAc/Hexane (1/9, v/v) ; $[\alpha]_D^{28}$ = +19.28 (*c* 4.29 $CHCl_3$); R_f 0.75 (1/9 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.46-3.47 (m, 2H) , 3.81-3.89 (m, 4H), 4.28-4.53 (m, 4H), 5.68-5.74 (m, 1H), 5.83-5.91 (m, 1H), 7.15-7.25 (m, 10H).^{13}C NMR (100 MHz, $CDCl_3$) : δ 31.7 (CH_2), 70.7 (CH_2), 70.8 (CH), 72.4 (CH_2), 73.5 (CH_2), 79.2 (CH), 127.9-128.5 (ArC), 131.5 (CH), 132.0 (CH), 138.0 (2×ArC_q). IR (neat, cm^{-1}) 3425, 3027, 1635, 1091, 609; ESI-HRMS m/z [M + H] $^+$: calcd for $C_{20}H_{23}BrO_3$ 391.0903, measured 391.0903.

(2R,3S,4S,10S,11R,E)-1,3,4,10,12-pentakis(Benzyloxy)-11-hydroxydodec-8-en-5-yn-2-yl chloromethanesulfonate (28g). Pale yellow oil, eluent for column chromatography : EtOAc/Hexane (1/9, v/v); $[\alpha]_D^{28}$ = + 5.02 (*c* 0.54 $CHCl_3$); R_f 0.63 (2/3 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.03-3.04 (m, 1H), 3.43-3.54 (m, 2H), 3.58 (dd, *J* = 2.2, 11.4 Hz, 1H), 3.68-3.75 (m, 2H) , 3.80-3.85 (m, 2H), 3.91-3.98 (m,1H), 4.22-4.75 (m, 13H), 5.10-5.33 (m,1H), 5.57-5.72 (m,1H), 5.87-6.08 (m, 1H), 7.17-7.24 (m, 25H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 22.2 (CH_2), 54.4 (CH_2), 65.5 (CH_2), 69.1 (CH_2), 70.6 (CH), 71.0 (CH_2), 72.6 (CH), 73.5 (CH_2), 73.6 (CH_2), 74.5 (CH_2), 80.1 (C_q), 81.0 (CH), 81.3 (CH_2), 84.6 (CH), 85.7 (C_q), 127.2 (CH), 127.8-129.9 (ArC), 129.2 (CH), 137.3 (ArC_q), 137.5 (ArC_q), 138.2 (ArC_q), 138.4 (ArC_q), 141.1 (ArC_q). IR (neat, cm^{-1}) 3396, 3019, 1217, 770, 669; ESI-HRMS m/z [M + H] $^+$: calcd for $C_{48}H_{51}ClO_9S$ 839.3051, measured 839.3016.

(2R,3R,E)-1,3-bis(Benzyloxy)-6-bromohex-4-en-2-ol (34). Clear viscous oil, eluent for column chromatography : EtOAc/Hexane (1/9, v/v); $[\alpha]_D^{28}$ = -13.15 (*c* 3.5 $CHCl_3$); R_f 0.75 (1/9 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.38-3.51 (m, 2H), 3.65-3.69 (m, 1H), 3.79-3.91 (m, 3H), 4.28-4.56 (m, 4H), 5.61-5.67 (m, 1H), 5.84-5.92 (m, 1H), 7.16-7.28 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.6 (CH_2), 70.4 (CH_2), 71.0 (CH), 73.0 (CH_2), 73.6 (CH_2), 79.3 (CH), 127.9-128.6 (ArC), 131.4 (CH), 132.0 (CH), 138.0 (ArC_q), 138.1 (ArC_q). IR (neat, cm^{-1}) 3065, 3019, 1631, 1216, 1069, 758; ESI-HRMS m/z [M + H] $^+$: calcd for $C_{20}H_{23}BrO_3$ 391.0903, measured 391.0902.

(2R,3S,4S,10R,11R,E)-1,3,4,10,12-pentakis(Benzyloxy)-11-hydroxydodec-8-en-5-yn-2-yl chloromethanesulfonate (28h). Pale yellow oil, eluent for column chromatography: EtOAc/Hexane (1/9, v/v); $[\alpha]_D^{28}$ = +23.33 (*c* 1.48 $CHCl_3$); R_f 0.63 (2/3 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 2.99-3.00 (m, 2H), 3.39 (dd, *J* = 5.5, 10 Hz, 1H), 3.67-3.71 (m, 2H), 3.85-3.88 (m, 1H), 3.92 (dd, *J* = 3.5, 5.5 Hz, 1H), 4.21-4.23 (m, 1H), 4.27 (d, *J* = 11.7, 1H), 4.34-4.46 (m, 6H), 4.52-4.74 (m, 6H), 5.16-5.20 (m, 1H), 5.66 (d, *J* = 4 Hz, 2H), 7.18-7.26 (m, 25H) . ^{13}C NMR (100 MHz, $CDCl_3$) : δ 22.1 (CH_2), 54.4 (CH_2), 69.1 (CH_2), 69.1 (CH), 70.7 (CH_2), 71.0 (CH_2) , 73.2 (CH), 73.6 (CH_2), 73.6 (CH_2) , 74.5 (CH_2) , 78.2 (C_q), 80.0 (CH), 81.0 (CH), 84.5 (CH), 85.5 (C_q), 127.8-128.7, (ArC), 129.1 (CH), 129.6 (CH), 137.3 (ArC_q), 137.5 (ArC_q), 137.6 (ArC_q), 138.3 (ArC_q), 138.4 (ArC_q). IR (neat, cm^{-1}) 3410, 3019, 1216, 1180, 699, 669; ESI-HRMS m/z [M + Na] $^+$: calcd for $C_{48}H_{51}ClO_9S$ 861.2835, measured 861.2820.

(4S,5R,6S)-3-allyl-4,5-bis(Benzyloxy)-6-(benzyloxymethyl)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole (29a). Colorless oil, eluent for column chromatography : EtOAc/Hexane (1/4, v/v); $[\alpha]_D^{28}$ = -11.85 (*c* 0.33 CH_3OH); R_f 0.71 (1/1 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.46-3.59 (m, 2H), 3.88-3.92 (m,1H), 4.11 (dd, J = 4.4 Hz, 1H), 4.48-4.81 (m,8H), 4.90-4.95 (m,1H), 5.09-5.13 (m, 2H), 5.92-6.02 (m,1H), 7.25- 7.33 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.6 (CH_2), 60.5 (CH), 69.4 (CH), 69.7 (CH), 72.0 (CH_2), 72.7 (CH_2), 73.5 (CH_2), 81.6 (CH), 117.0 (CH_2), 127.8-128.8 (ArC), 134.9 (CH), 135.3 (C_q), 137.0 (ArC_q), 137.5 (ArC_q), 138.0 (ArC_q), 141.0 (C_q). IR (neat, cm^{-1}) 3388, 3018, 1216, 771, 669; ESI-HRMS m/z [M + H] $^+$: calcd for $C_{30}H_{31}N_3O_3$ 482.2438, measured 482.2437.

(4S,5R,6S)-4,5-bis(Benzyloxy)-6-(benzyloxymethyl)-3-((E)-but-2-enyl)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole (29b). Colorless oil, eluent for column chromatography : EtOAc/Hexane (1/4, v/v); $[\alpha]_D^{28}$ = +50.5050 (*c* 0.02 CH_3OH); R_f 0.52 (2/3 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.57-1.59 (m, 3H), 3.33-3.45 (m, 2H), 3.82 (dd, *J* = 8.1, 10.5 Hz, 1H), 4.03 (dd, *J* = 4.5, 10.5 Hz, 1H), 4.40-4.71 (m, 8H), 4.82-4.87 (m, 1H), 5.46-5.52 (m, 2H), 7.17-7.27 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 60.5 (CH_2), 69.4 (CH), 69.8 (CH), 72.0 (CH_2), 72.7 (CH_2), 73.5 (CH_2), 81.6 (CH), 127.5 (CH), 128.5 (CH), 127.7-128.78 (ArC), 127.5 (CH), 128.4 (CH), 135.0 (C_q), 137.0 (ArC_q), 137.6 (ArC_q), 138.0 (ArC_q), 141.9 (C_q). IR (neat, cm^{-1}) 3378, 3014, 1199, 776, 660; ESI-HRMS m/z [M + H] $^+$: calcd for $C_{31}H_{33}N_3O_3$ 496.2595, measured 496.2595.

(4S,5R,6S)-4,5-bis(Benzyloxy)-6-(benzyloxymethyl)-3-(3-methylbut-2-enyl)-5,6-dihydro-4H-pyrrolo[1,2c][1,2,3]triazole (29c). Colorless oil, eluent for column chromatography : EtOAc/Hexane (11/39, v/v); $[\alpha]_D^{28}$ = -8.29 (*c* 0.80 $CHCl_3$); R_f 0.36 (2/3 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.71-1.75 (m, 6H), 3.50-3.53 (m, 2H), 3.92 (dd, *J* = 4.5, 10.5 Hz, 1H), 4.52 (dd, *J* = 5, 7.0 Hz, 1H), 4.56-4.64 (m, 4H), 4.71 (dd, *J* = 11.8, 14.4 HZ, 2H), 4.80 (d, *J* = 5 Hz, 1H), 4.92-4.97 (m, 1H), 5.34-5.38 (m, 1H), 7.26-7.37 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2 (CH_3), 25.2 (CH_2), 25.8 (CH_3), 60.4 (CH), 69.4 (CH_2), 70.0 (CH), 71.9 (CH_2), 72.8 (CH_2), 73.5 (CH_2), 81.7 (CH), 120.7 (CH), 127.7-128.8 (ArC), 133.8 (C_q), 134.8 (C_q), 137.1 (ArC_q), 137.6 (ArC_q), 138.1 (ArC_q), 142.6 (C_q). IR (neat, cm^{-1}) 3410, 3016, 1201, 1212, 771, 659; ESI-HRMS m/z [M + H] $^+$: calcd for $C_{32}H_{35}N_3O_3$ 510.2751, measured 510.2727.

(4S,5R,6S)-4,5-bis(Benzyloxy)-6-(benzyloxymethyl)-3-((2E,6E)-3-methylocta-2,6-dienyl)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole (29d). Colorless oil, eluent for column chromatography : EtOAc/Hexane (3/7, v/v); $[\alpha]_D^{28}$ = -10.48 (*c* 1.4 CH_3OH); R_f 0.60 (1/9 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.50-1.65 (m, 9H), 1.91-2.02 (m, 4H), 3.37-3.48 (m, 2H), 3.82 (dd, *J* = 8.1, 10.5 Hz, 1H), 4.01-4.05 (m, 1H), 4.39-4.53 (m, 5H), 4.57-4.64 (m, 2H), 4.71 (d, *J* = 5 Hz, 1H), 4.82-4.87 (m, 1H), 4.95-5.03 (m, 1H), 5.26-5.30 (dd, *J* = 6.4, 12.7 Hz, 1H), 7.15-7.28 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5 (CH_3), 17.8 (CH_3), 25.2 (CH_2), 25.8 (CH_3), 26.7 (CH_2), 39.8 (CH_2), 60.4 (CH), 69.4 (CH_2), 70.0 (CH), 71.8 (CH_2), 72.7 (CH_2), 73.5 (CH_2), 81.7 (CH), 120.5 (CH), 124.2 (CH), 127.7-128.7 (ArC), 131.7 (C_q), 134.7 (C_q), 137.0 (ArC_q), 137.5 (ArC_q), 137.6 (ArC_q), 138.0 (C_q), 142.6 (C_q). IR (neat, cm^{-1}) 3399, 3019, 1180, 699, 669; ESI-HRMS m/z [M + H] $^+$: calcd for $C_{37}H_{43}N_3O_3$ 578.3377, measured 578.3376.

(4S,5R,6S)-4,5-bis(Benzyloxy)-6-(benzyloxymethyl)-3-(cyclohex-2-enyl)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole (29e). Colorless oil, eluent for column chromatography: EtOAc/Hexane (1/4, v/v); $[\alpha]_D^{28}$ = -35.85 (*c* 5.55 $CHCl_3$); R_f 0.45 (2/3 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.49-1.80 (m, 4H), 1.92-2.00 (m, 3H), 3.56-3.62 (m, 1H), 3.80-3.85 (m, 1H), 4.01-4.05 (m, 1H), 4.40-4.69 (m, 7H), 4.76-4.86 (m, 2H), 5.68-5.85 (m, 2H), 7.15-7.28 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 21.0, 21.2 (CH_2), 25.0, 25.1 (CH_2), 30.4 (CH_2), 33.6, 33.7 (CH), 60.0, 60.0 (CH), 69.4, 69.5 (CH_2), 70.6, 70.7 (CH), 72.6 (CH_2), 72.8, 72.9 (CH_2), 73.4, 73.5 (CH_2), 82.1, 82.2 (CH), 127.7-128.7 (ArC), 129.5 (CH), 134.5, 134.6 (ArC_q), 137.1 (ArC_q), 137.7, 137.8 (ArC_q), 138.0 (C_q), 146.5, 146.6 (C_q). IR (neat, cm^{-1}) 3407, 3019, 1216, 699, 669; ESI-HRMS m/z [M + H] $^+$: calcd for $C_{33}H_{35}N_3O_3$ 522.2751, measured 522.2767.

(4S,5R,6S)-4,5-bis(Benzyloxy)-6-(benzyloxymethyl)-3-cinnamyl-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole (29f). Brown oil, eluent for column chromatography : EtOAc/Hexane (1/4, v/v); $[\alpha]_D^{28}$ = +275.27 (*c* 7.44 CH_3OH); R_f 0.9 (1/5 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.48-3.68 (m, 1H), 3.94 (dd, *J* = 9.1, 10.6 Hz), 4.10 (dd, *J* = 3.8, 10.7 Hz), 4.34-4.72 (m, 9H), 4.80-4.94 (m, 2H), 5.28 (d, *J* = 5.0 Hz), 7.12-7.27 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.9 (CH_2), 61.0 (CH), 69.5 (CH_2), 69.6 (CH), 72.1 (CH_2), 72.1 (CH_2), 73.5 (CH_2), 80.9 (CH), 126.4 (C_q), 127.8-128.8 (ArC+2xCH), 135.3 (ArC_q), 135.9 (ArC_q), 136.9 (ArC_q), 138.0 (ArC_q + C_q), 138.1 (ArC_q). IR (neat, cm^{-1}) 3417, 3010, 1215, 771, 669; ESI-HRMS m/z [M + H] $^+$: calcd for $C_{36}H_{35}N_3O_3$ 558.2751, measured 558.2750.

(2R,3S,E)-1,3-bis(Benzyloxy)-6-((4S,5R,6S)-4,5-bis(benzyloxy)-6 (benzyloxymethyl)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-3-yl)hex-4-en-2-ol (29g). Colorless oil, eluent for column chromatography : EtOAc/Hexane (3/7, v/v); $[\alpha]_D^{28}$ = +3.29 (*c* 0.304 CH_3OH); R_f 0.41 (3/2 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.54-3.78 (m, 4H), 3.87-3.97 (m, 3H), 4.04-4.16 (m, 3H), 4.23-4.26 (m, 1H), 4.33 (t, *J* = 6.6 Hz, 1H), 4.50-4.55 (m, 4H),4.63-4.73 (m, 6H), 5.87-5.98 (m, 1H), 6.17-6.29 (m, 1H), 7.28-7.38 (m, 25H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.9 (CH_2), 60.0 (CH), 66.6 (CH_2), 68.4 (CH_2), 70.9 (CH_2),71.4 (CH_2), 72.2 (CH), 72.8 (CH_2), 73.7 (CH_2), 74.1 (CH_2), 75.2 (CH_2), 75.9 (CH), 80.9 (CH), 117.8 (CH), 123.4 (CH), 127.7-129.0 (ArC), 131.1 (CH), 136.0 (C_q), 136.9 (ArC_q), 137.2 (ArC_q), 137.7 (ArC_q), 138.2 (2 x ArC_q), 140.4 (C_q). IR (neat, cm^{-1}) 3410, 3015, 1198, 1156, 780, 669; ESI-HRMS m/z [M + H] $^+$: calcd for $C_{47}H_{49}N_3O_6$ 752.3694, measured 752.3698.

(2R,3R,E)-1,3-bis(Benzyloxy)-6-((4S,5R,6S)-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-3-yl)hex-4-en-2-ol (29h). Colorless oil, eluent for column chromatography : EtOAc/Hexane (3/7, v/v); $[\alpha]_D^{28}$ = +57.02 (*c* 0.038 CH_3OH); R_f 0.41 (3/2 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.48-3.69 (m, 4H), 3.82-3.96 (m, 3H), 4.11-4.15 (m, 2H), 4.33-4.36 (m, 1H), 4.47 (dd, *J* = 5.0, 7.0 Hz, 1H), 4.52-4.57 (m, 2H), 4.59-4.64 (m, 4H), 4.67-4.73 (m, 2H), 4.87-4.95 (m, 2H), 5.56 (d, *J* = 7.8, 15.5 Hz, 1H), 5.87-5.94 (m, 1H), 7.24-7.76 (m, 25H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.3 (CH_2), 60.6 (CH), 69.3 (CH_2), 69.6 (CH), 70.1 (CH_2), 71.1 (CH_2), 71.9 (CH_2), 72.5 (CH), 72.7 (CH_2), 73.5 (CH_2), 73.6 (CH_2), 80.2 (CH), 81.6 (CH), 127.8-128.8 (ArC), 129.6 (CH), 132.4 (CH), 135.5 (C_q), 137.0 (ArC_q), 137.6 (ArC_q), 138.0 (ArC_q), 138.2 (ArC_q), 138.4 (ArC_q), 140.9 (C_q). IR (neat, cm^{-1}) 3410, 3019, 1636, 1215, 1156, 758, 669; ESI-HRMS m/z [M + H] $^+$: calcd for calcd for $C_{47}H_{49}N_3O_6$ 752.3694, measured 752.3693.

(4S,5R,6S)-6-(Hydroxymethyl)-3-propyl-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3] triazole-4,5-diol (30a). Colorless oil, eluent for column chromatography : MeOH/$CHCl_3$ (1/19, v/v); R_f 0.2 (1/9 MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 0.97 (t, *J* = 7.4 Hz, 3H), 1.69-1.78 (m, 2H), 2.70 (t, *J* = 7.5 Hz, 2H),

3.96-4.06 (m, 2H), 4.73-4.76 (m,1H), 4.87-4.89 (m, 1H), 4.95 (d, J = 5.7 Hz , 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (CH_3), 23.3 (CH_2), 28.2 (CH_2), 59.5 (CH_2), 64.1 (CH), 65.1 (CH), 76.0 (CH), 139.9 (C_q), 143.3 (C_q). IR (neat, cm^{-1}) 3396, 3019, 1639, 1403, 1216, 769, 669. ESI-HRMS m/z [M + H] $^+$: calcd for $C_9H_{15}N_3O_3$ 214.1186, measured 214.1181.

(4S,5R,6S)-3-butyl-6-(Hydroxymethyl)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3] triazole-4,5-diol (30b). Colorless oil, eluent for column chromatography : MeOH/$CHCl_3$ (1/24, v/v); $[\alpha]_D^{28}$ = -42.50 (*c* 8.0 CH_3OH); R_f 0.25 (1/9 MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 0.86 (t, J = 7.4 Hz, 3H), 1.27-1.33 (m, 2H), 1.58-1.65 (m, 2H), 2.63-2.66 (m, 2H), 3.86-3.96 (m, 2H), 4.63-4.67 (m, 1H), 4.77-4.79 (m, 1H), 4.85 (d, J = 5.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 23.3, 25.9, 32.2, 59.5, 64.2, 65.2, 76.1, 139.9, 143.6. ESI-HRMS m/z [M + H] $^+$: calcd for $C_{10}H_{17}N_3O_3$ 228.1343, measured 228.1360.

(4S,5R,6S)-6-(Hydroxymethyl)-3-isopentyl-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole-4,5-diol (30c). Colorless oil, eluent for column chromatography : MeOH/$CHCl_3$ (1/24, v/v); $[\alpha]_D^{28}$ = +37.14 (*c* 8.40 CH_3OH); R_f 0.2 (1/9 MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 0.95-0.97 (m, 6H), 1.57-1.66 (m, 3H), 2.73-2.77 (m, 2H), 3.96-4.06 (m, 2H), 4.73-4.76 (m, 1H), 4.87-4.89 (m, 1H), 4.95 (d, J = 5.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.7, 22.8, 24.1, 28.7, 39.1, 59.5, 64.1, 65.2, 76.1, 139.8, 143.6; ESI-HRMS m/z [M + H] $^+$: calcd for $C_{11}H_{19}N_3O_3$ 242.1499, measured 242.149.

(4S,5R,6S)-3-(3,7-Dimethyloctyl)-6-(hydroxymethyl)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole-4,5-diol (30d). Colorless oil, eluent for column chromatography : MeOH/$CHCl_3$ (1/24, v/v); $[\alpha]_D^{28}$ = +1.14 (*c* 17.6 CH_3OH); R_f 0.3 (1/9 MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 0.74-0.96 (m, 9H), 1.14-1.20 (m, 3H), 1.27-1.41 (m, 3H), 1.46-1.60 (m, 3H), 1.71-1.82 (m, 1H), 2.68-2.83 (m, 2H), 3.97-4.06 (m, 2H), 4.74-4.77 (m, 1H), 4.87-4.89 (m, 1H), 4.95 (d, J = 5.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8, 23.0, 23.1, 23.8, 25.8, 29.1, 33.6, 37.3, 38.2, 40.5, 59.5, 64.2, 65.3, 76.1, 139.9, 143.71; ESI-HRMS m/z [M + H] $^+$: calcd for $C_{16}H_{29}N_3O_3$ 312.2282, measured 312.2282.

(4S,5R,6S)-3-Cyclohexyl-6-(hydroxymethyl)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole-4,5-diol (30e). Colorless oil, eluent for column chromatography: MeOH/$CHCl_3$ (1/19, v/v); $[\alpha]_D^{28}$ = -25.84 (*c* 1.864 CH_3OH); R_f 0.2 (1/9 MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.27-1.36 (m, 1H), 1.38-1.50 (m, 2H), 1.53-1.63 (m, 2H), 1.73-1.77 (m, 1H), 1.82-1.86 (m, 2H), 2.04-2.07 (m, 2H), 2.75-2.82 (m, 1H), 3.95-4.05 (m, 2H), 4.72-4.75 (m, 1H), 4.86-4.88 (m, 1H), 4.96 (d, J = 5.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.1, 27.3, 27.4, 33.4, 33.9, 36.9, 59.5, 63.8, 65.6, 75.9, 139.1, 148.4; ESI-HRMS m/z [M + H] $^+$: calcd for $C_{12}H_{19}N_3O_3$ 254.1499, measured 254.1498.

(2R,3S)-6-((4S,5R,6S)-4,5-Dihydroxy-6-(hydroxymethyl)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-3-yl)hexane-1,2,3-triol (30g). R_f 0.51 (1/1 $CHCl_3$/MeOH); ^{1}H NMR (400 MHz, CD_3OD) : δ 1.29-1.39 (m, 2H), 1.51-1.64 (m, 2H), 2.61-2.80 (m, 3H), 3.96-4.13 (m, 4H), 4.19 (t, J = 6.5 Hz, 1H), 4.31-4.39 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 30.1 (CH_2), 30.6 (CH_2), 31.5 (CH_2), 40.1 (CH_2), 61.5 (CH), 62.6 (CH), 65.0 (CH_2), 66.6 (CH), 69.1 (CH), 72.9 (CH), 129.8 (C_q), 132.4 (C_q). ESI-HRMS m/z [M + H] $^+$: calcd for $C_{12}H_{21}N_3O_6$ 304.1430, measured 304.1430.

(2R,3R)-6-((4S,5R,6S)-4,5-Dihydroxy-6-(hydroxymethyl)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-3-yl)hexane-1,2,3-triol (30h). R_f 0.5 (1/1 $CHCl_3$/MeOH); ^{1}H NMR (400 MHz, CD_3OD) : δ 1.59-1.66 (m, 4H), 2.67-2.73 (m, 2H), 3.31-3.37 (m, 2H), 3.42-3.48 (m, 3H), 3.61 (dd, J = 3.3, 12.0 Hz, 2H), 3.92 (dd, J = 3.3, 12.0 Hz, 2H), 4.18-4.21 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1 (CH_2), 30.8 (CH_2), 33.5 (CH_2), 59.6 (CH_2), 64.2 (CH), 64.7 (CH), 65.2 (CH_2), 69.1 (CH), 73.2 (CH), 76.3 (CH), 129.9 (C_q), 132.40 (C_q). ESI-HRMS m/z [M + H] $^+$: calcd for $C_{12}H_{21}N_3O_6$ 304.1430, measured 304.1433.

(2R,3S,4S)-1,3,4-tris(Benzyloxy)oct-7-en-5-yn-2-yl chloromethanesulfonate (35). Colorless oil, eluent for column chromatography: EtOAc/Hexane (1/24, v/v); $[\alpha]_D^{28}$ = +157.22 (*c* 0.06 CH_3OH); R_f 0.70 (2/3 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.65-3.75 (m,2H), 3.95 (dd, J = 3.2 , 6.1 Hz, 1H), 4.28-4.30 (m, 1H), 4.36-4.48 (m, 4H), 4.58-4.75 (m, 4H), 5.16-5.20 (m, 1H), 5.49 (dd, J = 2.1 Hz, 11.0 Hz, 1H), 5.64 (dd, J = 2.1 Hz , 17.5 Hz, 1H), 5.74-5.82 (m, 1H), 7.18-7.25 (m,15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.4 (CH_2), 69.0 (CH_2), 69.2 (CH), 71.1 (CH_2), 73.7 (CH_2), 74.7 (CH_2), 80.8 (CH), 84.6 (CH), 85.6 (C_q), 86.7 (C_q), 116.5, 128.4 (CH_2), 128.1-128.7 (ArC), 137.2 (ArC_q), 137.5 (2× ArC_q). IR (neat, cm^{-1}) 3409, 1642, 1216, 771; ESI-HRMS m/z [M + H] $^+$: calcd for $C_{30}H_{31}ClO_6S$, 555.1603, measured 555.1605.

(4S,5R,6S)-4,5-bis(Benzyloxy)-6-(benzyloxymethyl)-3-vinyl-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole (36). Colorless oil, eluent for column chromatography: EtOAc/Hexane (1/4, v/v); $[\alpha]_D^{28}$ = -475.14 (*c* 7.08 CH_3OH); R_f 0.60 (2/3 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.85 (dd, J = 8.1, 10.5 Hz, 1H), 4.05 (dd, J = 4.5, 10.5 Hz, 1H), 4.45-4.51 (m, 3H), 4.54-4.67 (m, 4H), 4.83-4.88 (m, 2H), 5.30 (dd, J = 1.2, 11.2 Hz, 1H), 5.77-5.81 (m, 1H), 6.63 (dd, J = 11.2, 17.8 Hz, 1H), 7.17-7.28 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 60.5 (CH), 69.3 (CH_2), 69.6 (CH), 72.0 (CH_2), 72.9 (CH_2), 73.5 (CH_2), 81.6 (CH), 117.4 (CH_2), 125.6 (CH), 127.8-128.8 (ArC), 134.6 (ArC_q), 136.9 (ArC_q), 137.3 (ArC_q), 138.0 (ArC_q), 141.3 (ArC_q). IR (neat, cm^{-1}) 3318, 3018, 1215, 699; ESI-HRMS m/z [M + H] $^+$: calcd for $C_{29}H_{29}N_3O_3$ 468.2282, measured 468.2277.

(4S,5R,6S)-3-ethyl-6-(Hydroxymethyl)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole-4,5-diol (37). R_f 0.25 (1/9 $CHCl_3$/MeOH); ^{1}H NMR (400 MHz, CD_3OD) : δ 1.31 (t, J = 7.6 Hz, 3H), 2.76 (dd, J = 7.6, 15.3 Hz, 2H), 3.95-4.05 (m, 2H), 4.72-4.75 (m, 1H), 4.87-4.89 (m, 1H), 4.97 (d, J = 5.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7 (CH_3), 19.6 (CH_2), 59.6 (CH_2), 64.1 (CH), 65.2 (CH), 76.1 (CH), 139.7 (C_q), 144.8 (C_q). ESI-HRMS m/z [M + H] $^+$: calcd for $C_8H_{13}N_3O_3$ 200.0957, measured 200.0977.

(2R,3S,4S)-1,3,4-tris(Benzyloxy)-6-phenylhex-5-yn-2-yl chloromethanesulfonate (38). Colorless oil, eluent for column

chromatography : EtOAc/Hexane (1/24, v/v); R_f 0.56 (1/4 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.70-3.76 (m, 2H), 4.03 (dd, *J* = 3.1, 6.1 Hz, 1H), 4.37-4.51 (m, 5H), 4.59-4.81 (m, 4H), 5.24-5.27 (m, 1H), 7.16-7.27 (m, 18H), 7.38-7.41 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.4 (CH_2), 69.0 (CH_2), 69.3 (CH), 71.1 (CH_2), 73.7 (CH_2), 74.7 (CH_2), 81.0 (CH), 84.7 (CH), 85.0 (C_q), 88.2 (C_q), 122.3 (ArC_q), 126.1 (ArC), 128.1-129.0 (ArC), 132.1 (ArC), 137.2 (ArC_q), 137.5 (ArC_q). IR (neat, cm^{-1}) 3320, 3015, 1167, 699, 667; ESI-HRMS m/z [M + H] $^+$: calcd for $C_{34}H_{33}ClO_6S$, 605.1759, measured 605.1718.

(4S,5R,6S)-4,5-bis(Benzyloxy)-6-(benzyloxymethyl)-3-phenyl-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole (39). Colorless oil, eluent for column chromatography: EtOAc/Hexane (1/4, v/v); $[\alpha]_D^{28}$ = -91.30 (*c* 9.20 CH_3OH); R_f 0.50 (2/3 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.91 (dd, *J* = 7.7, 10.5 Hz, 1H), 4.10 (dd, *J* = 4.7, 10.5 Hz, 1H), 4.48-4.58 (m, 5H), 4.68 (s, 2H), 4.88-4.94 (m, 1H), 5.04 (d, *J* = 4.9 Hz, 1H), 7.12-7.28 (m, 18H), 7.65-7.67 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 60.4 (CH_2), 69.4 (CH), 70.3 (CH), 72.4 (CH_2), 73.1 (CH_2) 73.6 (CH_2), 82.1 (CH), 126.5-129.0 (ArC), 130.7 (C_q), 134.3 (ArC_q), 137.0 (ArC_q), 137.3 (ArC_q), 138.0 (ArC_q), 142.7 (C_q). IR (neat, cm^{-1}), 3011, 1198, 699, 669; ESI-HRMS m/z [M + H] $^+$: calcd for $C_{33}H_{31}N_3O_3$ 517.2365, measured 517.2368.

(4S,5R,6S)-6-(Hydroxymethyl)-3-phenyl-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole-4,5-diol (40). R_f 0.22 (1/9 $CHCl_3$/MeOH); ^{1}H NMR (400 MHz, CD_3OD) : δ 4.02-4.11 (m, 2H), 4.96-4.98 (m, 2H), 5.14 (d, *J* = 4.6 Hz, 1H), 7.35 (t, *J* = 5.9 Hz, 1H), 7.45 (t, *J* = 6.0 Hz, 2H), 7.90-7.92 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 59.5 (CH_2), 64.3 (CH), 65.9 (CH), 76.0 (CH), 127.2-130.0 (ArC), 130.5 (ArC), 131.7 (ArC_q), 139.6 (C_q), 142.9 (C_q). ESI-HRMS m/z [M + H] $^+$: calcd for $C_{12}H_{13}N_3O_3$ 248.0957, measured 248.0955.

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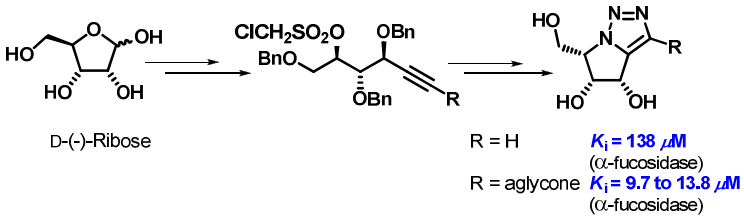

Appended Bicyclic Pyrrolidotriazoles as Glycosidase Inhibitors