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Design, synthesis and biological evaluation of bicyclic iminosugar hybrids: conformational constraint as an effective tool for tailoring the selectivity of α-glucosidase inhibitors†

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Principle guided design of glycan processing enzyme inhibitors involves embedding aromatic groups onto charge and shape mimics. Intramolecular azide–alkyne cycloaddition was used as a simple and versatile strategy for the synthesis of novel condensed bicyclic triazoles from carbohydrate derived Perlin aldehydes. These newly synthesised molecules were evaluated for glycosidase inhibition against 11 commercially available enzymes and were found to possess significant affinity (micromolar range) as well as high degree of selectivity for α-glucosidases. Conformational restriction was identified as an important tool to customize the selectivity of enzyme inhibition by five-membered iminosugars.

Introduction

Glycan processing enzymes are important targets for drug discovery amongst which glycosidases and glycosyltransferases hold prime importance. With the increasing knowledge of glycobiology, it is now well established that the small molecule inhibitors possess the potential to modulate the activities of glycan processing enzymes.[1] The mode of action of most small molecule inhibitors mainly involves the mimicry of the transition state of the enzyme catalysed reaction.[1b] Carbohydrate based inhibitors, built upon the knowledge of transition state structures in enzyme inhibition, have proven not only to be useful therapeutics but also as powerful tools to provide a deeper understanding of the mechanism of enzyme inhibition. The accumulating evidence suggests that a serious limitation associated with such carbohydrate based small molecule inhibitors is their 'class promiscuity' which is of major concern in glycobiology because enzymes of the same class harbour similar binding pockets.

Iminosugars, among the most important classes of glycosidase inhibitors,[2] are therapeutically relevant because of their ability to act as transition state analogs of carbohydrate processing enzymes.[3] The first generation iminosugar therapeutics have attracted interest as anti-cancer, anti-diabetic and antiviral agents. Additionally, they are active against tuberculosis, lysosomal storage disorder and cystic fibrosis.[3,4] Apart from Glyset and Zavesca (Fig. 1) being marketed for Type II diabetes and Gaucher's disease, respectively, many other iminosugar based drugs are currently under clinical trials.[5]

Recently, pyrrolidine iminosugars have attracted considerable interest as inhibitors of glycoside hydrolases. The synthesis of five-membered iminosugars[6] has attracted heightened interest after the disclosure of the first X-ray crystal structure of the pyrrolidine iminosugar, 2,5-imino-D-mannitol (DMDP) derivative, in complex with a retaining β-glucosidase.[7] Despite an attractive biological profile,[8] the full clinical potential of pyrrolidine iminosugars has not yet been realised due to the lack of specificity for a particular enzyme. For instance, the natural product DGDP inhibits α-glucosidase, β-glucosidase, β-galactosidase and trehalase. DMDP strongly inhibits β-gluco-

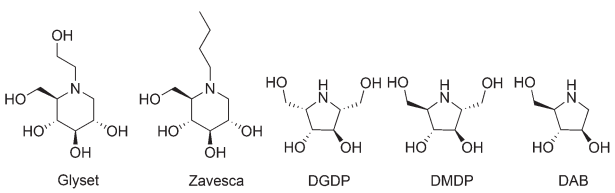

Fig. 1 Examples of some biologically active iminosugars.

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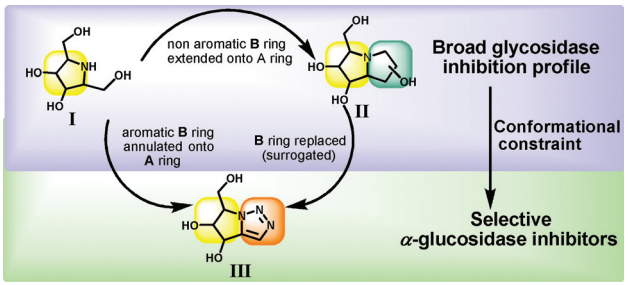


Fig. 2 Structural relationship between polyhydroxylated pyrrolidines **I**, polyhydroxylated pyrrolizidines **II** and proposed triazole surrogates of polyhydroxylated pyrrolizidines **III**. Fusing triazole to **I** results in hydrophobically modified iminosugar **III** showing better activity and selectivity towards α-glucosidases ▢ Ring **A**; ▢ and ▢ = Ring **B**.

sidases and α-galactosidases but shows weak inhibition of α-glucosidases. DAB is a good inhibitor of many α-glucosidases but also showed weak inhibition of β-glucosidases. Many structural variants of these natural products have been synthesised and a few inhibitors were realised which were both potent and selective. However, these synthetic modifications were primarily centred around either stereochemical variation or change in the substitution pattern but rare efforts were made for template modification of pyrrolidine iminosugars. Their lack of specificity can be attributed to their existence as rapidly interconverting flexible envelope conformations.[9] Hence, it is highly desirable to synthesise flattened pyrrolidine sugars.

Pyrrolizidine alkaloids (**II**, Fig. 2) are generally good to potent micromolar inhibitors of a range of glucosidases[8,10] but they are also less specific in their action probably because each of their rings has its own conformational preferences and it is difficult to predict the exact conformational outcome. With these considerations we envisaged the synthesis of condensed triazoles of general structure **III** where the replacement of ring **B** of pyrrolizidine alkaloids by an aromatic triazole ring (Fig. 2) would enforce planarity onto the polyhydroxylated pyrrolidine core (ring **A**) so that it could adapt a conformation to mimic the oxacarbenium ion like the transition state which is one of the important pre-requisites for glycosidase inhibition. The growing impact of hybrid molecules (Fig. 3) in the field of

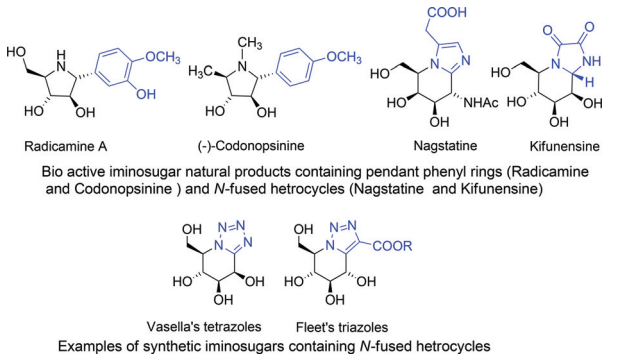


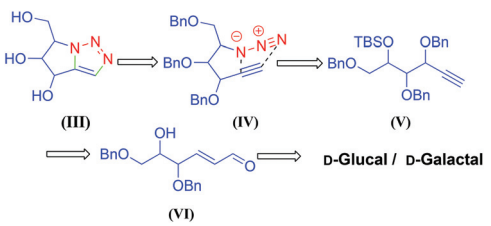
Fig. 3 Examples of some natural (above) and synthetic (below) hybrid iminosugars.

medicinal chemistry and an urge for the discovery of iminosugar based selective small molecule inhibitors motivated us to synthesise the iminosugar triazole hybrids **III**.

Results and discussion

To synthesize these hydrophobically modified, conformationally locked iminosugars, the triazole moiety turned out to be of prime interest owing to the widespread applications of triazoles as the privileged class of molecules in medicinal chemistry,[11] and their ease of installation *via* 'click' chemistry.[12] A careful literature survey revealed that when triazoles were annulated to piperidinoses,[1b,13] they resulted in complete loss of activity against β-glucosidases as compared to the parent molecule. So, it seemed interesting to synthesise triazoles annulated to pyrrolidinoses to know whether the activity results could contribute to the distinction between conformational behaviour of the piperidine and pyrrolidine rings in the catalytic site of glucosidases and to predict the differences in conformational changes of enzymes upon binding to the inhibitor. On the basis of above discussions, herein we wish to report bicyclic iminosugar hybrids (**III**) as α-glucosidase inhibitors.[14] For the synthesis of pyrrolidotriazoles, only three reports from synthetic and structure elucidation point of view have been published.[15] The pyranoid glycal derived Perlin aldehydes (**VI**) are versatile building blocks and have recently been reviewed.[16] In continuation of our interest to utilize Perlin aldehydes to design the syntheses of small organic molecules and natural products,[16] we have now embarked upon exploiting these chiral building blocks to synthesize novel iminosugar constructs (**III**). Its retrosynthetic pathway using intramolecular 'click' chemistry[17] is depicted in Scheme 1. The key intermediate (**V**) could be synthesised from Perlin aldehyde (**VI**). The acetylene (**V**) could be converted to azido-alkyne (**IV**) after silyl ether deprotection and could thus serve as a template for intramolecular azide–alkyne cycloaddition to form **III**.

Synthesis of C-3(*R*) configured precursors **9a**, **9b** and **9c** for the azide–alkyne cycloaddition is represented in Scheme 2. The synthesis of acetylene precursors was achieved starting from the Perlin aldehyde derived allylic alcohols **2a** and **2b** which were readily prepared from pyranoid glycals in two steps on a multi-gram scale.[18] Protecting group manipulations involved di-O-protection of hydroxyl functionalities at C1 and C5 using TBDMSOTf followed by selective deprotection of



Scheme 1 Retrosynthetic analysis.

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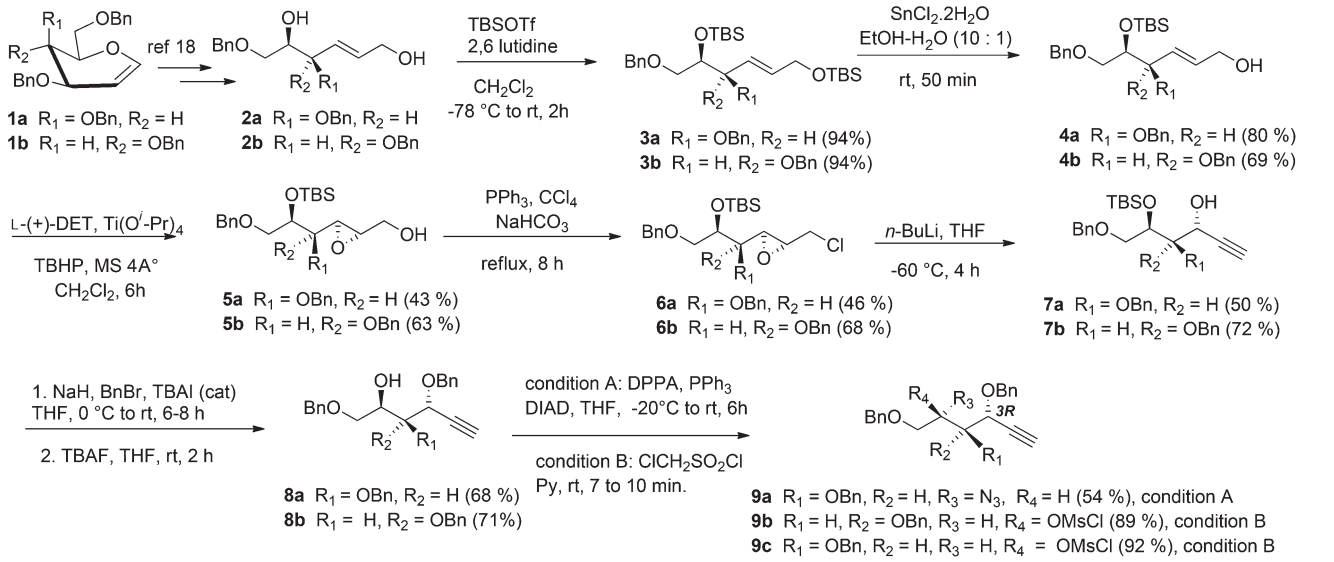
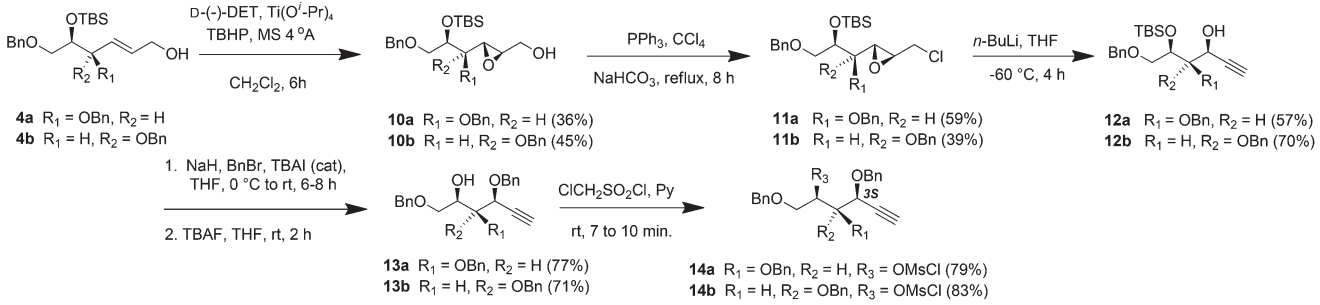


Scheme 2 Synthesis of precursors **9a**, **9b** and **9c**.



Scheme 3 Synthesis of precursors **14a** and **14b**.

primary TBS ether using $SnCl_2{\cdot}2H_2O$[19] affording compound **4** in good yield. The protected allylic alcohol **4** was subjected to Sharpless asymmetric epoxidation[20] with L-(+)-DET to provide (2*S*,3*R*) epoxide **5** which on chlorination with CCl_4 in the presence of PPh_3 and a catalytic amount of $NaHCO_3$ under reflux yielded epoxy chloride **6**. It was then fragmented by base induced double elimination using 3 equiv. of *n*-BuLi at −60 °C in dry THF under an argon atmosphere to furnish the desired chiral alkynol **7**.[21]

In the subsequent step, the propargylic hydroxyl group of **7** (Scheme 2) was protected as benzyl ether which on desilylation afforded the desired acetylene **8** which could now serve as an appropriate substrate for Mitsunobu azidation. Our initial attempts for azidation under Mitsunobu conditions with 4 equiv. each of PPh_3, DPPA (diphenylphosphoryl azide) and DIAD (diisopropyl azodicarboxylate) in dry THF under inert conditions were futile.[22] However, in the case of the D-galactal derived substrate **8a**, it was observed that on increasing the stoichiometry of the reagents to 8 equiv., the azido acetylene **9a** was obtained in 54% yield. Moreover, the reaction did not take place with the alkyne **8b** synthesized from D-glucal derived epoxy chloride **6b**.

To overcome the drawbacks experienced during Mitsunobu azidation that could be due to the use of excess reagents, long reaction times, low yields and more importantly the risk of handling organic azides, the desired bicyclic triazoles were obtained directly from their respective *in situ* generated azides. Thus, a one-pot protocol for thermal tandem azidation/intramolecular 'click' was tried. The acetylene **8a** was subjected to chloromesylation to yield **9c** in 84% yield which could serve as an appropriate substrate for the tandem process to obtain the title molecule. We were also interested to extend our study with C-3(*S*) configured precursors **14a** and **14b** whose azide–alkyne cycloaddition was completed in the same manner as described for **9b** and **9c** (Scheme 3). Having the alkynes **9** and **14** in our hand, we moved towards the synthesis of condensed bicyclic triazoles **15** and **16**. Thus, the azido acetylene **9a** on intramolecular 1,3 dipolar cycloaddition in dry degassed toluene under uncatalysed thermal conditions for 4.5 h afforded the condensed bicyclic triazole **15a** as a single regioisomer in 78% yield (Scheme 4). Its detailed ^1H, ^{13}C, and HSQC data analyses confirmed it to be a 1,5 regioisomer. The recently described one dimensional proton gated decoupled ^{13}C NMR spectroscopy technique serves as a useful method for

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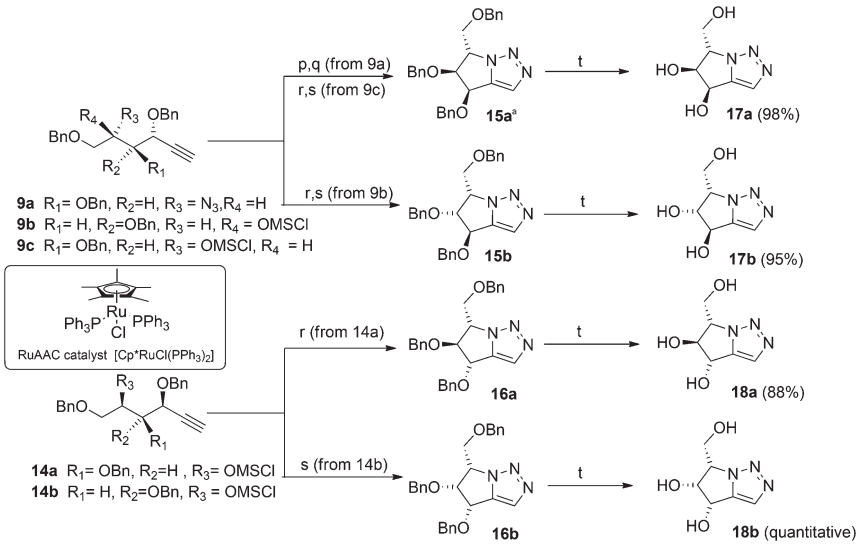

Scheme 4 Synthesis of fused bicyclic triazoles **17a**, **17b**, **18a** and **18b**. *Reagents and conditions*: (p) toluene, 100 °C, 4.5 h; (q) Cp*RuCl(PPh$_3$)$_2$, toluene, 100 °C, 2 h; (r) NaN_3, DMF, 120 °C, 4 to 6 h; (s) (1) NaN_3, DMF, microwave heating, 80 °C, 2 h, (2) Cp*RuCl(PPh$_3$)$_2$, microwave heating, 120 °C, 20 min; (t) Pd(OH)$_2$, MeOH, rt, 10 h. [a]Time taken and % yields vary for different isomers (Table 1).

structure assignment to 1,2,3 triazoles.[23] On applying this method to our bicyclic system, the observed value of the coupling constant was in fair agreement with those reported for simple monocyclic 1,5 disubstituted triazoles (ESI†).

This reaction was also carried out under ruthenium catalyzed azide–alkyne cycloaddition (RuAAC) conditions developed by Fokin and Jia[24] in the presence of 5 mol% Cp*RuCl(PPh$_3$)$_2$. The reaction was completed in lesser time (2 h) with better yield (88%) as compared to the uncatalysed reaction described above. Here, it is worth mentioning that the Ru catalyst has been used for regioselective intermolecular AAC to form 1,5-triazoles; our finding thus indicates that the RuAAC can also be effectively applied to intramolecular 'click' reaction to obtain condensed 1,5-triazoles with improved yield. When **9c** was refluxed with NaN_3 in dry DMF at 120 °C under inert conditions for the tandem one-pot azidation/1,3-dipolar cycloaddition, complete disappearance of the starting material was observed on TLC in 4 h. The product was obtained in quantitative yield and identified to be **15a** whose synthesis has already been discussed above. With these results in hand, microwave (μw) assisted one-pot ruthenium catalysed 'click' reaction was also tried but it did not lead to the formation of the desired triazole owing to deactivation of the catalyst by sodium azide.[25] In order to overcome this problem, the μw assisted one-pot sequential ruthenium catalysed reaction as developed by Johansson's group[26] was carried out whereby the chloromesyl (instead of halide) was first allowed to convert completely into the azido alkyne under μw conditions at 80 °C for 2 h. This was then followed by the addition of the ruthenium catalyst (5 mol%) and μw heating was further continued at 120 °C for 30 min to obtain the triazole **15a** in 90% yield. To the best of our knowledge, this is the first example of μw assisted intramolecular one-pot sequential RuAAC. Here, it is worth mentioning that this reaction was not successful with secondary alkyl halides even at higher temperature despite the fact that secondary azides do participate in RuAAC reactions albeit with slow reactivity compared to primary azides.[26] Gratifyingly, in our case even the secondary chloromesylates reacted readily to deliver the desired triazoles **15a**, **15b**, and **16a** in commendable yields. These results are indicative of the scope of using sterically hindered activated secondary alcohols as substrates for RuAAC reaction. Debenzylation of **15a**, **15b**, **16a** and **16b** by hydrogenolysis using Pd(OH)$_2$/C in MeOH furnished triols **17a**, **17b**, **18a** and **18b** respectively in excellent yields.

Glycosidase inhibition

All the compounds were assayed against a panel of 11 carbohydrate processing enzymes. The results are summarised in Table 2. Three out of four compounds (**17a**, **17b** and **18a**) were found to be potent and completely specific inhibitors of α-glucosidase from rice and *A. niger*. However, in addition to α-glucosidase inhibition, triazole **18b** also displayed potent inhibition (92% inhibition at 1000 μM) of α-L-fucosidase from bovine kidney. These compounds were consistently active even at concentrations as low as 400 μM (ESI†).

Compound **17b** showed improved activity and selectivity over known α-glucosidase inhibitors like monocyclic parent compounds (natural product DGDP **A** and its L-*ido* configured isomer **B**), pyrrolizidine alkaloids (3-*epi*-australine, **D**, and 3-*epi*-casuarine, **E**) and quaternary centered monocyclic analogues (isoDGDP, **C**) (see Table 3). The natural product DGDP, **A**, is a modest α-glucosidase inhibitor but is non-specific as it also inhibits β-glucosidase, β-galactosidase and trehalase. This study revealed that compound **17b** is 6 times more potent than DGDP and is highly selective for α-glucosidase (Table 3). The enforced planarity imparted by the triazole ring to the pyrro-

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Table 1 Results for intramolecular 'click' reaction on different isomeric alkynes under various conditions (Scheme 4)

Substrate	Product	Method[a]	Yield[b] (%)	*t* (h)
9a	**15a**	p	78%	4.5
9a	**15a**	q	88%	2
9c	**15a**	r	Quantitative	4–6
9c	**15a**	s	90%	2.5
9b	**15b**	r	81%	8
9b	**15b**	s	Quantitative	2.5
14a	**16a**	r	83%	6
14a	**16a**	s	82%	2.5
14b	**16b**	r	85%	8–10

[a] Methods p, q, r and s are as follows: p = uncatalysed from the azido-alkyne substrate; q = Ru catalysed from the azido-alkyne substrate; r = one pot uncatalysed from chloromesyl substrate; s = μw assisted one pot sequential ruthenium catalysed from the chloromesyl substrate. [b] The yield of the product isolated after column purification.

lidine core of DGDP seems to help in achieving selectivity with enhanced potency.

The natural product DMDP (Fig. 1) is a strong inhibitor of β-glucosidases and α-galactosidases but exhibits weak inhibition of α-glucosidases. Its unnatural enantiomer L-DMDP, **F**, was found to be highly specific and a potent inhibitor of α-glucosidases (also inhibits α-trehalase with a IC_{50} value of 48 μM) and LAB, **G**, is also a potent and specific inhibitor of α-glucosidases with moderate inhibition of α-trehalase and β-galactosidase. The activity profile of the triazole analogue **18a** is comparable to parent compounds L-DMDP, **F**, and LAB, **G**, yet **18a** is more selective molecule with enhanced lipophilicity. However Fleet's C-branched analogue L-isoDMDP, **H**, has been so far the most potent and the most specific for α-glucosidase scaffolds with similar stereochemistry.

Compound **18b** also displayed potent inhibition although the parent monocyclic pyrrolidines **I** and the *N*-alkylated analogue, **K**, are completely inactive against rice α-glucosidase. **K** is a selective rhamnosidase inhibitor with K_i of 13 μM. The alteration in conformational flexibility could provide an opportunity for switching over the glucosidase inhibitory activity. The triazole analogue (**18b**) of the monocyclic inhibitor LIL, **J**, shows considerably improved selectivity profile.

As per literature precedence, grafting triazoles onto piperidine iminosugars caused a complete loss of activity against β-glucosidase,[1b,13] leading to the conclusion that the hetero atom attached to the anomeric carbon makes an important interaction with the acid/base residue of the enzyme. However, the increase in potency and specificity of pyrrolidotriazoles for α-glucosidase indicates that an sp^2 hybridised carbon attached to the anomeric centre might be a feature specific to the catalytic site of α-glucosidase (thus distinguishing it from other enzymes) as also exemplified by natural products radicamines and codonopsines (Table 3) which are potent α-glucosidase inhibitors. Also, the triazole ring might promote an enzyme dependent induced fit resulting in high favourable entropy for binding. Further studies are required for such structural insights to understand the mode of action of α-glucosidases and to decipher the features responsible for the observed results.

Conclusion

In summary, stereochemically pure polyhydroxylated bicyclic triazoles **17a**, **17b**, **18a** and **18b** have been synthesised *via* intramolecular 'click' reaction and proved to be a new class of

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

IC_{50} in μM				
Enzyme	**17a**	**17b**	**18a**	**18b**
α-glucosidase				
Yeast	NI[b] (3)[c]	NI (2)	NI (1)	NI (1)
Rice	40 [K_i = 38.37][d]	20 [K_i = 24.87]	8 [K_i = 11.48]	13.75 [K_i = 15.75]
Aspergillus niger	47.5 [K_i = 49.00]	22 [K_i = 38.40]	9 [K_i = 15.32]	8 [K_i = 22.63]
β-Glucosidase				
Almond	NI (1)	NI (13)	NI (3)	NI (2)
α-Galactosidase				
Green coffee beans	NI (7)	NI (7)	NI (5)	NI (6)
β-Galactosidase				
Bovine liver	NI (7)	NI (8)	NI (6)	NI (3)
α-Mannosidase				
Jack bean	NI (1)	NI (6)	NI (4)	NI (1)
β-*N*-Acetyl glucosaminidase				
Jack bean	NI (2)	NI (7)	NI (2)	NI (1)
Trehalase				
Porcine kidney	NI (5)	NI (4)	NI (1)	NI (2)
Amyloglycosidase				
Aspergillus niger	NI (3)	NI (3)	NI (4)	NI (4)
α-L-Fucosidase				
Bovine kidney	NI (1)	NI (0)	NI (1)	96.8 [K_i = 138]

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

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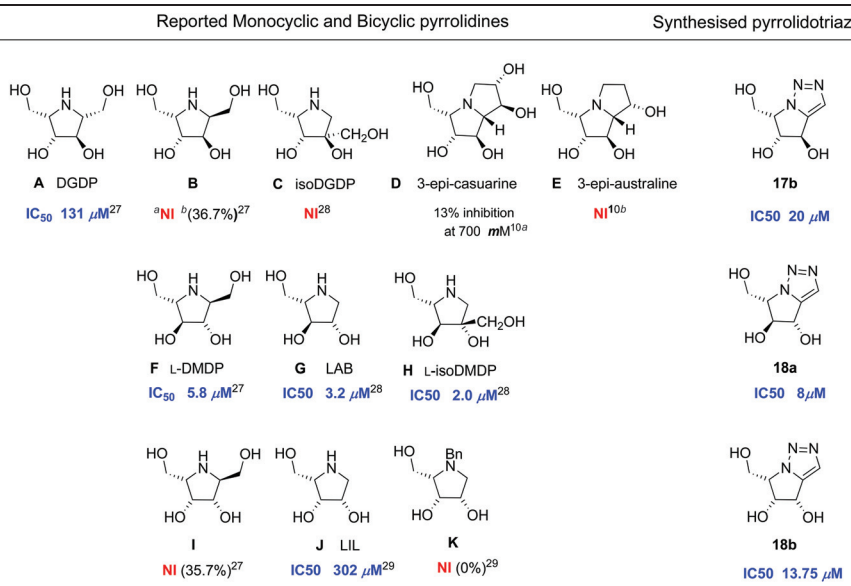
Table 3 Comparative study of rice α-glucosidases inhibition by fused bicyclic triazoles **17b**, **18a** and **18b** with known inhibitors of similar stereochemistry



[a] NI = no inhibition at 1000 μm. [b] All % inhibition at 1000 μm.

potent and specific α-glucosidase inhibitors. Grafting of an aromatic residue led to attain selectivity without the loss of potency and these results were consistent in all cases. These molecules possibly act both as shape and charge mimics of the transition state of the enzyme catalysed reaction as they incorporate all three features[1] that are supposed to be essential for inhibition of a targeted enzyme. Additionally, in order to capture the aglycone binding energy, these molecules feature a site for appending a lipophilic group that is assumed to interact with the apparent aromatic residues that are close to the aglycone binding site of the enzyme. For pyrrolidine based inhibitors, other structural modifications which aim at improving selectivity have led to either a decrease or complete loss of potency in some cases. Our findings thus indicate that embedding aromatic groups onto existing inhibitors or modification of the template so as to mimic the transition state appears to be a more consistent approach to finely tune the potency and selectivity of inhibition.

Our future efforts involve validation of this concept by synthesising and analysing other conformationally restricted hybrid iminosugars. Fine tuning of **18b** for selective fucosidase inhibition by constructing aglycone mimics is 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) and IR spectroscopy, and ESI-MS. NMR spectra of the synthesized compounds were recorded in $CDCl_3$ at 25° at 300 MHz (^{1}H) and 50, 75 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 chloroform as the solvent; concentrations mentioned are in g per 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 the hot plate. Silica gel (100–200 and 230–400 mesh) was used for column chromatography. Low-temperature reactions were performed using an immersion cooler with ethanol as the cooling agent.

General procedure for the enzyme inhibition assay

All the enzymes and their corresponding substrates used in this study were purchased from Sigma-Aldrich Chemical Co. Inhibition studies of compounds (**17a**, **17b**, **18a** and **18b**) were determined by measuring residual hydrolytic activities of the glycosidase. The substrate and enzymes were prepared as 50 mM solutions in the respective pH buffer solution of the corresponding enzyme. In all cases, the substrates used were the corresponding *p*-nitrophenyl glycopyranosides. The incubation mixture consisted of 100 μL of enzyme solution, and 100 μL of (12.5 μM to 1000 μM) test compound in an appropriate buffer solution of the optimum pH for the enzyme. After incubation at the optimal temperature for 1 h, 100 μL of the substrate solution was added and allowed to react for 1.5 h. The optimum temperature and respective buffer used for the enzyme are given in Table 1. The reaction was terminated by addition of 1 M Na_2CO_3. In all cases, control experiments were

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carried out simultaneously in the absence of the test compound. A series of blank experiments for the substrate were also carried out in the respective buffer solutions without the enzyme or test compounds. The absorbance of the liberated *p*-nitrophenol in each reaction (both test and control reactions) was recorded using a spectrophotometer at 405 nm. Percentage inhibition was calculated as the ratio of the observed absorbances of the test and control reactions to the observed absorbance of the control reaction. Results have thus been reported as IC_{50} values, which is the concentration of the test compound that causes 50% inhibition of the enzyme.[30,31]

(8*R*,9*R*,*E*)-8-(Benzyloxy)-9-(benzyloxymethyl)-2,2,3,3,11,11,12,-12-octamethyl-4,10-dioxa-3,11-disilatridec-6-ene (3a). To a stirred solution of compound **2a** (540 mg, 1.646 mmol) in dry DCM at −78 °C were added 2,6-lutidine (1.6 mL, 13.7 mmol) and TBSOTf (1.2 mL, 5.23 mmol) under a N_2 atmosphere. The mixture was allowed to stir for 2 h at −78 °C to room temperature. On completion, the reaction was quenched with aqueous $NaHCO_3$ solution. The reaction mixture was extracted with DCM. The extracted organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to obtain clear oil which on column purification yielded **3a** (865 mg, 94% from **2a**). **Analytical data of 3a**: colorless oil, the eluent for column chromatography: EtOAc–hexane (1/49, v/v); $[\alpha]_D^{28}$ = +0.41 (*c* 0.60 $CHCl_3$); R_f 0.50 (1/19, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 3H, CH_3), 0.03 (s, 3H, CH_3), 0.06 (s, 6H, 2 × CH_3), 0.87 (s, 9H, 3 × CH_3), 0.91 (s, 9H, 3 × CH_3), 3.37–3.42 (m, 1H, 6-H), 3.61–3.65 (m, 1H, 6-H), 3.89–3.90 (m, 2H, 4-H + 5-H), 4.19 (d, *J* = 4.0 Hz, 2H, 1-H), 4.37–4.64 (m, 4H, 2 × CH_2Ph), 5.64–5.71 (m, 1H, 3-H), 5.75–5.83 (m, 1H, 2-H), 7.25–7.32 (m, 10H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.01 (2 × CH_3, OTBS), −4.52 (CH_3, OTBS), −4.40 (CH_3, OTBS), 18.41 (C_q, OTBS), 18.58 (C_q, OTBS), 26.12 (6 × CH_3, OTBS), 63.38 (CH_2, 1-C), 70.78 (CH_2, CH_2Ph), 72.39 (CH_2, 6-C), 73.50 (CH_2, CH_2Ph), 74.33 (CH, 4-C), 80.68 (CH, 5-C), 126.88 (CH, 3-C), 127.55–128.40 (ArC), 133.25 (CH, 2-C), 138.72 (ArC_q), 138.89 (ArC_q); IR (neat, cm^{-1}) 2932, 2858, 2366, 1676, 1217, 1108, 772; ESI-HRMS *m*/*z* $[M + H]^+$: calcd for $C_{32}H_{52}O_4Si_2$ 557.3477, measured 557.3480.

(8*S*,9*R*,*E*)-8-(Benzyloxy)-9-(benzyloxymethyl)-2,2,3,3,11,11,12,-12-octamethyl-4,10-dioxa-3,11-disilatridec-6-ene (3b). The experimental procedure for synthesis of **3b** is the same as that of compound **3a**. **Analytical data of 3b**: colorless oil, the eluent for column chromatography: EtOAc–hexane (1/49, v/v); $[\alpha]_D^{28}$ = + 17.28 (*c* 0.30 CH_3OH); R_f 0.50 (1/19, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 6H, 2 × CH_3), 0.07 (s, 6H, 2 × CH_3), 0.86 (s, 9H, 3 × CH_3), 0.91 (s, 9H, 3 × CH_3), 3.47–3.49 (m, 2H, 6-H), 3.87–3.96 (m, 2H, 4-H + 5-H), 4.14–4.24 (m, 2H, 1-H) 4.34–4.60 (m, 4H, 2 × CH_2Ph), 5.64–5.79 (m, 2H, 2-H + 3-H), 7.25–7.30 (m, 10H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.02 (CH_3, OTBS), −4.39 (CH_3, OTBS), 18.40 (C_q, OTBS), 18.57 (C_q, OTBS), 26.13 (3 × CH_3, OTBS), 63.31 (CH_2, 1-C), 70.53 (CH_2, CH_2Ph), 72.20 (CH_2, 6-C), 73.47 (CH_2, CH_2Ph), 74.24 (CH, 4-C), 80.93 (CH, 5-C), 127.14–128.44 (ArC + CH, 3-C), 134.59 (CH, 2-C), 138.64 (ArC_q), 138.99 (ArC_q); IR (neat, cm^{-1}) 3037, 1217, 767; ESI-HRMS *m*/*z* $[M + H]^+$: calcd for $C_{32}H_{52}O_4Si_2$ 557.3477, measured 557.3038.

(4*R*,5*R*,*E*)-4,6-Bis(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-hex-2-en-1-ol (4a). To a stirred solution of compound **3a** (1.089 g, 1.96 mmol) in EtOH–H_2O (10 mL + 1 mL) at room temperature was added $SnCl_2{\cdot}2H_2O$ in small portions (200 mg, 0.88 mmol). The reaction mixture was allowed to stir at room temperature for 45–50 minutes. On completion, the reaction was quenched with aqueous $NaHCO_3$ solution. The reaction mixture was dissolved in ethyl acetate, and filtered through a Celite pad. The organic layer was then extracted with water. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to obtain clear oil which on column purification yielded **4a** (870 mg, 80% from **3a**). **Analytical data of 4a**: colorless oil, the eluent for column chromatography: EtOAc–hexane (9/91, v/v); $[\alpha]_D^{28}$ = +1.94 (*c* 0.89 $CHCl_3$); R_f 0.50 (1/4, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 3H, CH_3), 0.05 (s, 3H, CH_3), 0.88 (s, 9H, 3 × CH_3), 3.40–3.45 (m, 1H, 6-H), 3.62–3.66 (m, 1H, 6-H), 3.91–3.92 (m, 2H, 4-H + 5-H), 4.14 (d, *J* = 4.9 Hz, 2H, 1-H), 4.41–4.63 (m, 4H, 2 × CH_2Ph), 5.65–5.73 (m, 1H, 3-H), 5.83–5.91 (m, 1H, 2-H), 7.26–7.33 (m, 10H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.53 (CH_3, OTBS), −4.40 (CH_3, OTBS), 18.41 (C_q, OTBS), 26.07 (3 × CH_3, OTBS), 63.24 (CH_2, 1-C), 71.00 (CH_2, CH_2Ph), 72.22 (CH_2, 6-C), 73.51 (CH_2, CH_2Ph), 74.26 (CH, 4-C), 80.75 (CH, 5-C), 127.59 (ArC), 127.62–128.43 (ArC), 128.78 (CH, 3-C), 132.82 (CH, 2-C), 138.62 (ArC_q), 138.82 (ArC_q); IR (neat, cm^{-1}) 3446, 2929, 2366, 1655, 1219, 1100, 771; ESI-HRMS *m*/*z* $[M + H]^+$: calcd for $C_{26}H_{38}O_4Si$ 443.2612, measured 443.2612.

(4*S*,5*R*,*E*)-4,6-Bis(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-hex-2-en-1-ol (4b). The experimental procedure for synthesis of **4b** is the same as that of compound **4a**. **Analytical data of 4b**: colorless oil, the eluent for column chromatography: EtOAc–hexane (9/91, v/v); $[\alpha]_D^{28}$ = +1.03 (*c* 0.10 CH_3OH); R_f 0.50 (1/4, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 6H, 2 × CH_3), 0.87 (s, 9H, 3 × CH_3), 3.47–3.50 (m, 2H, 6-H), 3.89–3.96 (m, 2H, 4-H + 5-H), 4.16 (bs, 2H, 1-H), 4.38–4.59 (m, 4H, 2 × CH_2Ph), 5.65–5.73 (m, 1H, 3-H), 5.78–5.86 (m, 1H, 2-H), 7.26–7.31 (m, 10H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.44 (CH_3, OTBS), −4.35 (CH_3, OTBS), 18.37 (C_q, OTBS), 26.04 (3 × CH_3, OTBS), 63.23 (CH_2, 1-C), 70.83 (CH_2, CH_2Ph), 72.08 (CH_2, 6-C), 73.48 (CH_2, CH_2Ph), 74.24 (CH, 4-C), 80.87 (CH, 5-C), 127.50–129.02 (10 ArC + CH, 3-C), 133.89 (CH, 2-C), 138.54 (ArC_q), 138.87 (ArC_q); IR (neat, cm^{-1}) 3399, 2932, 2365, 1589, 771; ESI-HRMS *m*/*z* $[M + H]^+$: calcd for $C_{26}H_{38}O_4Si$ 443.2612, measured 443.2612.

(2*S*,3*R*)-3-((1*R*,2*R*)-1,3-Bis(benzyloxy)-2-(*tert*-butyldimethylsilyloxy)propyl oxiran-2-yl)methanol (5a). A solution of Ti(O-i-Pr)$_4$ (0.02 mL, 0.07 mmol) and L-(+)-diethyltartarate (0.01 mL, 0.06 mmol) in dry DCM (5 mL) was stirred at −25 °C for 0.5 h in the presence of MS 4 Å. To this mixture, a solution of substrate **4a** (97 mg, 0.219 mmol) in dry DCM (5 mL) was added and the mixture was stirred at the same temperature. After 0.5 h of stirring, a 6.0 M solution of *t*-BuOOH (0.09 mL, 0.54 mmol) was added and the temperature of the reaction was raised to 0 °C and was left for stirring till the completion

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of the reaction. After completion, 10% solution of tartaric acid (5 mL) was added to quench the reaction at 0 °C and stirred for 0.5 h. The solution was filtered through a Celite pad. The organic layer was extracted with DCM, concentrated, dissolved in ether (7 mL) and again cooled to 0 °C. To this 4% NaOH in brine solution was added and stirred for 15–20 minutes. The organic layer was extracted with ether, dried over Na_2SO_4, concentrated and evaporated under reduced pressure to obtain clear oil which on column purification yielded **5a** (43 mg, 43% from **4a**). **Analytical data of 5a**: pale yellow oil, the eluent for column chromatography: EtOAc–hexane (9/91, v/v); $[\alpha]_D^{28}$ = +1.09 (*c* 0.10 $CHCl_3$); R_f 0.46 (1/4, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 3H, CH_3), 0.05 (s, 3H, CH_3), 0.89 (s, 9H, 3 × CH_3), 3.09 (bs, 1H, 2-H), 3.18–3.20 (m, 1H, 3-H), 3.48–3.53 (m, 3H, 1-H + 4-H + 6-H), 3.62–3.73 (m, 2H, 1-H + 6-H), 3.94 (dd, *J* = 4.9, 9.3 Hz, 1H, 5-H), 4.50–4.59 (m, 4H, 2 × CH_2Ph), 7.26–7.31 (m, 10H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.81 (CH_3, OTBS), −4.38 (CH_3, OTBS), 18.32 (C_q, OTBS), 26.04 (3 × CH_3, OTBS), 54.93 (CH, 3-C), 56.65 (CH, 2-C), 61.71 (CH_2, 1-C), 71.20 (CH_2, 6-C), 72.34 (CH, 5-C), 73.64 (CH_2, CH_2Ph), 73.70 (CH_2, CH_2Ph), 77.80 (CH, 4-C), 127.80 (ArC), 127.88 (ArC), 127.93 (ArC), 128.52 (ArC), 138.36 (ArC_q), 138.75 (ArC_q); IR (neat, cm^{-1}) 3450, 2927, 2342, 1622, 1218, 769; ESI-HRMS *m*/*z* $[M + H]^+$: calcd for $C_{26}H_{38}O_5Si$ 459.2561, measured 459.2562.

(2*S*,3*R*)-3-(1*S*,2*R*)-1,3-Bis(benzyloxy)-2-(*tert*-butyldimethylsilyloxy)propyl(oxiran-2-yl) methanol (5b). The experimental procedure for synthesis of **5b** is the same as that of compound **5a** **Analytical data of 5b**: pale yellow oil, the eluent for column chromatography: EtOAc–hexane (9/91, v/v); $[\alpha]_D^{28}$ = −5.53 (*c* 0.26 CH_3OH); R_f 0.33 (1/4, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 3H, CH_3), 0.07 (s, 3H, CH_3), 0.88 (s, 9H, 3 × CH_3), 2.95–2.98 (m, 1H, 3-H), 3.19–3.22 (m, 1H, 2-H), 3.35–3.39 (m, 1H, 4-H), 3.52–3.60 (m, 3H, 6-H + 1-H), 3.82 (d, *J* = 12.3 Hz, 1H, 1-H), 3.99 (dd, *J* = 5.0, 9.9 Hz, 1H, 5-H), 4.44–4.78 (m, 4H, 2 × CH_2Ph), 7.24–7.32 (m, 10H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.55 (CH_3, OTBS), −4.49 (CH_3, OTBS), 18.29 (C_q, OTBS), 26.00 (3 × CH_3, OTBS), 55.47 (CH, 3-C), 56.42 (CH, 2-C), 61.69 (CH_2, 1-C), 71.53 (CH_2, 6-C), 72.82 (CH2, CH_2Ph), 73.00 (CH, 5-C), 73.62 (CH2, CH_2Ph), 80.37 (CH, 4-C), 127.67–128.55 (ArC), 138.11 (ArC_q), 138.54 (ArC_q); IR (neat, cm^{-1}) 3439, 2367, 1634, 772; ESI-HRMS *m*/*z* $[M + H]^+$: calcd for $C_{26}H_{38}O_5Si$ 459.2561, measured 459.2557.

((1*R*,2*R*)-1,3-Bis(benzyloxy)-1-((2*S*,3*R*)-3-(chloromethyl)oxiran-2-yl)propan-2-yloxy)(*tert*-butyl)dimethylsilane (6a). A stirred mixture of epoxy alcohol **5a** (44 mg, 0.09 mmol), PPh_3 (61 mg, 0.23 mmol) and $NaHCO_3$ (2 mg, 4.5 wt%) in CCl_4 (0.62 mL) was heated at reflux, under a N_2 atmosphere for 7–8 h. After completion of the reaction, CCl_4 was removed under pressure and the residue was purified by silica gel column chromatography to furnish epoxy chloride **6a** as a colorless liquid (20 mg, 46% from **5a**). **Analytical data of 6a**: colorless oil, the eluent for column chromatography: EtOAc–hexane (1/99, v/v); $[\alpha]_D^{28}$ = −0.75 (*c* 0.20 $CHCl_3$); R_f 0.68 (1/4, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 3H, CH_3), 0.05 (s, 3H, CH_3), 0.88 (s, 9H, 3 × CH_3), 3.13–3.19 (m, 2H, 2-H + 3-H), 3.34–3.67 (m, 5H, 1-H + 4-H + 6-H), 3.98 (dd, *J* = 4.5, 10.2 Hz, 1H, 5-H), 4.49–4.65 (m, 4H, 2 × CH_2Ph), 7.25–7.31 (m, 10H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ −4.83 (CH_3, OTBS), −4.38 (CH_3, OTBS), 18.30 (C_q, OTBS), 26.03 (3 × CH_3, OTBS), 44.63 (CH_2, 1-C), 55.58 (CH, 2-C), 57.52 (CH, 3-C), 71.23 (CH_2, 6-C), 72.24 (CH, 5-C), 73.61 (CH_2, 2 × CH_2Ph), 77.39 (CH, 1-C), 127.75–128.53 (ArC), 138.38 (ArC_q), 138.53 (ArC_q); IR (neat, cm^{-1}) 3948, 2364, 1217, 769; ESI-HRMS $[M + H]^+$: calcd for $C_{26}H_{37}ClO_4Si$ 477.2222, measured 477.2221.

((1*S*,2*R*)-1,3-Bis(benzyloxy)-1-((2*S*,3*R*)-3-(chloromethyl)oxiran-2-yl)propan-2-yloxy)(*tert*-butyl) dimethylsilane (6b). The experimental procedure for synthesis of **6b** is the same as that of compound **6a**. **Analytical data of 6b**: colorless oil, the eluent for column chromatography: EtOAc–hexane (1/99, v/v); $[\alpha]_D^{28}$ = −20.01 (*c* 0.26 CH_3OH); R_f 0.68 (1/4, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 3H, CH_3), 0.07 (s, 3H, CH_3), 0.88 (s, 9H, 3 × CH_3), 3.01–3.06 (m, 1H, 3-H), 3.16–3.19 (m, 1H, 2-H), 3.34–3.38 (m, 1H, 4-H), 3.48–3.52 (m, 4H, 1-H + 6-H), 4.01 (dd, *J* = 5.3 Hz, 9.7 Hz, 1H, 5-H), 4.43–4.77 (m, 4H, 2 × CH_2Ph), 7.26–7.33 (m, 10H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ −4.54 (2 × CH_3, OTBS), 18.28 (C_q, OTBS), 25.98 (3 × CH_3, OTBS), 44.60 (CH_2, 1-C), 54.42 (CH, 2-C), 58.96 (CH, 3-C), 71.35 (CH_2, 6-C), 72.74 (CH_2, CH_2Ph), 72.88 (CH, 5-C), 73.54 (CH_2, CH_2Ph), 79.77 (CH, 4-C), 127.69–128.56 (ArC), 138.08 (ArC_q), 138.42 (ArC_q); IR (neat, cm^{-1}) 3423, 1637, 772; ESI-HRMS *m*/*z* $[M + H_2O]^+$: calcd for $C_{26}H_{37}ClO_4Si$ 494.2250, measured 494.2481.

(3*R*,4*R*,5*R*)-4,6-Bis(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-hex-1-yn-3-ol (7a). To a stirred solution of epoxy chloride **6a** (160 mg, 0.34 mmol) in dry THF (7.5 mL) at −60 °C was added *n*-BuLi (1.8 mL, 3.6 mmol) dropwise in 3 lots at an interval of 0.5 h between successive additions. The mixture was allowed to stir at −35 °C for additional 2 h. The reaction mixture was quenched with saturated aqueous solution of NH_4Cl (5 mL) and THF was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate, dried with Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to furnish alkyne **7a** as clear oil (80 mg, 50% from **6a**). **Analytical data of 7a**: colorless oil, the eluent for column chromatography: EtOAc–hexane (1/39, v/v); $[\alpha]_D^{28}$ = −6.29 (*c* 0.20 $CHCl_3$); R_f 0.36 (1/9, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 3H, CH_3), 0.11 (s, 3H, CH_3), 0.90 (s, 9H, 3 × CH_3), 2.46 (d, *J* = 2.3 Hz, 1H, 1-H), 3.60 (d, *J* = 3.8 Hz, 2H, 6-H), 3.75–3.79 (m, 1H, 5-H), 4.03–4.08 (m, 1H, 4-H), 4.51 (s, 2H, CH_2Ph), 4.59–4.61 (m, 1H, 3-H), 4.69 (d, *J* = 11.0 Hz, 1H, CH_2Ph), 4.83 (d, *J* = 11.0 Hz, 1H, CH_2Ph), 7.30–7.32 (m, 10H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.76 (CH_3, OTBS), −4.24 (CH_3, OTBS), 18.25 (C_q, OTBS), 26.03 (3 × CH_3, OTBS), 61.49 (CH, 3-C), 71.26 (CH_2, 6-C), 71.83 (CH, 4-C), 73.53 (CH_2, CH_2Ph), 73.73 (CH, 1-C),74.78 (CH_2, CH_2Ph), 81.24 (CH, 5-C), 83.73 (C_q, 2-C), 127.82–128.59 (ArC), 137.97 (ArC_q), 138.18 (ArC_q); IR (neat, cm^{-1}) 3457, 2357, 1092, 773; ESI-HRMS *m*/*z* $[M + H]^+$: calcd for $C_{26}H_{36}O_4Si$ 441.2456, measured 441.2456.

(3*R*,4*S*,5*R*)-4,6-Bis(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-hex-1-yn-3-ol (7b). The experimental procedure for synthesis of

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7b is the same as that of compound **7a**. **Analytical data of 7b**: colorless oil, the eluent for column chromatography: EtOAc–hexane (1/39, v/v); $[\alpha]_D^{28}$ = −5.37 (*c* 0.06 $CHCl_3$); R_f 0.36 (1/9, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 3H, CH_3), 0.11 (s, 3H, CH_3), 0.90 (s, 9H, 3 × CH_3), 2.47 (d, *J* = 3.5 Hz, 1H, 1-H), 2.97, 3.60 (d, *J* = 5.7 Hz, 2H, 6-H), 3.75–3.80 (m, 1H, 4-H), 4.01–4.08 (m, 1H, 5-H), 4.51 (s, 2H, CH_2Ph), 4.57–4.64 (m, 1H, 3-H), 4.66–4.86 (m, 2H, CH_2Ph), 7.30–7.35 (m, 10H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.74 (CH_3, OTBS), −4.23 (CH_3, OTBS), 18.25 (C_q, OTBS), 26.04 (3 × CH_3, OTBS), 61.52 (CH, 3-C), 71.40 (CH_2, 6-C), 71.93 (CH, 5-C), 73.56 (CH_2, CH_2Ph), 73.71 (CH, 1-C), 74.80 (CH_2, CH_2Ph), 81.53 (CH, 4-C), 83.80 (CH, 2-C), 127.80–128.58 (ArC), 138.06 (ArC_q), 138.25 (ArC_q); IR (neat, cm^{-1}) 3438, 1632, 772; ESI-HRMS *m*/*z* $[M + H]^+$: calcd for $C_{26}H_{36}O_4Si$ 441.2456, measured 441.2446.

(2*R*,3*S*,4*R*)-1,3,4-Tris(benzyloxy)hex-5-yn-2-ol (8a). To a stirred solution of compound **7a** (49 mg, 0.11 mmol) in dry THF (1 mL), sodium hydride (8 mg, 60% suspension in mineral oil), benzyl bromide (0.013 mL, 0.11 mmol) and TBAI (catalytic amount) were added at 0 °C and stirred at room temperature for 6 to 8 h. After completion of the reaction, THF was evaporated, extracted with $CHCl_3$, dried over Na_2SO_4, concentrated and evaporated under reduced pressure to obtain the crude product. This was dissolved in dry THF, cooled to 0 °C and TBAF (0.18 mmol, 1.0 M solution in THF) was slowly added. The mixture was allowed to stir at room temperature for 2 h. After completion of the reaction, the reaction mixture was quenched with water, THF was evaporated, extracted with $CHCl_3$, dried over Na_2SO_4 and concentrated under reduced pressure. The residue on purification by silica gel column chromatography afforded **8a** as a clear liquid (33.32 mg, 68% from **7a** over two steps). **Analytical data of 8a**: colorless oil, the eluent for column chromatography: EtOAc–hexane (1/19, v/v); $[\alpha]_D^{28}$ = −31.02 (*c* 0.20 $CHCl_3$); R_f 0.31 (3/17, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.54 (d, *J* = 1.9 Hz, 1H, 1-H), 3.46–3.56 (m, 2H, 6-H_a, 6-H_b), 3.70–3.79 (m, 1H, 4-H), 4.13 (s, 1H, 5-H), 4.39–4.43 (m, 1H, 3-H), 4.47–4.56 (m, 4H, 2 × CH_2Ph), 4.83–4.89 (m, 2H, CH_2Ph), 7.29–7.35 (m, 15H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 69.21 (CH, 3-C), 69.65 (CH, 5-C), 70.95 (CH_2, 6-C), 71.18 (CH_2, CH_2Ph), 73.52 (CH_2, CH_2Ph), 74.54 (CH_2, CH_2Ph), 75.78 (CH, 1-C), 79.59 (CH, 4-C), 81.01 (C_q, 2-C), 127.88–128.61 (ArC), 137.34 (C_q), 137.93 (C_q), 137.98 (C_q), 138.16 (C_q); IR (neat, cm^{-1}) 3451, 2919, 2367, 1644, 1218, 768; ESI-HRMS *m*/*z* $[M + H]^+$: calcd for $C_{27}H_{28}O_4$ 417.2060, measured 417.2059.

(2*R*,3*R*,4*R*)-1,3,4-Tris(benzyloxy)hex-5-yn-2-ol (8b). The experimental procedure for synthesis of **8b** is the same as that of compound **8a**. **Analytical data of 8b**: colorless oil, the eluent for column chromatography: EtOAc–hexane (1/19, v/v); $[\alpha]_D^{28}$ = −50.77 (*c* 0.11 $CHCl_3$); R_f 0.31 (3/17, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.55 (d, *J* = 2.1 Hz, 1H, 1-H), 3.59–3.65 (m, 2H, 6-H), 3.73–3.76 (m, 1H, 4-H), 4.10–4.14 (m, 1H, 5-H), 4.41–4.64 (m, 5H, 2 × CH_2Ph + 3-H), 4.81–4.88 (m, 2H, CH_2Ph), 7.26–7.33 (m, 15H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 68.92 (CH, 3-C), 70.36 (CH, 5-C), 70.87 (CH_2, 6-C), 71.22 (CH_2, CH_2Ph), 73.58 (CH_2, CH_2Ph), 74.59 (CH_2, CH_2Ph), 76.18 (CH, 4-C), 80.28 (CH, 1-C), 80.57 (C_q, 2-C) 127.88–128.10 (ArC), 128.34–128.59 (ArC), 137.37 (ArC_q), 138.22 (ArC_q); IR (neat, cm^{-1}) 3429, 1636, 1217, 765; ESI-HRMS *m*/*z* $[M + H]^+$: calcd for $C_{27}H_{28}O_4$ 417.2060, measured 417.2060.

(2*S*,3*R*,4*R*)-1,3,4-Tris(benzyloxy)hex-5-yn-2-yl azide (9a). To a stirred solution of compound **8a** (114 mg, 0.273 mmol) and PPh_3 (574 mg, 2.19 mmol) in anhydrous THF (24 mL) were added DEAD (0.43 mL, 2.18 mmol) and DPPA (0.47 mL, 2.18 mmol) at −20 °C. The stirring was continued at −20 °C for 6 h and then the reaction mixture was gradually brought to room temperature and stirred overnight. On complete disappearance of the starting material on TLC, the solvent was evaporated under reduced pressure and the residue was subjected to flash column chromatography to give **9a** as a brown syrup (61.56 mg, 54% from **8a**). **Analytical data of 9a**: brown syrup, the eluent for column chromatography: EtOAc–hexane (1/49, v/v); $[\alpha]_D^{28}$ = −23.02 (*c* 0.0.43 $CHCl_3$); R_f 0.66 (3/17, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.49 (d, *J* = 2.2 Hz 1H, 1-H), 3.55–3.60 (m, 1H, 6-H), 3.66–3.76 (m, 3H, 4-H, 5-H, 6-H), 4.33–4.35 (m, 1H, 3-H), 4.42–4.55 (m, 4H, 2 × CH_2Ph), 4.76–4.81 (m, 2H, CH_2Ph), 7.22–7.26 (m, 15H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 61.84 (CH, 5-C), 69.68 (CH_2, 6-C), 70.34 (CH, 3-C), 71.25 (CH_2, CH_2Ph), 73.51 (CH_2, CH_2Ph), 74.64 (CH_2, CH_2Ph), 76.20 (CH, 1-C), 79.67 (CH, 4-C), 79.78 (C_q, 2-C), 127.82–128.61 (ArC), 137.46 (ArC_q), 138.00 (ArC_q); IR (neat, cm^{-1}) 3425, 2924, 2102, 1218, 766; ESI-HRMS *m*/*z* $[M + H]^+$: calcd for $C_{27}H_{27}N_3O_3$ 442.2125, measured 442.2125.

(2*R*,3*S*,4*R*)-1,3,4-Tris(benzyloxy)hex-5-yn-2-yl chloro(oxo)-methanesulfinate (9b). A solution of compound **8b** (89 mg, 0.21 mmol) and chloromethanesulphonyl chloride (0.02 mL, 0.22 mmol) in pyridine (1.5 mL) was stirred at rt for 7 to 10 minutes. On completion of the reaction, the mixture was diluted with ethyl acetate and washed with water and brine and dried over Na_2SO_4. The compound on purification by column chromatography yielded **9b** as a clear oil (100 mg, 88.5% from **8b**). **Analytical data of 9b**: reddish brown oil, the eluent for column chromatography: EtOAc–hexane (1/49, v/v); $[\alpha]_D^{28}$ = +15.12 (*c* 0.07 $CHCl_3$); R_f 0.46 (3/17, EtOAc–hexane) ^{1}H NMR (75 MHz, $CDCl_3$): δ 2.57 (d, *J* = 2.1 Hz, 1H, 1-H), 3.77–3.84 (m, 1H, 6-H_a), 3.89–3.94 (m, 1H, 6-H_b), 4.03–4.06 (m, 1H, 4-H), 4.29–4.31 (m, 1H, 5-H), 4.47–4.85 (m, 8H, 3 × CH_2Ph + 2H of OMsCl), 5.22–5.27 (m, 1H, 3-H), 7.30–7.32 (m, 15H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$): δ 54.23 (CH_2, OMsCl), 68.71 (CH_2, 6-C), 68.81 (CH, 5-C), 71.28 (CH_2, CH_2Ph), 73.55 (CH_2, CH_2Ph), 75.18 (CH_2, CH_2Ph), 77.20 (CH, 1-C), 79.30 (C_q, 2-C), 80.42 (CH, 4-C), 83.61 (CH, 3-C), 128.04–128.61 (ArC), 137.13 (ArC_q), 137.39 (ArC_q), 137.50 (ArC_q); IR (neat, cm^{-1}) 3230, 1638, 1217, 770; ESI-HRMS *m*/*z* $[M + H_2O]^+$: calcd for $C_{28}H_{29}ClO_6S$ 546.1474, measured 546.1700.

(2*R*,3*R*,4*R*)-1,3,4-Tris(benzyloxy)hex-5-yn-2-yl chloro(oxo)-methanesulfinate (9c). The experimental procedure for synthesis of **9c** is the same as that of compound **9b**. **Analytical data of 9c**: light orange oil, the eluent for column chromatography: EtOAc–hexane (1/49, v/v); $[\alpha]_D^{28}$ = −19.65 (*c* 0.15 CH_3OH) R_f 0.46 (3/17, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58 (d, *J* = 1.6 Hz, 1H, 1-H), 3.56–3.60 (m, 1H, 6-H),

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3.72–3.77 (m, 1H, 6-H), 3.88–3.91 (m, 1H, 4-H), 4.39–4.65 (m, 7H, 2 × CH_2Ph + CH_2 of OMsCl + 3-H), 4.81–4.94 (m, 2H, CH_2Ph), 5.11–5.15 (m, 1H, 5-H), 7.30–7.32 (m, 15H, ArH); ^{13}C NMR (200 MHz, $CDCl_3$): δ 54.43 (CH_2, OMsCl), 68.59 (CH, 3-C), 69.30 (CH_2, 6-C), 71.32 (CH_2, CH_2Ph), 73.70 (CH_2, CH_2Ph), 75.13 (CH_2, CH_2Ph), 76.42 (CH, 1-C), 78.79 (C_q, 2-C), 80.31 (CH, 4-C), 82.48 (CH, 5-C), 128.14–128.72 (ArC), 137.21 (ArC_q), 137.47 (ArC_q); IR (neat, cm^{-1}) 3436, 3020, 2400, 1216, 757; ESI-HRMS m/z $[M + Na]^+$: calcd for $C_{28}H_{29}ClO_6S$ 551.1266, measured 551.1268.

(2*R*,3*S*)-3-(1*R*,2*R*)-1,3-Bis(benzyloxy)-2-(*tert*-butyldimethylsilyloxy)propyl(oxiran-2-yl) methanol (10a). A solution of Ti (O-i-Pr)$_4$ (1.83 mL, 6.24 mmol) and D-(−)-diethyltartarate (1.16 mL, 6.79 mmol) in dry DCM (20 mL) was stirred at −25 °C for 0.5 h in the presence of MS 4 Å. To this mixture, a solution of substrate **4a** (6.24 g, 14.09 mmol) in dry DCM (20 mL) was added and the mixture was stirred at the same temperature. After 0.5 h of stirring, a 6.0 M solution of *t*-BuOOH (11.25 mL, 67.5 mmol) was added and the temperature of the reaction was raised to 0 °C and was left for stirring till the completion of the reaction. After completion, 10% solution of tartaric acid (20 mL) was added to quench the reaction at 0 °C and stirred for 0.5 h. The solution was filtered through a Celite pad. The organic layer was extracted with DCM, concentrated, dissolved in ether (15 mL) and again cooled to 0 °C. To this 4% NaOH in brine solution was added and stirred for 15–20 minutes. The organic layer was extracted with ether, dried over Na_2SO_4, concentrated and evaporated under reduced pressure to obtain clear oil which on column purification yielded **10a** (2.3 g, 35.6% from **4a**). **Analytical data of 10a**: pale yellow oil, the eluent for column chromatography: EtOAc–hexane (9/91, v/v); $[\alpha]_D^{28}$ = −6.57 (*c* 0.25 CH_3OH) R_f 0.46 (1/4, EtOAc–hexane); ^1H NMR (300 MHz, $CDCl_3$): δ 0.00–0.09 (m, 6H, 2 × CH_3), 0.87–0.89 (m, 9H, 3 × CH_3), 3.06–3.26 (m, 2H, 2-H + 3-H), 3.48–4.02 (m, 6H, 1-H + 4-H + 5-H + 6-H), 4.40–4.83 (m, 4H, 2 × CH_2Ph), 7.31–7.36 (m, 10H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.76 (CH_3, OTBS), −4.46 (CH_3, OTBS),18.24 (C_q, OTBS), 25.98 (3 × CH_3, OTBS), 54.76 (CH, 3-C), 56.38 (CH, 2-C), 61.71 (CH_2, 1-C), 71.56 (CH_2, 6-C), 72.37 (CH_2, CH_2Ph), 72.88 (CH, 5-C), 73.68 (CH_2, CH_2Ph), 81.21 (CH, 4-C), 127.93–128.51 (ArC), 138.22 (ArC_q), 138.42 (ArC_q); IR (neat, cm^{-1}) 3433, 2925, 2856, 1366, 698 ESI-HRMS m/z $[M + Na]^+$: calcd for $C_{26}H_{38}O_5Si$, 481.2381, measured 481.2408.

((2*R*,3*S*)-3-((1*S*,2*R*)-1,3-Bis(benzyloxy)-2-(*tert*-butyldimethylsilyloxy)propyl)oxiran-2-yl) methanol (10b). The experimental procedure for synthesis of **10b** is the same as that of compound **10a**. **Analytical data of 10b**: colorless oil, the eluent for column chromatography: EtOAc–hexane (9/91, v/v); $[\alpha]_D^{28}$ = +8.12 (*c* 0.51 CH_3OH), R_f 0.46 (1/4, EtOAc–hexane); ^1H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 6H, 2 × CH_3), 0.89 (s, 9H, 3 × CH_3), 3.13–3.15 (m, 1H, 3-H), 3.20–3.22 (m, 1H, 2-H), 3.48–3.63 (m, 4H, 6-H + 1-H + 4-H), 3.82 (dd, *J* = 2.28, 12.6, 1H, 1-H), 4.03 (dd, *J* = 5.4, 9.15, 1H, 5-H), 4.50 (s, 2H, CH_2Ph), 4.59 (s, 2H, CH_2Ph), 7.24–7.31 (m, 10H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.67 (CH_3, OTBS), −4.45 (CH_3, OTBS), 18.29 (C_q, OTBS), 25.98 (3 × CH_3, OTBS), 54.91 (CH, 2-C), 55.98 (CH, 3-C), 61.68 (CH_2, 1-C), 71.70 (CH_2, 6-C), 73.26 (CH, 5-C), 73.55 (CH_2, CH_2Ph), 73.57 (CH_2, CH_2Ph), 78.38 (CH, 4-C), 127.76–128.49 (ArC), 138.31 (ArC_q), 138.62 (ArC_q); IR (neat, cm^{-1}) 3264, 2924, 1638, 1217, 762; ESI-HRMS m/z $[M + Na]^+$: calcd for $C_{26}H_{38}O_5Si$ 481.2381, measured 481.2379.

((1*R*,2*R*)-1,3-Bis(benzyloxy)-1-((2*R*,3*S*)-3-(chloromethyl)oxiran-2-yl)propan-2-yloxy)(*tert*-butyl)dimethylsilane (11a). The experimental procedure for synthesis of **11a** is the same as that of compound **6a**. **Analytical data of 11a**: colorless oil, the eluent for column chromatography: EtOAc–hexane (1/99, v/v); $[\alpha]_D^{28}$ = −1.13 (*c* 0.07 CH_3OH) R_f 0.68 (1/4, EtOAc–hexane); ^1H NMR (300 MHz, $CDCl_3$): δ 0.01–0.08 (m, 6H, 2 × CH_3), 0.86–0.89 (m, 9H, 3 × CH_3), 3.12–3.27 (m, 3H, 2-H + 3-H + 4-H), 3.35–3.87 (m, 4H, 1-H + 6-H), 3.93–4.06 (m, 1H, 5-H), 4.50–4.81 (m, 4H, 2 × CH_2Ph), 7.26–7.34 (m, 10H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.82 (CH_3, OTBS), −4.47 (CH_3, OTBS), 18.15 (C_q, OTBS), 25.94 (3 × CH_3, OTBS), 44.51 (CH_2, 1-C), 53.85 (CH, 3-C), 58.81 (CH, 2-C), 71.51 (CH_2, 6-C), 72.35 (CH_2, CH_2Ph), 72.85 (CH, 5-C), 73.51 (CH_2, CH_2Ph), 80.43 (CH, 4-C), 127.74–128.39 (ArC), 138.16–138.25 (ArC_q); IR (neat, cm^{-1}) 3269, 1639, 1217, 764 ESI-HRMS m/z $[M + Na]^+$: calcd for $C_{26}H_{37}ClO_4Si$, 499.2042, measured 499.2039.

((1*S*,2*R*)-1,3-Bis(benzyloxy)-1-((2*R*,3*S*)-3-(chloromethyl)oxiran-2-yl)propan-2-yloxy) (*tert*-butyl)dimethylsilane (11b). The experimental procedure for synthesis of **11b** is the same as that of compound **6a**. **Analytical data of 11b**: colorless oil, the eluent for column chromatography: EtOAc–hexane (1/99, v/v); $[\alpha]_D^{28}$ = +7.44 (*c* 0.37, CH_3OH), R_f0.68 (1/4, EtOAc–hexane); ^1H NMR (300 MHz, $CDCl_3$): 0.06 (s, 6H, 2 × CH_3), 0.89 (s, 9H, 3 × CH_3), 3.15–3.22 (m, 2H, 2-H + 3-H), 3.41–3.63 (m, 5H, 1-H + 4-H + 6-H), 4.03 (dd, *J* = 5.3, 9.1, 1H, 5-H), 4.49–4.64 (m, 4H, 2 × CH_2Ph), 7.24–7.31 (m, 10H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.62 (CH_3, OTBS), −4.42 (CH_3, OTBS), 18.32 (C_q, OTBS), 26.01 (3 × CH_3, OTBS), 44.70 (CH_2, 1-C), 54.97 (CH, 2-C), 57.73 (CH, 3-C), 71.65 (CH_2, 6-C), 73.30 (CH, 5-C), 73.56 (CH_2, 2 × CH_2Ph), 78.15 (CH, 4-C), 127.78–128.77 (ArC), 138.32 (ArC_q), 138.51 (ArC_q); IR (neat, cm^{-1}) 2923, 2853, 1218, 770; ESI-HRMS m/z $[M + Na]^+$: calcd for $C_{26}H_{37}ClO_4Si$ 499.2042, measured 499.2039.

(3*S*,4*R*,5*R*)-4,6-Bis(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-hex-1-yn-3-ol (12a). The experimental procedure for synthesis of **12a** is the same as that of compound **7a**. **Analytical data of 12a**: colorless oil, the eluent for column chromatography: EtOAc–hexane (1/39, v/v); $[\alpha]_D^{28}$ = −3.34 (*c* 0.15, CH_3OH) R_f 0.36 (1/9, EtOAc–hexane); ^1H NMR (300 MHz, $CDCl_3$): δ 0.05–0.07 (m, 6H, 2 × CH_3), 0.87–0.88 (m, 9H, 3 × CH_3), 2.45–2.46 (m, 1H, 1-H), 3.53–3.70 (m, 3H, 4-H, 6-H), 4.01–4.06 (m, 1H, 5-H), 4.47–4.56 (m, 2H, CH_2Ph), 4.61–4.66 (m, 1H, 3-H), 4.70–4.87 (m, 2H, CH_2Ph), 7.32–7.36 (m, 10H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.83 (CH_3, OTBS), −4.39 (CH_3, OTBS), 18.33 (C_q, OTBS), 26.01 (3 × CH_3, OTBS), 61.21 (CH, 3-C), 71.59 (CH_2, 6-C), 71.96 (CH, 5-C), 73.60 (2 × CH_2, 1-C + CH_2Ph), 74.61 (CH_2, CH_2Ph), 82.33 (CH, 4-C), 83.92 (C_q, 2-C), 127.83–128.56 (ArC), 138.11 (ArC_q), 138.23 (ArC_q); IR (neat, cm^{-1}) 3278, 2921, 1217, 764; ESI-HRMS m/z $[M + Na]^+$: calcd for $C_{26}H_{36}O_4Si$, 463.2275, measured 463.2274.

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(3*S*,4*S*,5*R*)-4,6-Bis(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-hex-1-yn-3-ol (12b). The experimental procedure for synthesis of **12b** is the same as that of compound **7a**. **Analytical data of 12b**: colorless oil, the eluent for column chromatography: EtOAc–hexane (1/39, v/v); $[\alpha]_D^{28}$ = +16.11 (*c* 0.24, CH_3OH) R_f 0.36 (1/9, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 3H, CH_3), 0.09 (s, 3H, CH_3), 0.89 (s, 9H, 3 × CH_3), 2.46 (d, *J* = 2.0 Hz, 1H, 1-H), 3.53–3.58 (m, 1H, 6-H), 3.70–3.77 (m, 2H, 4-H + 6-H), 4.11–4.16 (m, 1H, 5-H), 4.48–4.76 (m, 5H, 3-H + 2 × CH_2Ph), 7.22–7.33 (m, 10H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.75 (CH_3, OTBS), −4.30 (CH_3, OTBS), 18.18 (C_q, OTBS), 25.98 (3 × CH_3, OTBS), 63.75 (CH, 3-C), 71.12 (CH_2, 6-C), 72.81 (CH, 5-C), 73.59 (CH_2, CH_2Ph), 74.40 (CH_2, CH_2Ph), 74.40 (CH, 1-C), 82.41 (CH, 4-C), 82.86 (CH, 2-C), 127.88–128.55 (ArC), 137.83 (ArC_q), 138.39 (ArC_q); IR (neat, cm^{-1}) 2849, 1637, 1217, 670; ESI-HRMS *m*/*z* $[M + Na]^+$: calcd for $C_{26}H_{36}O_4Si$ 463.2275, measured 463.2271.

(2*R*,3*S*,4*S*)-1,3,4-Tris(benzyloxy)hex-5-yn-2-ol (13a). The experimental procedure for synthesis of **13a** is the same as that of compound **8a**. **Analytical data of 13a**: colorless oil, the eluent for column chromatography: EtOAc–hexane (1/19, v/v); $[\alpha]_D^{28}$ = +35.96 (*c* 0.04); R_f 0.31 (3/17, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57 (d, *J* = 2.0 Hz, 1H, 1-H), 3.40–3.51 (m, 2H, 6-H), 3.75–3.78 (m, 1H, 4-H), 4.19 (d, *J* = 4.8 Hz, 1H, 3-H), 4.40–4.60 (m, 5H, 5-H + 2 × CH_2Ph), 4.85–4.94 (m, 2H, CH_2Ph), 7.28–7.34 (m, 15H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 70.26 (CH, 3-C), 71.17 (CH + CH_2, 5-C + 6-C), 71.49 (CH_2, CH_2Ph), 73.45 (CH_2, CH_2Ph), 75.29 (CH_2, CH_2Ph), 76.57 (CH, 1-C), 80.01 (CH, 4-C), 80.29 (C_q, 2-C), 128.01–128.56 (ArC), 137.60–138.21 (ArC_q); IR (neat, cm^{-1}) 3371, 2923, 1639, 766; ESI-HRMS *m*/*z* $[M + NH_4]^+$: calcd for $C_{27}H_{28}O_4$ 434.2326, measured 434.2316.

(2*R*,3*R*,4*S*)-1,3,4-Tris(benzyloxy)hex-5-yn-2-ol (13b). The experimental procedure for synthesis of **13b** is the same as that of compound **8a**. **Analytical data of 13b**: colorless oil, the 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, 1-H), 3.54–3.66 (m, 2H, 6-H), 3.77–3.85 (m, 1H, 4-H), 3.94 (s, 1H, 5-H), 4.42–4.92 (m, 7H, 3 × CH_2Ph + 3-H), 7.23–7.35 (m, 10H, ArH); ^{13}C NMR (300 MHz, $CDCl_3$): δ 70.66 (CH, 5-C), 70.88 (CH_2, 6-C), 71.25 (CH, 3-C), 71.40 (CH_2, CH_2Ph), 73.49 (CH_2, CH_2Ph), 74.30 (CH_2, CH_2Ph), 76.90 (CH, 1-C), 80.00 (C_q, 2-C), 80.31 (CH, 4-C), 127.78–128.54 (ArC), 137.72 (ArC_q), 138.05 (ArC_q), 138.37 (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.

(2*R*,3*R*,4*S*)-1,3,4-Tris(benzyloxy)hex-5-yn-2-yl chloro(oxo)-methanesulfinate (14a). The experimental procedure for synthesis of **14a** is the same as that of compound **9b**. **Analytical data of 14a**: reddish brown oil, the eluent for column chromatography: EtOAc–hexane (1/49, v/v); $[\alpha]_D^{28}$ = +29.44 (*c* 0.31 CH_3OH) R_f 0.46 (3/17, EtOAc–hexane) ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.62 (d, *J* = 1.7 Hz, 1H), 3.59–3.71 (m, 2H, 6-H), 3.89 (t, *J* = 5.2 Hz, 1H, 4-H), 4.32–4.36 (m, 1H, 3-H), 4.40–4.88 (m, 8H, 3 × CH_2Ph + 2 × CH_2 of OMsCl), 5.11–5.16 (m, 1H, 5-H), 7.25–7.32 (m, 15H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 54.41 (CH_2, OMsCl), 68.91 (CH, 3-C), 69.17 (CH_2, 6-C), 71.39 (CH_2 CH_2Ph), 73.62 (CH_2 CH_2Ph), 75.35 (CH_2 CH_2Ph), 78.89 (CH, 4-C), 79.14 (C_q, 2-C), 83.58 (CH, 5-C), 128.13–128.68 (ArC), 137.00–137.51 (ArC_q); IR (neat, cm^{-1}) 3436, 1635, 1219, 772; ESI-HRMS *m*/*z* $[M + NH_4]^+$: calcd for $C_{28}H_{29}ClO_6S$, 546.1712, measured 546.1699.

(2*R*,3*S*,4*S*)-1,3,4-Tris(benzyloxy)hex-5-yn-2-yl chloro(oxo)-methanesulfinate (14b). The experimental procedure for synthesis of **14b** is the same as that of compound **9b**. **Analytical data of 14b**: light orange oil, the eluent for column chromatography: EtOAc–hexane (1/49, v/v); $[\alpha]_D^{28}$ = +14.80 (*c* 0.28 CH_3OH) R_f 0.46 (3/17, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.56 (d, *J* = 1.7 Hz, 1H, 1-H), 3.69–3.81 (m, 2H, 6-H), 4.02 (dd, *J* = 3.4, 5.9 Hz, 1H, 4-H), 4.24–4.27 (m, 1H, 3-H), 4.41–4.84 (m, 8H, 3 × CH_2Ph + CH_2 of OMsCl), 5.19–5.23 (m, 1H, 5-H), 7.24–7.32 (m, 15H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 54.35 (CH_2, OMsCl), 68.68 (CH, 3-C), 68.84 (CH_2, 6-C), 71.08 (CH_2, CH_2Ph), 73.64 (CH_2, CH_2Ph), 74.79 (CH_2, CH_2Ph), 76.36 (CH, 1-C), 79.68 (C_q, 2-C), 80.40 (CH, 4-C), 84.19 (CH, 5-C), 128.06–128.68 (ArC), 136.94 (ArC_q), 137.45 (ArC_q); IR (neat, cm^{-1}) 2853, 1606, 1461, 1217, 763; ESI-HRMS *m*/*z* $[M + NH_4]^+$: calcd for $C_{28}H_{29}ClO_6S$ 546.1712, measured 546.1708.

(4*R*,5*S*,6*S*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazole (15a). Any of the procedure **p**, **q**, **r** or **s** can be followed for the cycloaddition reaction.

***Procedure p*:** To a 20 mL two necked oven dried round bottom flask fitted with a reflux condenser and septum was added a solution of compound **9a** (39 mg, 0.088 mmol) dissolved in dry degassed toluene (3 mL) through a syringe. The reaction mixture was refluxed for 4.5 h. After complete disappearance of azido alkyne (as indicated by monitoring the reaction by TLC), the reaction mixture was cooled to room temperature. The solvent was removed under vacuum and the product was purified by silica gel chromatography to yield the 1,5-triazole **15a** as a clear oil (30.5 mg, 78% from **9a**).

***Procedure q*:** To a 20 mL two necked oven dried round bottom flask fitted with a reflux condenser and septum was added Cp*RuCl$(PPh_3)_2$ (3.3 mg, 5 mol%) under a nitrogen atmosphere. To this was added a solution of compound **9a** (42 mg, 0.10 mmol) dissolved in dry degassed toluene (3 mL) through a syringe. The reaction mixture was refluxed for 2 h. After complete disappearance of azido alkyne (as indicated by monitoring the reaction by TLC), the reaction mixture was cooled to room temperature. The solvent was removed under vacuum and the product was purified by silica gel chromatography to yield **15a** as a brown oil (37 mg, 88% from **9a**).

***Procedure r*:** To a 20 mL two necked oven dried round bottom flask fitted with a reflux condenser was added sodium azide (5 mg, 0.076 mmol), sealed with a septum and flushed with nitrogen. To this was added a solution of compound **9c** (20.5 mg, 0.038 mmol) dissolved in dry DMF (2 mL) through a syringe under a 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

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water. The aqueous layer was extracted with ethyl acetate, dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography to furnish **15a** as a clear oil (17 mg, 99% from **9c**).

***Procedure s*:** A sealed microwave vial containing sodium azide (6 mg, 0.092 mmol) was flushed with N_2 and to it was added chloromesylate **9c** (20 mg, 0.037 mmol) dissolved in dry DMF (2 mL) (kept in another flask under a N_2 atmosphere). The reaction mixture was heated to 80 °C for 2 h in a microwave reactor to allow the complete formation of the azido alkyne intermediate. CAUTION! The reaction should only be carried out in a microwave reactor that can withstand an explosion of the reaction vial as the reaction generating small alkyl azides is potentially explosive. The vial was taken out of the reactor and to it was injected a solution of the Cp*RuCl-$(PPh_3)_2$ catalyst (5 mol%, 1.5 mg) in dry DMF (0.5 mL) under a N_2 atmosphere. The reaction mixture was again heated up to 120 °C for 20 minutes. The resulting reaction mixture was diluted with water. The aqueous layer was extracted with ethyl acetate, dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography to furnish **15a** as pale brown oil (15 mg, 90% from **9c**).

Analytical data of 15a: pale brown liquid, the eluent for column chromatography: EtOAc–hexane (3/7, v/v); $[\alpha]_D^{28}$ = −28.19 (*c* 0.34 $CHCl_3$); R_f 0.19 (2/3, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92–3.96 (m, 1H, 9-H_a), 4.24–4.28 (m, 1H, 9-H_b), 4.43–4.78 (m, 8H, 3 × CH_2Ph + 7-H + 8-H), 4.86–4.87 (m, 1H, 6-H), 7.13–7.15 (m, 2H, ArH), 7.26–7.35 (m, 13H, ArH), 7.58 (s, 1H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 62.76 (CH, 8-C), 66.04 (CH_2, 9-C), 68.96 (CH, 6-C), 71.33 (CH_2, CH_2Ph), 72.75 (CH_2, CH_2Ph), 73.64 (CH_2, CH_2Ph), 81.87 (CH, 7-C), 127.82–128.76 (ArC), 129.46 (CH, 4-C), 136.98 (ArC_q), 137.16 (ArC_q), 137.50 (ArC_q), 138.80 (C_q, 5-C); IR (neat, cm^{-1}) 3419, 2925, 2363, 1637, 771; ESI-HRMS *m*/*z* $[M + H]^+$: calcd for $C_{27}H_{27}N_3O_3$ 442.2125, measured 442.2120.

(4*R*,5*R*,6*S*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazole (15b). For synthesis of **15b** procedures **r** and **s** were followed. **Analytical data of 15b**: colorless oil, the eluent for column chromatography: EtOAc–hexane (3/7, v/v); $[\alpha]_D^{28}$ = −58.95 (*c* 0.08 $CHCl_3$); R_f 0.19 (2/3, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88–3.99 (m, 2H, 9-H), 4.34–4.46 (m, 2H, CH_2Ph), 4.68–4.80 (m, 5H, 2 × CH_2Ph + 7-H), 4.86–4.89 (m, 1H, 8-H), 5.06 (d, *J* = 4.8 Hz, 1H, 6-H), 7.13–7.35 (m, 16H, ArH + 4-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 60.28 (CH, 8-C), 66.87 (CH_2, 9-C), 72.74 (CH_2, CH_2Ph), 73.53 (CH_2, CH_2Ph), 73.58 (CH_2, CH_2Ph), 77.48 (CH, 6-C), 87.39 (CH, 7-C), 127.59–128.79 (Ar C + CH), 137.16 (Ar C_q), 137.27 (Ar C_q), 137.71 (Ar C_q), 139.06 (C_q, 5-C); IR (neat, cm^{-1}) 3067, 1638, 1217, 767; ESI-HRMS *m*/*z* $[M + H]^+$: calcd for $C_{27}H_{27}N_3O_3$ 442.2125, measured 442.2125.

(4*S*,5*S*,6*S*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazole (16a). For synthesis of **16a** procedures **r** and **s** were followed. **Analytical data of 16a**: pale yellow syrup, the eluent for column chromatography: EtOAc–hexane (3/7, v/v); $[\alpha]_D^{28}$ = −0.42 (*c* 0.26 CH_3OH) R_f 0.19 (2/3, EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82–3.93 (m, 2H, 9-H), 4.45–4.58 (m, 7H, 8-H + 3 × CH_2Ph), 4.71 (t, *J* = 3.0 Hz, 1H, 7-H), 4.85 (d, *J* = 2.3 Hz, 6-H), 7.18–7.28 (m, ArH, 15H), 7.42 (s, 1H, 4-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 64.03 (CH, 8-C), 68.40 (CH_2, 9-C), 72.02 (CH_2, CH_2Ph), 72.49 (CH_2, CH_2Ph), 73.73 (CH_2, CH_2Ph), 76.98 (CH, 6-C), 89.96 (CH, 7-C), 127.91–128.96 (ArC + 4-C), 136.93–137.49 (ArC_q), 139.15 (C_q, 5-C); IR (neat, cm^{-1}) 3438, 1638, 767; ESI-HRMS *m*/*z* $[M + H]^+$: calcd for $C_{27}H_{27}N_3O_3$ 442.2125, measured 443.2172.

(4*S*,5*R*,6*S*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazole (16b). For synthesis of **16b** procedure **r** was followed. **Analytical data of 16b**: colorless oil, the 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, 9-H_a), 4.11 (dd, *J* = 4.4, 10.5 Hz, 1H, 9-H_b), 4.50–4.79 (m, 8H, 3 × CH_2Ph + 7-H + 8-H), 4.91–4.98 (m, 1H, 6-H), 7.25–7.36 (m, 15H, ArH), 7.56 (s, 1H, 4-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 60.63 (CH, 6-C), 69.11 (CH_2, 9-C), 69.23 (CH, 8-C), 71.57 (CH_2, CH_2Ph), 72.76 (CH_2, CH_2Ph), 73.49 (CH_2, CH_2Ph), 81.16 (CH, 7-C), 125.18 (CH, 4-C), 127.80–128.78 (ArC), 136.87–137.96 (C_q, ArC_q + 5-C); 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.

(4*R*,5*S*,6*S*)-6-(Hydroxymethyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*c*]-[1,2,3]triazole-4,5-diol (17a). Conventional catalytic hydrogenation of **15a** was carried out with $Pd(OH)_2$ in MeOH for 10 h at room temperature. Then, the catalyst was filtered over Celite and the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to give **17a** as a colorless oil (17 mg from 44 mg **15a**, quantitative).

Analytical data of 17a: colorless oil, the eluent for column chromatography: MeOH–$CHCl_3$ (3/7, v/v); $[\alpha]_D^{28}$ = −23.60 (*c* 0.02 CH_3OH) R_f 0.5 (3/7, MeOH–$CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD): δ 7.68 (s, 1H, 4-H), 5.11 (d, *J* = 5.4 Hz, 1H, 6-H), 4.78 (t, *J* = 5.2 Hz, 1H, 7-H), 4.46–4.49 (m, 1H, 8-H), 4.25 (dd, *J* = 2.92, 12.20 Hz, 1H, 9-H), 4.03 (dd, *J* = 3.2, 12.20 Hz, 1H, 9-H). ^{13}C NMR (100 MHz, CD_3OD): 144.05 (C_q, 5-C), 129.14 (4-C), 78.25 (7-C), 68.19 (6-C), 65.96 (8-C), 60.49 (9-C); ESI-HRMS *m*/*z* $[M + H]^+$: calcd for $C_6H_9N_3O_3$ 172.07222, measured 172.06881.

(4*R*,5*R*,6*S*)-6-(Hydroxymethyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*c*]-[1,2,3]triazole-4,5-diol (17b). The experimental procedure for synthesis of **17b** is the same as that of compound **17a**. **Analytical data of 17b**: colorless oil, the eluent for column chromatography: MeOH–$CHCl_3$ (3/7, v/v); $[\alpha]_D^{28}$ = −27.70 (*c* 0.02 CH_3OH) R_f 0.5 (3/7, MeOH–$CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD): δ 7.64 (s, 1H, 4-H), 5.08 (d, *J* = 5 Hz, 1H, 6-H), 4.81–4.82 (m, 1H, 7-H), 4.75–4.78 (m, 1H, 8-H), 4.01–4.13 (m, 2H, 9-H).^{13}C NMR (100 MHz, CD_3OD): 143.35 (C_q, 5-C), 128.59 (4-C), 84.04 (7-C), 73.04 (6-C), 64.45 (8-C), 60.24 (9-C); ESI-HRMS *m*/*z* $[M + H]^+$: calcd for $C_6H_9N_3O_3$ 172.07222, measured 172.07208.

(4*S*,5*S*,6*S*)-6-(Hydroxymethyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*c*]-[1,2,3]triazole-4,5-diol (18a). The experimental procedure for synthesis of **18a** is the same as that of compound **17a**. **Analytical data of 18a**: colorless oil, the eluent for column chromatography: MeOH–$CHCl_3$ (3/7, v/v); $[\alpha]_D^{28}$ = −22.79 (*c* 0.02 CH_3OH)

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R_f 0.5 (3/7, MeOH–$CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD): δ 7.65 (s, 1H, 4-H), 4.92 (d, J = 3.2, 1H, 6-H), 4.67 (t, J = 3.84, 7.64 Hz, 1H, 7-H), 4.37 (dd, J = 3.9, 8.0 Hz, 1H, 8-H), 4.22 (dd, J = 3.9, 12.0 Hz, 1H, 9-H), 4.00 (dd, J = 3.9, 12.0 Hz, 1H, 9-H). ^{13}C NMR (100 MHz, CD_3OD): 143.62 (C_q, 5-C), 128.92 (4-C), 85.11 (7-C), 72.73 (6-C), 69.03 (8-C), 60.81 (9-C). ESI-HRMS m/z $[M + H]^+$: calcd for $C_6H_9N_3O_3$ 172.07222, measured 172.0717.

(4*S*,5*R*,6*S*)-6-(Hydroxymethyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*c*]-[1,2,3]triazole-4,5-diol (18b). The experimental procedure for synthesis of **18b** is the same as that of compound **17a. Analytical data of 18b**: colorless oil, the 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, 4-H), 5.22 (s, 1H, 6-H), 5.04 (s, 2H, 7-H + 8-H), 4.12 (dd, J = 18.36, 12.63 Hz, 2H, 9-H). ^{13}C NMR (100 MHz, CD_3OD): 143.43 (5-C), 129.01 (4-C), 76.29 (7-C), 65.27 (6-C), 64.27 (8-C), 59.60 (9-C). ESI-HRMS m/z $[M + H]^+$: calcd for $C_6H_9N_3O_3$ 172.07222, measured 172.07287.

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