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Ketenimine mediated synthesis of lactam iminosugars: development of one-pot process *via* tandem hydrative amidation of amino-alkynes and intramolecular transamidation

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ABSTRACT

Cu-catalysed ketenimine mediated multicomponent reaction led to an efficient installation of *N*-allyl *N*-sulfonyl amide functionality onto a sugar derived terminal alkyne via intramolecular 3,3 sigmatropic rearrangement of an initially formed *N*-sulfonyl imidate. This strategy is further extended to the application of hydrative amide synthesis on chiral alkynyl amines followed by in situ intramolecular transamidation which led to the development of a novel one-pot reaction for the construction of a δ-lactam iminosugar.

1. Introduction

Iminosugars are monosaccharide mimics with a nitrogen atom in place of ring oxygen atom.[1] Fig. 1 represents some biologically active polyhydroxylated piperidine iminosugars. Currently counted amongst the most promising classes of glycosidase inhibitors,[2] iminosugars are therapeutically relevant[3] largely because of their ability to act as transition state analogs of glycosidase catalysed pathway.[4] This analogy corresponds to the mimicry of the transition state of enzyme catalysed reaction by iminosugars either in terms of charge or shape or both.[5] Charge mimics are anticipated to replicate the positive charge distribution of the oxocarbenium ion-like transition state whereas compounds that mimic the planar geometry of the transition state are classified as Shape mimics. An important feature of the shape mimics is the presence of a trigonal centre at the anomeric position and/or the endocyclic oxygen of the corresponding substrate. Examples of non-iminosugar shape mimics include glyconohydroximolactam **8** and gluconolactam **9** (Fig. 2) which show low micromolar inhibition of glycosidases and iminosugar shape mimics **10** (Zanamivir or Relenza) and **11**

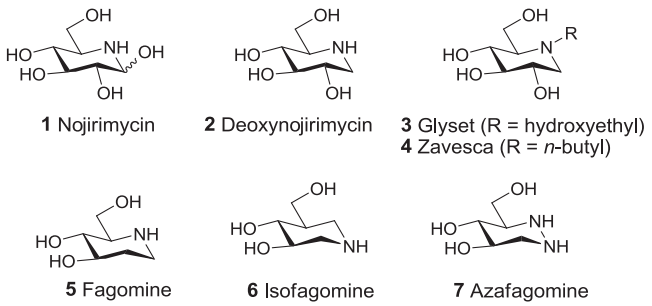

Fig. 1. Representative examples of polyhydroxylated piperidine iminosugars.

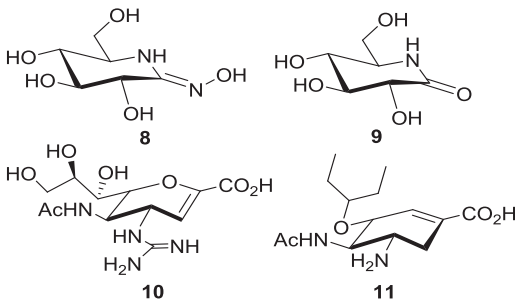

Fig. 2. Examples of shape mimics of transition state of glycosyl hydrolases.

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(Oseltamivir or Tamiflu) which are approved drugs and act against viral neuraminidases.

According to literature reports,[6] it is evident from the kinetic isotopic effect studies that during glycoside hydrolysis the transition state has various degrees of sp^2 hybridisation at the anomeric carbon. Lactone and lactam sugars have sp^2 carbon at the anomeric centre and thus inhibit glycosidases despite being uncharged which suggests that these molecules mimic the shape of the transition state very closely. Additionally the carbonyl group interacts with the catalytic acid residues thereby enhancing the binding affinity. Consequently, various lactam iminosugars have been synthesised and evaluated for glycosidase inhibition.[7] Some selected lactam iminosugars and their activity against glycosidases are represented in Fig. 3. For example, Isofagomine lactam **14** was found to be a xylanase inhibitor.[8a] The X-ray crystallographic studies revealed that this lactam bound to the enzyme as the amide tautomer.[8b]

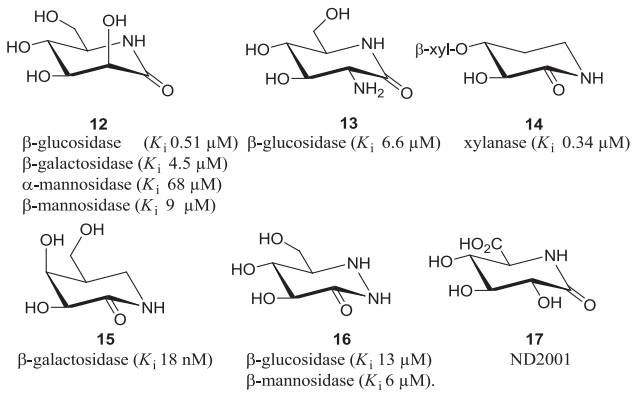


Fig. 3. Examples of iminosugar lactams as glycosidase inhibitors.

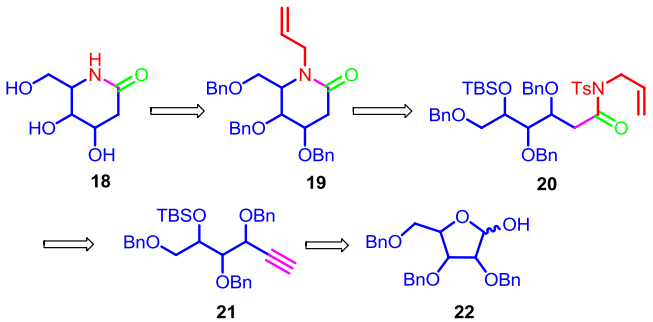
Lactam iminosugars are also known to act as anti-cancer agents. Inhibitors of both tumor metastasis and tumor angiogenesis are rapidly emerging as important drug candidates for cancer therapy. Iminosugars are found to interact with enzymes involved in metabolic pathway of glycans responsible for tumor cell invasion and migration. Sodium D-glucuro-*δ*-lactam (ND2001) **17** (Fig. 3) derived from Nojirimycin is known as a potent competitive β-D-glucoronidase inhibitor in vitro (IC_{50} 0.18 μM, bovine liver) and in vivo[9] and also inhibits invasion and metastasis of tumor cells.[10] Thus, lactam iminosugars hold promise for new drug candidates for cancer chemotherapy. A recent report describes N-arylated lactam iminosugars as potent immunosuppressive agents.[11]

Ketenimines, the imine analogues of ketenes, are an important class of reactive species and useful synthetic intermediates. Except for a few isolable ketenimines, these species are exceptionally labile and mostly prepared in situ as reactive intermediates followed by their use in one-pot reactions. They have been reported to undergo nucleophilic additions, radical additions, cycloaddition reactions, electrocyclic ring closure reactions and sigmatropic rearrangements.[12] Various methodologies involving these intermediates have been utilised to construct complex organic compounds and biologically attractive heterocycles. One of the interesting applications of ketenimines demonstrated by Chang and co-workers is the synthesis of amides via a copper-catalysed MCR involving the intermediacy of *N*-sulfonyl imidates.[13]

Our recent efforts in the construction of conformationally restricted iminosugars as glycosidase inhibitors gained success.[14] Inspired by the activity of lactam iminosugars and reactivity of ketenimine intermediates to form amides, we intended to install the amide functionality onto sugar motifs employing carbohydrate derived alkynes and alkynyl amines as one of the components of a three-component MCR. This would involve generation of sugar ketenimines followed by their conversion to sugar amides by trapping them with appropriate nucleophiles. These sugar amides could then be intramolecularly cyclised for the construction of lactam iminosugars. To the best of our knowledge, the use of ketenimine intermediates in sugar chemistry has so far not been explored. Furthermore, from the synthetic point of view, these polyhydroxylated lactams can also be exploited for the construction of iminosugar aglycone mimics through reductive alkylation to create quaternary centered and C-alkylated iminosugars which may further be elaborated to bicyclic and spiro templates for the synthesis of novel second-generation iminosugars.

2. Results and discussion

The retrosynthetic strategy for the construction of fagomine based lactam iminosugar **18** is represented in Scheme 1. Enantiopure acetylenes of general structure **21** are easily accessible from pentoses of type **22** employing Bestmann-Ohira reagent. The protected acetylene **21** could be used as the alkyne component of *N*-sulfonyl ketenimine mediated MCR to yield amide **20**. Amide **20** on deprotection of silyl ether and desulfonylation followed by subsequent cyclisation would furnish N-allylated iminosugar lactam **19** which after required deprotections would yield the desired fagomine lactam iminosugar **18**.



Scheme 1. Retro-analysis for the synthesis of Fagomine lactam iminosugars.

The proposed lactam derivative **36** of L-4-*epi*-fagomine **35** (Scheme 2) should be accessible from D-Ribose according to the above described strategy. To begin with, D-(−)-ribose was converted to its *O*-benzyl protected hemiacetal **23** according to literature procedures.[15] The hemiacetal **23** on treating with freshly prepared Bestmann-Ohira reagent[16] and K_2CO_3 as a base in MeOH at room temperature for 8–12 h furnished enantiopure terminal alkyne **24**.[17] The free hydroxyl group of **24** was protected as silyl ether using TBDMSCl and imidazole in DCM to give fully protected alkyne **25** for examining the intramolecular imidate-amide rearrangement on carbohydrate derived substrate.[18] The key reaction comprised of the synthesis of *N*-sulfonylimidate **26** from acetylene **25** via copper-catalysed MCR. For this **25** was treated with *p*-toluenesulfonyl azide and allyl alcohol using catalytic amount of copper (I) iodide and Et_3N as a base in anhydrous chloroform and N_2 atmosphere at room temperature to yield imidate **26** in 78% yield (Scheme 2).[13a]

The allylic imidate **26** was then subjected to a Pd-catalysed rearrangement to form tertiary amide **27** (Scheme 2) by treating it with 7–15 mol % of Pd (II) catalyst in DCE whereby it undergoes 3,3 sigmatropic rearrangement to yield *N*-allyl *N*-tosyl amide **27**.[19,20] This efficiency of this transformation was explored with two palladium catalysts *viz*. bis(acetonitrile)palladium (II) chloride,

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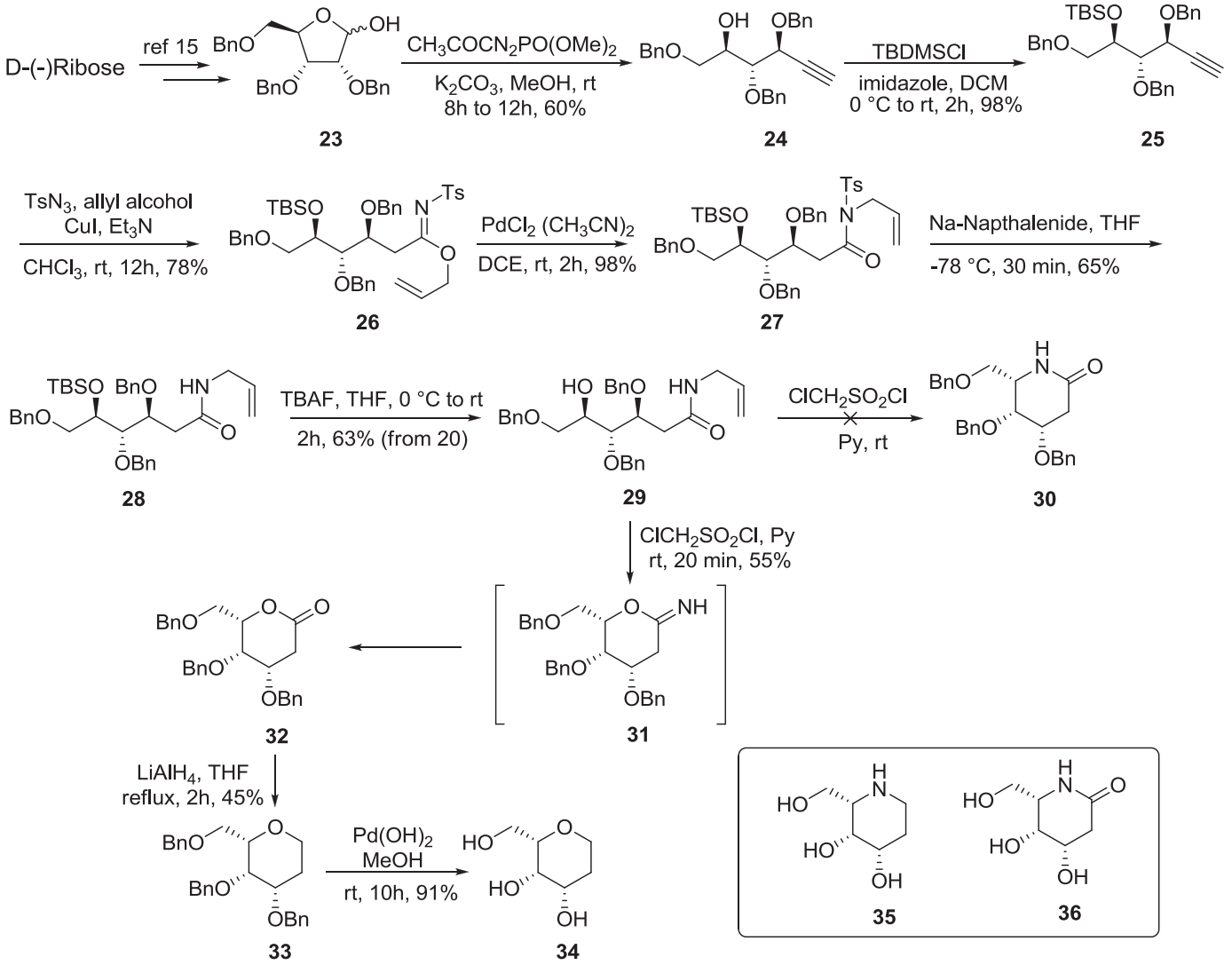

Scheme 2. Attempted synthesis of L-4-*epi*-fagomine.

$PdCl_2(CH_3CN)_2$ and bis(benzonitrile)palladium (II) dichloride, $PdCl_2(C_6H_5CN)_2$. The former palladium catalyst gave better yield in this case with lower catalyst loadings (7 mol% for $PdCl_2(CH_3CN)_2$ and 15 mol% for $PdCl_2(C_6H_5CN)_2$). An excess of catalyst loading or stirring for a prolonged time led to reduced yield due to formation of by-products. The rearranged product **27** could not be distinguished from its precursor **26** solely on the basis of TLC, ^{1}H NMR spectrum and HRMS. For imidate **26**, the ^{13}C NMR signal for oxygen bonded methylene carbon of *O*-allyl group appeared at δ 69.31 in ^{13}C NMR spectrum. For amide **27** this signal disappeared and instead a new signal appeared at δ 48.72 which corresponds to the nitrogen bonded methylene carbon of *N*-allyl group. Structure of amide **27** was thus assigned on the basis of ^{13}C and 2D NMR (Supplementary data).

The desulfonylation of *N*-sulfonyl functionality of amide **27** was then affected with sodium naphthalenide in THF at −78 °C under inert conditions whereby complete disappearance of starting material was observed in 15–20 min. The crude desulfonylated product **28** can be used without further purification for the silyl ether deprotection to furnish N-allylated tertiary amide **29**. When the free hydroxyl group of **29** was activated by its esterification either with methanesulfonyl or chloromethanesulphonyl chloride, formation of a single product was indicated (TLC). This product was completely characterised by its ^{1}H and ^{13}C NMR spectra which showed the disappearance of signals for allylic functionality and thus indicated that deallylation had taken place presumably due to the nucleophilicity of chloride ions from chloromethanesulfonyl chloride.

The structure was initially assigned as a cyclised product **30** on the basis of further support from DEPT and 2D spectra. However, the observed HRMS of product **30** was not in agreement with the calculated value (For compound **30**, the observed peak corresponding to $[M+H]^+$ ion was 433.1981 and was one unit more than the expected $[M+H]^+$ ion peak calculated 431.2097 for $C_{27}H_{29}NO_4$) which indicated that O-cyclisation has taken place instead of N-cyclisation. This could be attributed to the ambident nature of the amide functionality. The actual product formed was indicated to be **32** ($[M+H]^+$ calculated 433.2010 for $C_{27}H_{28}O_5$) which could have been formed by the initial formation of cyclic imidate **31** which is prone to hydrolysis under aqueous work up conditions.

To confirm this, the so formed product **32** was subjected to LAH reduction followed by debenzylation to afford **34**. The ^{1}H NMR of **34** did not match exactly with the supposed natural product, L-4-*epi*-fagomine, **35**. Thus **32** was identified to be a pyranone which on LAH reduction gave protected pyran **33** which on subsequent debenzylation led to the formation of a pyran **34** whose structure

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has not been previously reported in literature. The ambident nature of amide during its cyclisation onto alkene[21] and alkynes[22] and methods for regioselective N- or O-cyclisation is well documented in literature and is a current field of explorations.

Discouraged by the above results, we switched over to another cyclisation strategy which would involve oxidation of the secondary hydroxyl functionality of **29** to a ketone and simultaneous in situ generation of a cyclic *N*-acyliminium ion **37**.[23] For this purpose, oxidation under Albright Goldman conditions[24] was considered to be a method of choice for our sterically crowded substrate. Thus **29** was treated with a large excess of acetic anhydride in DMSO and the reaction mixture was either warmed to 40 °C for 2 h or allowed to stir at room temperature for 8−10 h. This led to the formation of cyclic N-allylated *N*-acyliminium ion **37** whose mass was confirmed by its HRMS data ($[M]^+$ calculated for $C_{30}H_{32}NO_4^+$ 470.2326 observed 470.2331). This *N*-acyl iminium ion was then reduced with $NaCNBH_3$ under acidic conditions using formic acid. This reaction proceeded with a concomitant deallylation to afford protected lactam iminosugar **30** as the major diastereomer. Lactam **30** was then debenzylated with H_2 in the presence of a catalytic $Pd(OH)_2/C$ in MeOH to yield the desired L-4-*epi*-fagomine lactam **36** (90% from **30**) (dr 89:11). For compound **30** NOESY correlations between H_4 and H_6 (Fig. 4) established the stereochemistry at *C*-6 and thus the stereochemical outcome of $NaCNBH_3$ reduction of *N*-acyliminium ion to form **30** as the major isomer can be explained as shown in Fig. 5.

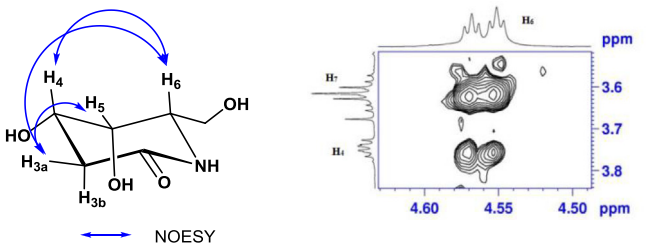


Fig. 4. (a) Selected NOESY interactions for L-4-*epi*-fagomine lactam **36**. (b) NOESY expansion of **36** showing correlation between $\mathbf{H_4}$ and $\mathbf{H_6}$.

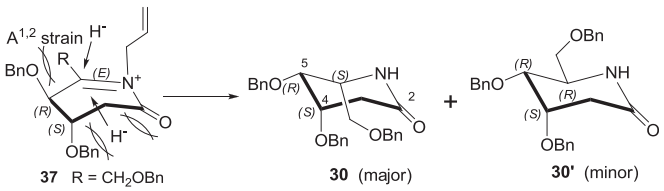
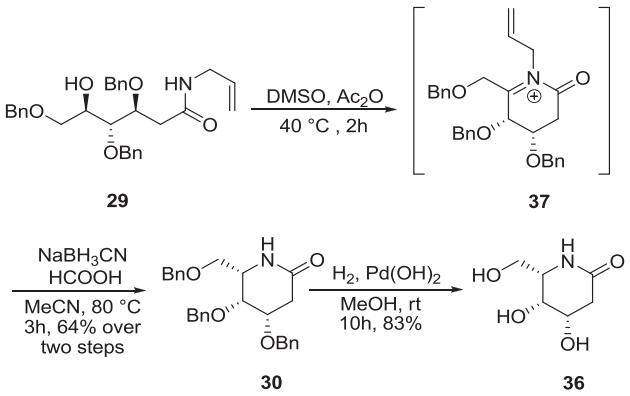


Fig. 5. Hydride ion attack on *N*-acyliminium ion **37** is favoured from the β-face of the iminium ion double bond to form **30** as a predominant product.

The *N*-acyliminium ion on reduction with hydride ion gives a mixture of **30** and **30′** (with concomitant deallylation) of which **30** is the predominant product formed which implicates the steric features of the transition state of the hydride addition to the intermediate **37**. The allylic 1,2 strain owing to C5-OBn and R (=CH_2OBn) in the transition state **37** (Fig. 5) favours the approach of the hydride ion from the β-face of the iminium ion double bond. Its approach from α-face of the iminium ion double bond will find steric crowding due to the axial C4-OBn and carbonyl functionality thus resulting in the formation of **30** as the major product. The enzyme inhibition studies of lactam iminosugar **36** and its reduction to natural product **35** are currently underway.

In continuation of our present efforts for application of MCRs for the synthesis of lactam type iminosugars, we tried the direct hydrative amide synthesis on alkynes. In this process water (instead of allyl alcohol) was employed as a nucleophile to trap the intermediate ketenimine to form amide directly from terminal alkynes.[13b] The application of this process to terminal alkyne with free hydroxyl group **17** led to the formation of desired amide in very low yield. When silyl ether protected terminal alkyne **25** was used, the desired amide was formed but on further deprotection of silyl ether functionality, the product obtained degraded on column purification. Similarly, when O-sulfonylated (mesylated/chloromesylated) alkyne substrates were subjected to similar reaction conditions, it formed a mixture of two inseparable products in low yield.

Since, the application of hydrative amide synthesis on variously modified alkyne substrates did not yield any promising result as described above, we turned our attention to the hydration of amino substituted alkynes to form amino-amides. Since amino-amides are prone to intramolecular transamidation reaction[25] under base catalysed conditions, we envisioned a one-pot procedure where the application of hydrative amide synthesis on alkynyl amine **38** would lead to the generation of amino-amide **40** with a concomitant base-mediated intramolecular aminolysis (transamidation) at room temperature yielding the protected lactam ring **30** in a one-pot fashion (Scheme 3).



Scheme 3. Synthesis of L-4-*epi*-fagomine.

We envisaged two different routes for the one-pot process. First route involved the conversion of alkyne functionality of amino-alkyne **38** to amide **40** with in situ base catalysed transamidation to form lactam **30** (Scheme 4). An alternative pathway would involve conversion of alkyne functionality of azido-alkyne **39** to azido-amide **41** followed by Staudinger ligation[26] that would again lead to in situ base mediated transamidation and hence formation of lactam **30**.

To accomplish this we synthesised the suitable alkynyl amine substrate **38** starting from D-ribose derived alkyne **24** (Scheme 5). For this, the terminal alkyne **24** was subjected to Mitsunobou[27] amination reaction conditions whereby it was treated with 2 equiv each of phthalimide, TPP and DIAD (diisopropyl azodicarboxylate) in dry THF under inert conditions to obtain the desired inverted phthalimido substituted alkyne **42** as a single stereoisomer. Complex **42** was column purified (65% from **24**) and subsequently hydrolysed by treating with $MeNH_2$[28] (40% aq soln) for 48 h to yield the required alkynyl amine **38**. Alternatively, the free hydroxyl functionality of **24** was esterified to **43** with chloromethanesulfonyl chloride. Compound **43** was then subjected to azidation by refluxing with NaN_3 in DMF at 80 °C for 4 h to obtain

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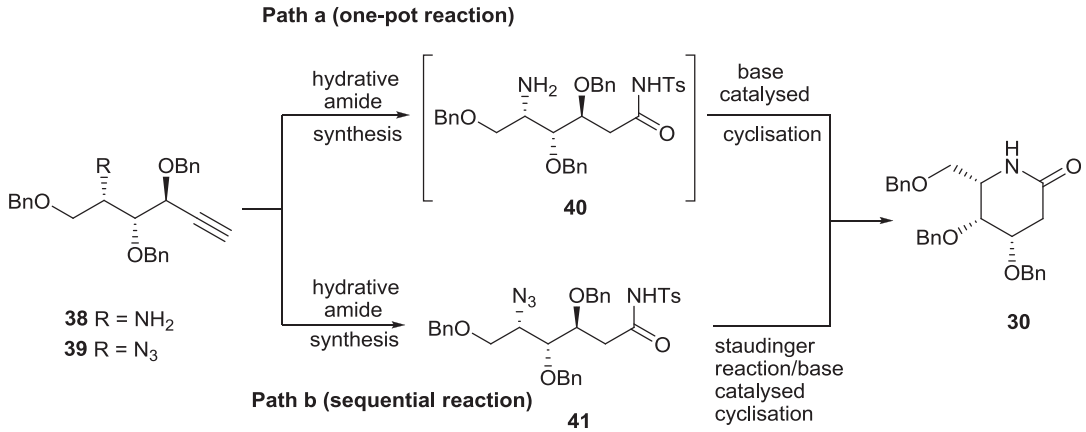
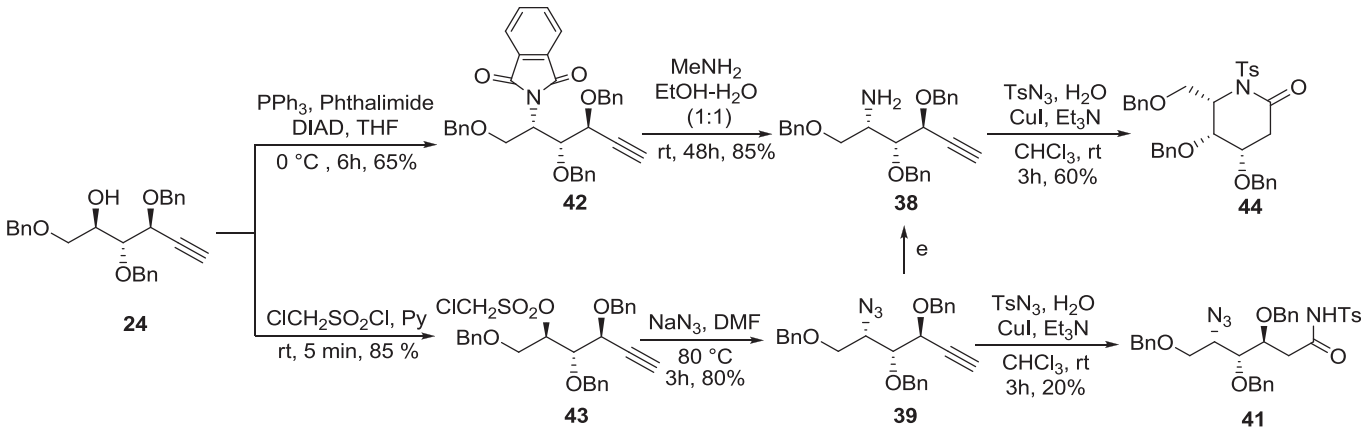


Scheme 4. Strategy for the synthesis of lactam **30** via one-pot reaction from alkynyl amine **38** (Path a) through intermediate amino-amide **40** or a sequential process from azido-alkyne **39** through intermediate azido-amide **41** (Path b).

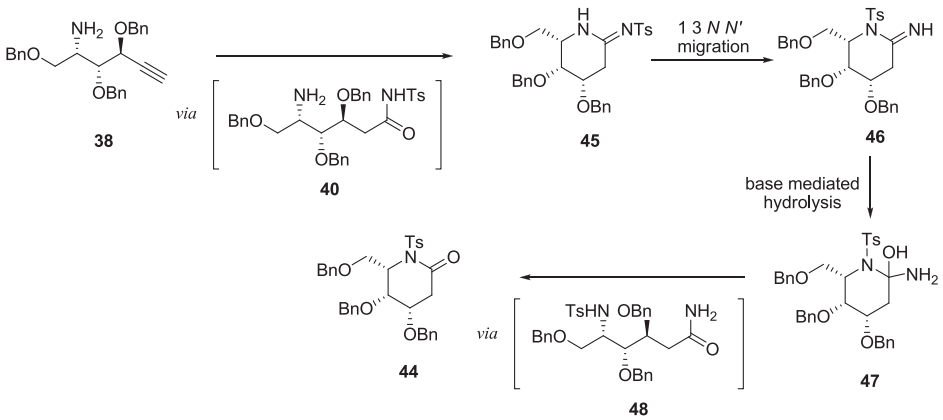


Scheme 5. Synthesis of *N*-sulfonyl lactam **44**.

the azido-alkyne **39**. Refluxing **39** with TPP, H_2O and THF under Staudinger ligation conditions afforded **38** in 75% yield.

This alkynyl amine **38** was then treated with *p*-toluenesulfonyl azide, water and CuI in $CHCl_3$ at room temperature under N_2 environment followed by slow addition of Et_3N and was allowed to stir till complete disappearance of starting material as monitored by TLC.[13b] To our surprise, we obtained a product whose mass neither corresponded to the *N*-sulfonyl amide product **40** (Scheme 4) nor to the expected cyclised product **30** that would have been formed via one pot sequence. It rather corresponded to the N-sulfonylated cyclised product **44** whose structure was later confirmed by NMR analysis. However, when **39** was subjected to hydrative amidation via similar method as described for alkynyl amine **38**, it led to the formation of azido-amide **41** with low yields and thus the method (Path b, Scheme 4) was not suitable for further transformations.

The formation of **44** can be explained by the initial formation of the *N*-sulfonyl amide **40** under reaction conditions from the alkynyl amine **38**, which then undergoes a base catalysed intramolecular transamidation reaction to form cyclic amidine **45** (Scheme 6). At



Scheme 6. Explanation for the formation of **44** from **38** involving 1, 3 *N*, *N*′ sulfonyl migration followed by hydrolysis of intermediate cyclic amidine **46**.

this stage 1, 3 *N*, *N*′ intramolecular tosyl migration takes place to form a rearranged cyclic amidine **46** whose hydrolysis then takes place which involves the formation of a tetrahedral intermediate **47**. This cyclic hemi-orthoamide **47** cleaves to amino-amide **48** first (kinetic product) which then cyclises to *N*-sulfonyl lactam **44** (thermodynamic product).[29]

3. Conclusions

In summary, the application of a copper-catalysed MCR employing carbohydrate derived terminal alkynes as one of the components led to the efficient installation of *N*-sulfonyl amide functionality on sugar substrates. The transformation of this sugar amide into sp^2 iminosugar, L-4-*epi*-fagomine lactam **36** was achieved, which shall be evaluated for glycosidase inhibition to explore the effect of sp^2 carbon at anomeric position. Lactam iminosugars of this type are synthetically useful intermediates as they are amenable to the construction of bicyclic, multibranched and spiro iminosugars in addition to N-alkylated and C-alkylated analogues. This feature opens up the possibility to synthesize and explore a range of structurally modified iminosugars for biological evaluation from a single template. The intramolecular reactions of the *N*-acyliminium ions have been widely used in the stereocontrolled syntheses of a variety of nitrogen heterocycles. Our current efforts involve exploitation of intermediate endocyclic *N*-allyl *N*-acyliminium ion **30** for the construction of bicyclic hybrid iminosugars.

The application of hydrative amide synthesis on chiral alkynyl amine followed by in situ transamidation led to the development of a novel one-pot reaction for the construction of *N*-sulfonyl δ-lactams from alkynes. The application of this one-pot process to construct lactams of various ring sizes in general, its substrate scope and synthesis of iminosugar lactams in particular is currently underway.

4. Experimental section

4.1. General methods

Organic solvents used in the present study were dried by standard methods. All the products were characterized by ^1H, ^{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 400 MHz (^1H) 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 chloroform 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.

4.2. *tert*-Butyldimethyl((2*R*,3*S*,4*S*)-1,3,4-tris(benzyloxy)hex-5-yn-2-yloxy)silane (25)

To a stirred solution of **24** (530 mg, 1.27 mmol) in DCM (10 mL), was added imidazole (370 mg, 5.43 mmol) and *tert*-butyl dimethylsilylchloride (530 mg, 150.72 mmol) at 0 °C and the reaction mixture was allowed to stir for 2 h. On completion, the reaction was quenched with aqueous NH_4Cl 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 **25** (662 mg, 98% from **24**). **Analytical data of 25**: Colorless oil, eluent for column chromatography: EtOAc/Hexane (1/49, 1/49 v/v); $[\alpha]_D^{28}$=+37.13 (*c* 0.00400 $CHCl_3$); R_f 0.8 (1/4, EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.82 (s, 9H), 2.52 (d, *J*=2.2 Hz, 1H), 3.52–3.61 (m, 2H), 3.8H (dd, *J*=6.9, 4.0 Hz, 1H), 3.99–4.03 (m, 1H), 4.44 (s, 2H), 4.50–4.54 (m, 2H), 4.67 (d, *J*=11.4 Hz, 1H), 4.90 (q, *J*=11.3 Hz, 2H), 7.25–7.38 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.9, −4.1, 18.2, 26.0, 71.0, 71.10, 72.3, 73.4, 74.6, 75.8, 80.5, 81.2, 127.6–128.5, 137.8, 138.5, 138.8; IR (neat, cm^{-1}) 3397, 1631, 1403, 1217, 770; ESI-HRMS *m*/*z* $[M+H]^+$: calcd for $C_{33}H_{42}O_4Si$ 531.2925, measured 531.2923.

4.3. (3*S*,4*S*,5*R*,*Z*)-Allyl3, 4, 6-tris (benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-*N*-tosylhexanimidate (26)

To a stirred mixture of protected alkyne **25** (472 mg, 0.89 mmol), *p*-toluenesulfonyl azide (0.16 mL, 1.07 mmol), allyl alcohol (0.072 mL, 1.07 mmol) and CuI (16.9 mg, 0.089 mmol) in $CHCl_3$ (5.0 mL) was slowly added Et_3N (0.12 mL, 0.89 mol) at room temperature under N_2 atmosphere. After stirring the reaction mixture for 12 h at room temperature, it was diluted with CH_2Cl_2 and then with aqueous NH_4Cl solution. The mixture was stirred for an additional 10 min at room temperature and two layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to obtain clear oil which on column purification yielded **26** (526 mg, 78% from **25**). **Analytical data of 26**: Colorless oil, eluent for column chromatography: EtOAc/Hexane (3/47, v/v); $[\alpha]_D^{28}$=−6.33 (*c* 0.00366 $CHCl_3$); R_f (0.46, 1/9 EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 0.14 (s, 6H), 0.98 (s, 9H), 2.46 (s, 3H), 3.23 (dd, *J*=15.4, 4.6 Hz, 1H), 3.60–3.73 (m, 3H), 3.86 (t, *J*=4.7 Hz, 1H), 4.05–4.15 (m, 1H), 4.39–4.64 (m, 7H), 4.73–4.85 (m, 2H), 5.22–5.29 (m, 2H), 5.77–5.87 (m, 1H), 7.26–7.42 (m, 17H), 7.85 (d, *J*=8.2, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.7 (CH_3), −4.3 (CH_3), 18.3 (C_q), 21.7 (CH_3), 26.1 (CH_3), 35.7 (CH_2), 69.2 (CH_2), 72.1 (CH_2), 72.3 (CH_2), 72.4 (CH), 73.5 (CH_2), 73.7 (CH_2), 76.8 (CH), 81.3 (CH), 119.7 (CH_2), 126.9 (CH), 127.5–128.4 (ArC), 129.4 (CH), 131.2 (CH), 138.4 (ArC_q), 138.5 (ArC_q), 138.8 (ArC_q), 139.4 (ArC_q), 143.1 (ArC_q), 173.8 (C_q). IR (neat, cm^{-1}) 3411, 1642, 1403, 1216, 699, 669; ESI-HRMS *m*/*z* $[M+H]^+$: calcd for $C_{43}H_{55}NO_7SSi$ 758.3541, measured 758.3525.

4.4. (3*S*,4*S*,5*R*)-*N*-Allyl-3, 4, 6-tris (benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-*N*-tosylhexanamide (27)

A mixture of imidate **26** (200 mg, 0.26 mmol) and $PdCl_2(CH_3CN)_2$ (6 mg, 0.02 mmol) in 1,2-dichloroethane (4 mL) was stirred for 2 h at room temperature. The organic solvent was evaporated under reduced pressure and the crude residue was purified by flash column chromatograph to give the desired product **27** (196 mg, 98% from **26**). **Analytical data of 27**: Colorless oil, eluent for column chromatography: EtOAc/Hexane (1/25, v/v); $[\alpha]_D^{28}$=−21.25 (*c* 0.00360 $CHCl_3$); R_f (0.46, 1/9 EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.91 (s, 9H), 2.37 (s, 3H), 2.28 (dd, *J*=16.8, 2.6 Hz, 1H), 3.09 (dd, *J*=16.8, 9.3 Hz, 1H), 3.53–3.62 (m, 2H), 3.73–3.76 (m, 1H), 3.95 (dd, *J*=9.6, 4.9 Hz, 1H), 4.30–4.34 (m, 1H), 4.93–4.64 (m, 8H), 5.20–5.30 (m, 2H), 5.83–5.92 (m, 1H), 7.13–7.16 (m, 4H), 7.26–7.37 (m, 13H), 7.80 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.7 (CH_3), −4.3 (CH_3), 18.3 (C_q), 21.7 (CH_3), 26.1 (CH_3), 38.4 (CH_2), 48.7 (CH_2), 72.2 (CH_2), 72.4 (CH), 72.7 (CH_2), 73.5 (CH_2), 73.8 (CH_2), 77.0 (CH), 80.7 (CH), 118.1 (CH_2), 127.5–128.5 (ArC), 129.6 (CH), 133.1 (CH), 137.0 (ArC_q), 138.4 (ArC_q), 138.7 (ArC_q), 138.8 (ArC_q), 144.5 (ArC_q), 171.8 (C_q); IR (neat, cm^{-1}) 4305, 3019, 2929, 1643, 1216, 669; ESI-HRMS *m*/*z* $[M+H]^+$: calcd for $C_{43}H_{55}NO_7SSi$ 758.3541, measured 758.3513.

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4.5. (3*S*,4*R*,5*R*)-*N*-Allyl-3, 4, 6-tris (benzyloxy)-5-hydroxyhexanamide (29)

To a solution of naphthalene (422 mg, 3.2 mmol) in dry THF (12 mL), sodium (94 mg, 4.1 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 1 h. A deep green color appeared. Then the stirring was stopped and the solution was allowed to stand for 30 min. *N*-sulfonyl amide **27** (248 mg, 0.32 mmol) was dissolved in THF (10 mL) and cooled to −78 °C. Then the Na-naphthalenide solution that was prepared initially was cannulated into it with stirring. After 15 min, the reaction was quenched with H_2O (5 mL) and extracted with EtOAc. EtOAc layer was washed sequentially with H_2O, brine and dried over anhydrous Na_2SO_4. The reaction mixture was concentrated in vacuo to obtain **28** (R_f (0.2, 1/9 EtOAc/Hexane)) which can be column purified (eluent for column chromatography: EtOAc/Hexane (1/9, v/v)) or can be used as such for silyl ether deprotection. Compound **28** (140 mg, 0.2 mmol) was dissolved in dry THF (7 mL), cooled to 0 °C and TBAF (0.67 mL, 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 **29** as a clear liquid (101 mg, 62.7% from **27**). **Analytical data of 29**: Colorless oil, eluent for column chromatography: EtOAc/Hexane (3/7, v/v); $[\alpha]_D^{28}$=+27.54 (*c* 0.00210 $CHCl_3$); R_f (0.2, 3/7 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.48–2.59 (m, 2H), 3.49 (dd *J*=9.6, 5.8 Hz, 1H), 3.57 (dd, *J*=9.7, 3.0 Hz, 1H), 3.67 (dd, *J*=7.8, 2.5 Hz, 1H), 3.71–3.78 (m, 3H), 4.22–4.25 (m, 1H), 4.40–4.51 (m, 4H), 4.58–4.71 (m, 2H), 4.97–5.07 (m, 2H), 5.62–5.72 (m, 1H), 5.93 (br s, 1H), 7.16–7.27 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.9, 37.9, 42.1, 70.4, 71.4, 72.6, 73.6, 73.9, 77.7, 79.8, 116.6, 127.9–128.6, 134.2, 138.1, 138.2, 138.4, 171.5; IR (neat, cm^{-1}) 3401, 3019, 2921, 1644, 1216, 699, 669; ESI-HRMS *m*/*z* $[M+H]^+$: calcd for $C_{30}H_{35}NO_5$ 490.2588, measured 490.2587.

4.6. (4*S*,5*S*,6*S*-4,5-bis (Benzyloxy)-6-(benzyloxymethyl) tetrahydro-2*H*-pyran-2-one (32)

A solution of compound **29** (100 mg, 0.2 mmol) and chloromethanesulphonyl chloride (0.01 mL, 0.12 mmol) in pyridine (1.5 mL) was stirred at room temperature for 20 min. On completion of the reaction, the mixture was diluted with ethyl acetate and washed with water and brine and dried over Na_2SO_4 and concentrated under reduced pressure. The residue on purification by column chromatography yielded **32** as a clear oil (48 mg, 54.5% from **29**). **Analytical data of 32**: Colorless oil, eluent for column chromatography: EtOAc/Hexane (3/17, v/v); $[\alpha]_D^{28}$=+4.50 (*c* 0.00200 $CHCl_3$); R_f (0.5, 3/7 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.78–2.93 (m, 2H), 3.59 (dd, *J*=9.2, 5.5 Hz, 1H), 3.66–3.70 (m, 1H), 3.77–3.82 (m, 1H), 4.10 (s, 1H), 4.24–4.27 (m, 1H), 4.37–4.58 (m, 5H), 4.87 (d, *J*=11.4 Hz, 1H), 7.18–7.31 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.2, 68.1, 70.5, 70.9, 73.9, 74.5, 74.6, 78.4, 127.7–128.8, 137.5, 137.7, 138.2, 169.2; IR (neat, cm^{-1}) 3400, 3256, 1755, 1631, 1443, 1217, 772; ESI-HRMS *m*/*z* $[M+H]^+$: calcd for $C_{27}H_{28}O_5$ 433.2010, measured 433.1981.

4.7. (2*S*,3*S*,4*S*)-3,4-bis (Benzyloxy)-2-(benzyloxymethyl) tetrahydro-2*H*-pyran (33)

A solution of **32** (57 mg, 0.13 mmol) in dry THF (3 mL) was stirred under nitrogen atmosphere 0 °C and $LiAlH_4$ (20 mg, 0.53 mmol) was added dropwise. The reaction mixture was then brought to room temperature and refluxed for 2 h, until TLC analysis showed the disappearance of the starting material. After completion, H_2O and a 15% aqueous NaOH solution were successively added to the mixture. The resulting mixture was filtered over a Celite pad and the filtrate was concentrated to afford a viscous liquid which on purification by column chromatography yielded **33** as a clear oil (25 mg, 45.4% from **32**). **Analytical data of 33**: Colorless oil, eluent for column chromatography: EtOAc/Hexane (1/19, v/v); $[\alpha]_D^{28}$=−13.31 (*c* 0.29 $CHCl_3$); R_f (0.4, 3/7 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.86–1.99 (m, 2H), 3.56–3.59 (m, 2H), 3.73–3.80 (m, 3H), 3.90–3.94 (m, 1H), 3.98–3.99 (m, 1H), 4.51–4.62 (m, 4H), 4.78 (dd, *J*=11.3, 36.0 Hz, 2H), 7.28–7.39 (m, 15 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.4 (CH_2), 60.2 (CH_2), 70.2 (CH), 71.2 (CH_2), 72.8 (CH_2), 73.6 (CH_2), 74.2 (CH_2), 78.5 (CH), 79.4 (CH), 128.0–128.7 (ArC), 138.0 (ArC_q), 138.1 (ArC_q), 138.1 (ArC_q); IR (neat, cm^{-1}) 3390, 1443, 1217, 772, 669; ESI-HRMS *m*/*z* $[M+H]^+$: calcd for $C_{27}H_{30}O_4$ 419.2217, measured 419.2175.

4.8. (2*S*,3*S*,4*S*)-2-(Hydroxymethyl) tetrahydro-2*H*-pyran-3,4-diol (34)

Conventional catalytic hydrogenation of **33** 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 removed under reduced pressure and residue was purified by silica gel column chromatography to give **34** as a colorless oil (8 mg, 91% from **33**). **Analytical data of 34**: Colorless oil, eluent for column chromatography: MeOH/$CHCl_3$ (3/17, v/v); $[\alpha]_D^{28}$=−14.80 (*c* 0.35 $CHCl_3$); R_f (0.5, 3/7 MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD): δ 1.67–1.74 (m, 1H), 1.96–2.04 (m, 1H), 3.5 (dd, *J*=7.4, 2.7 Hz, 1H), 3.65–3.73 (m, 2H), 3.75–3.86 (m, 3H), 3.93–3.97 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 34.7 (CH_2), 58.6 (CH_2), 63.1 (CH_2), 68.2 (CH), 70.5 (CH), 73.5 (CH); IR (neat, cm^{-1}) 3405, 3391, 786, 668; ESI-HRMS *m*/*z* $[M+H]^+$: calcd for $C_6H_{12}O_4$ 149.0808, measured 149.0793.

4.9. (4*S*,5*R*,6*S*)-4,5-bis (Benzyloxy)-6-(benzyloxymethyl) piperidine-2-one (30)

A solution of **29** (141 mg, 0.29 mmol) and acetic anhydride (0.60 mL, 6.38 mmol) in DMSO (1.2 mL) was warmed to 40 °C and allowed to stir at same temperature for 4 h. The mixture was then cooled to 0 °C and H_2O (2 mL) was added. The mixture was stirred for another 15 min and then extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The product was used for the next step without further purification. The resulting liquid was dissolved in CH_3CN (5.5 mL) and formic acid (1.2 mL) was added $NaCNBH_3$ (60 mg, 0.95 mmol) was then added and the mixture heated under reflux for 3 h. The mixture was then cooled at 0 °C and a 0.1 M aqueous HCl solution (8 mL) was added. The resulting mixture was poured into a 1:1 mixture of ethyl acetate/saturated aqueous $NaHCO_3$ (15 mL). The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue on purification by silica gel column chromatography afforded **30** as a clear liquid (79 mg, 63.7% over two steps from **29**). **Analytical data of 30**: Colorless oil, eluent for column chromatography: EtOAc/Hexane (1/9, v/v); $[\alpha]_D^{28}$=+20.14 (*c* 0.00230 $CHCl_3$); R_f (0.4, 3/7 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.55 (dd, *J*=3.7, 17.7 Hz, 1H), 2.91 (dd, *J*=17.7, 5.0 Hz, 1H), 3.69–3.77 (m, 2H), 3.95 (dd, *J*=7.8, 2.2 Hz, 1H), 4.00–4.03 (m, 1H), 4.46–4.63 (m, 6H), 4.70–4.74 (m, 1H), 7.24–7.33 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.8 (CH_2), 68.8 (CH_2), 70.0 (CH), 71.7 (CH_2), 72.3 (CH_2), 72.8 (CH), 73.8 (CH_2), 78.0 (CH), 127.9–128.7 (ArC), 137.6 (ArC_q), 137.9 (ArC_q), 168.9 (ArC_q); IR (neat, cm^{-1}) 3407, 3019, 1630, 1155, 669; ESI-HRMS *m*/*z* $[M+H]^+$: calcd for $C_{27}H_{29}NO_4$ 431.2169, measured 431.2097.

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4.10. (4*S*,5*R*,6*S*)-4,5-Dihydroxy-6-(hydroxymethyl)piperidin-2-one (36)

Conventional catalytic hydrogenation of **30** 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 removed under reduced pressure. The residue was purified by silica gel column chromatography to give **36** as a colorless oil (25 mg, 83.3% from **30**). **Analytical data of 36**: Colorless oil, eluent for column chromatography: MeOH/$CHCl_3$ (1/49, v/v); R_f (0.2, 1/4 MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD): δ 2.33 (dd, J=2.1, 18.0 Hz, 1H), 2.90 (dd, J=18.0, 6.8 Hz, 1H), 3.57–3.66 (m, 2H), 3.72–3.75 (m, 1H), 4.4 (dd, J=4.2, 1.6 Hz, 1H), 4.56 (td, J=1.9, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 39.1 (CH_2), 63.7 (CH_2), 68.3 (CH), 72.5 (CH), 90.1 (CH), 178.7 (C_q); IR (neat, cm^{-1}) 3431, 3258, 1711, 1631, 1443, 1217, 772, 669; ESI-HRMS m/z $[M+Na]^+$: calcd for $C_6H_{11}NO_4$ 185.0659, measured 185.0422.

4.11. 2-((2*S*,3*R*,4*S*)-1,3,4-tris (Benzyloxy) hex-5-yn-2-yl) isoindoline-1,3-dione (42)

A solution of phthalimide (70.6 mg, 0.48 mmol), triphenylphosphine (125 mg, 0.48 mmol), and alkyne **24** (100 mg, 0.24 mmol) in dry THF (2 mL) was cooled to 0 °C under argon atmosphere. An ice cooled solution of DIAD (0.09 mL, 0.48 mmol) in dry THF (0.5 mL) was added dropwise to the solution and then the reaction mixture was stirred at the same temperature for 2 h and then at room temperature until complete disappearance of starting material. The reaction mixture was evaporated under reduced pressure to give a residue, which on column chromatographic purification provided compound **42** (85 mg, 65% from **24**). **Analytical data of 42**: Colorless oil, eluent for column chromatography: EtOAc/Hexane (1/19, v/v); R_f (0.31, 3/17 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60–2.61 (m, 1H), 3.89–3.94 (m, 1H), 4.07–4.12 (m, 1H), 4.34–4.72 (m, 6H), 4.83–4.99 (m, 3H), 7.03–7.12 (m, 4H), 7.22–7.43 (m, 11H), 7.67–7.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.4 (CH), 67.0 (CH_2), 70.8 (CH), 71.2 (CH_2), 72.7 (CH_2), 74.3 (CH_2), 76.6 (CH), 78.2 (CH), 79.5 (C_q), 123.2 (CH), 127.4–128.5 (ArC), 132.0 (C_q), 133.7 (CH), 137.5 (ArC_q), 137.9 (ArC_q), 138.0 (ArC_q), 168.5 (C_q); IR (neat, cm^{-1}) 3425, 3305, 3019, 1633, 699, 669; ESI-HRMS m/z $[M+H]^+$: calcd for $C_{35}H_{31}NO_5$ 546.2275, measured 546.2274.

4.12. (2*S*,3*R*,4*S*)-1,3,4-tris(Benzyloxy)hex-5-yn-2-amine (38)

A solution of compound **42** (85 mg, 0.16 mmol) in EtOH/H_2O (1:1, 10 mL) was treated with a 40% aqueous solution of methyl amine (20 equiv) and stirred at room temperature for 48 h. The reaction mixture was then concentrated under reduced pressure, dissolved in water, and extracted with ethyl acetate. The combined organic extracts were washed twice with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was subjected to column for purification to obtain pure **38** as a clear oil (55 mg, 85% from **42**). **Analytical data of 38**: Colorless oil, eluent for column chromatography: EtOAc/Hexane (3/2, v/v); $[\alpha]_D^{28}$=+75.1781 (c 0.01731 $CHCl_3$); R_f (0.2, 3/7 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44 (d, J=2.08, 1H), 3.20–3.24 (m, 1H), 3.30–3.37 (m, 2H), 3.68 (dd, J=6.2, 3.1 Hz, 1H), 4.28–4.45 (m, 5H), 4.75–4.83 (m, 2H), 7.41–7.29 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.5 (CH), 69.2 (CH), 70.9 (CH_2), 72.5 (CH_2), 73.3 (CH_2), 74.6 (CH_2), 80.5 (CH), 81.6 (C_q), 127.8–128.6 (ArC), 137.6 (ArC_q), 138.3 (ArC_q), 138.5 (ArC_q); IR (neat, cm^{-1}) 3399, 3018, 2928, 1935, 698, 668; ESI-HRMS m/z $[M+H]^+$: calcd for $C_{27}H_{29}NO_3$ 416.2220, measured 416.2220.

4.13. (4*S*,5*R*,6*S*)-4,5-bis(Benzyloxy)-6-(benzyloxymethyl)-1-tosylpiperidin-2-one (44)

To a stirred mixture of *p*-toluenesulfonyl azide (0.17 mL, 1.44 mmol), amino-alkyne **38** (500 mg, 1.2 mmol), H_2O (0.02 mL, 1.2 mmol) and CuI (10 mg, mmol) in $CHCl_3$ (1.7 mL) was slowly added Et_3N (0.2 mL, 1.4 mmol) at room temperature under N_2 atmosphere. After stirring the reaction mixture for 3 h at room temperature under N_2, it was diluted by adding CH_2Cl_2 (1 mL) and saturated NH_4Cl solution (1.5 mL). The mixture was stirred for additional 30 min and two layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatograph on silica gel to obtain pure **44** as a clear viscous oil (422 mg, 60% from **38**). **Analytical data of 44**: Colorless oil, eluent for column chromatography: EtOAc/Hexane (3/7, v/v); $[\alpha]_D^{28}$=+23.4985 (c 0.00222 $CHCl_3$); R_f (0.6, 2/3 EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 3H), 2.71–2.87 (m, 2H), 3.39 (dd, J=8.4, 3.7 Hz, 1H), 3.46–3.55 (m, 2H), 3.66–3.70 (m, 1H), 3.87- (m, 1H), 4.37–4.51 (m, 5H), 4.79 (d, J=11.64, 1H), 7.11–7.28 (m, 17H), 7.69 (d, J=8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6 (CH_3), 33.1 (CH_2), 56.2 (CH), 69.8 (CH_2), 71.0 (CH_2), 71.2 (CH), 73.8 (CH_2), 74.0 (CH_2), 74.5 (CH), 126.6–129.4 (ArC), 137.4 (ArC_q), 137.6 (ArC_q), 137.9 (ArC_q) 139.8 (ArC_q), 142.7 (ArC_q), 164.0 (ArC_q); IR (neat, cm^{-1}) 3402, 3021, 1601, 1276, 669, 566; ESI-HRMS m/z $[M]^+$: calcd for $C_{34}H_{35}NO_6S$ 585.2258, measured 585.2384.

4.14. (2*R*,3*S*,4*S*)-1,3,4-tris (Benzyloxy) hex-5-yn-2-yl chloromethanesulfonate (43)

A solution of compound **24** (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 min. After completion of the reaction, the mixture was diluted with ethyl acetate and washed with water and brine and dried over Na_2SO_4 and concentrated under reduced pressure. The residue on purification by column chromatography yielded **43** as a clear oil (200 mg, 88.5% from **24**). **Analytical data of 43**: Colorless oil, eluent for column chromatography: EtOAc/Hexane (1/49, v/v); $[\alpha]_D^{28}$=+73.7674 (c 0.00622 $CHCl_3$) 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, 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.

4.15. (2*R*,3*R*,4*S*)-1,3,4-tris (Benzyloxy) hex-5-yn-2-yl azide (39)

To a 20 mL two necked oven dried round bottom flask fitted with a reflux condenser was added sodium azide (10 mg, 0.156 mmol), sealed with septum and flushed with nitrogen. To this was added a solution of compound **43** (42 mg, 0.072 mmol) dissolved in dry DMF (3 mL) through a syringe under nitrogen atmosphere. The reaction mixture was heated to 80 °C for 2 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 and concentrated under vacuum. The residue was purified by silica gel column chromatography to furnish **39** as a clear oil (30 mg, 80% from **43**). **Analytical data of 39**: Colorless oil, eluent for column chromatography: EtOAc/Hexane (1/49, v/v); R_f 0.50 (3/17, EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (d, J=2 Hz, 1H), 3.44–3.55 (m, 2H), 3.71–3.79 (m, 2H), 4.25

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(dd, J=7.3, 2.1 Hz, 1H), 4.34–4.51 (m, 4H), 4.75–4.85 (m, 2H), 7.15–7.27 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 61.1, 68.7, 69.5, 71.1, 73.6, 75.1, 75.8, 79.7, 81.2, 127.9–128.6, 137.2, 137.8, 137.9; IR (neat, cm^{-1}) 3400, 2954, 2090, 1219, 766; ESI-HRMS m/z $[M+H]^+$: calcd for $C_{27}H_{27}N_3O_3$ 442.2125, measured 442.2176.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2016.07.036.

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