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Phthalate tethered strategy: carbohydrate nitrile oxide cycloaddition to 12-15 member chiral macrocycles with alkenyl chain length controlled orientation of bridged isoxazolines

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The highly selective synthesis of phthalate templated bridged isoxazoline macrocyclic lactones is demonstrated using readily accessible carbohydrate precursors via intramolecular nitrile oxide-alkene cycloaddition. The structures of the macrocycles were established by 2D NMR as well as X-ray diffraction study. The orientation of the bridged isoxazoline ring is dependent on the distance between the 1,3-dipole and dipolariphile. The macrocycles are amenable to further transformations to higher amino sugars by sequential removal of phthalate template and reductive cleavage of isoxazoline moiety.

The use of macrocyclic skeletons is well known as hosts in the supramolecular chemistry in recognition of ionic and neutral molecules.[1] Importance of macrocyclic structures, including nucleosides as antibacterial agents based on novel targets as gene and drug-delivery systems are well documented.[2] Generally, the synthesis of medium and large ring compounds by conventional cyclization methods is difficult to synthesize, and only recently with the introduction of efficient ring-closing metathesis has led to the preparation of such rings become easier. Therefore, the development of strategies for the synthesis of macrocycles remains an ever-important task for synthetic chemists. Of particular importance is the construction of chiral macrocyclic frameworks from chiral precursors, because chirality has a profound influence[3] on the biological activity of drugs and related molecules. 1,3-Dipolar cycloaddition of nitrile oxides with olefin is one of the most powerful synthetic tools in organic synthesis[4] due to the operational simplicity, atom-economic nature and above all the product cycloadducts are amenable to transformations that can lead to the introduction of extra functionalities. The intermolecular cycloaddition of nitrile oxides with olefins produces isoxazoline derivatives, whereas its intramolecular version furnishes bicyclic fused and/or bridged isoxazolines in a highly regio- and stereoselective fashion.[5] The isoxazoline ring has been revealed to be a latent precursor for a variety of corresponding bi-functional compounds such as γ-amino alcohols and β-hydroxy-ketones by reductive cleavage of the N-O bond; therefore the isoxazoline heterocycles has been utilized for construction of natural products having such functionalities.[6] In this context, 8 to 12-membered chiral oxa- and azacycles were successfully synthesized via tether or structural constrain based on carbohydrate/amino acid derived nitrile oxide–olefin cycloaddition.[7] On the other hand, the amino sugars constitute integral components of many natural products and medicinally relevant compounds.[8] They are also important compounds for antibiotic research,[9] anticancer therapies,[10] nucleic acid research[11] and biopolymers.[12] Higher amino sugars are interesting targets for synthetic, biological and pharmaceutical research because of their limited availability from natural sources.[13] Thus, in order to investigate their biological function, the development of facile and adaptable routes to this class of compounds is of fundamental importance. Our recent research interest is to synthesize chiral isoxazoline derivatives **2** or **3** from the reaction between nitrile oxide (**1**) and allyl alcohol, because reductive cleavage of resultant cycloadduct isoxazoline leads to construction of important precursors for higher and branched amino sugars **4** or **5** (Scheme 1). It was reported in the literature that the intermolecular nitrile oxide cycloaddition between allyl alcohols and nitrile oxides **1** (R = Bn) or related nitrone produced mixtures of regio- and diastereomeric isoxazolines or isoxazolidines.[14] Herein we envisaged that on installation of the

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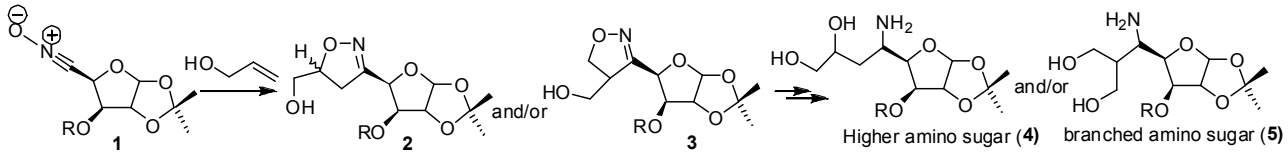
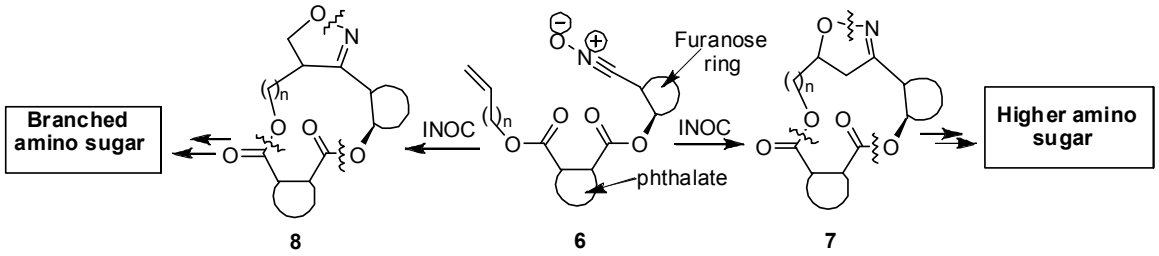
†Electronic Supplementary Information (ESI) available: Details experimental procedure, physical and spectroscopic characterization data, ^{1}H and ^{13}CNMR spectra for all compounds and CIF files of **15a** and **15f**. See DOI: 10.1039/



Scheme 1 Possible route to higher amino sugar via intermolecular nitrile oxide cycloaddition



Scheme 2 Phthalate tether strategy to chiral macrocycles and higher amino sugar via INOC

phthalate moiety between the alkenyl and carbohydrate moieties, the intramolecular nitrile oxide cycloaddition (INOC) of this rigid phthalate tethered bearing carbohydrate nitrile oxide **6** is expected to construct isoxazoline fused chiral macrolide **7** in a highly regio- and diastereo-selective manner (Scheme 2).

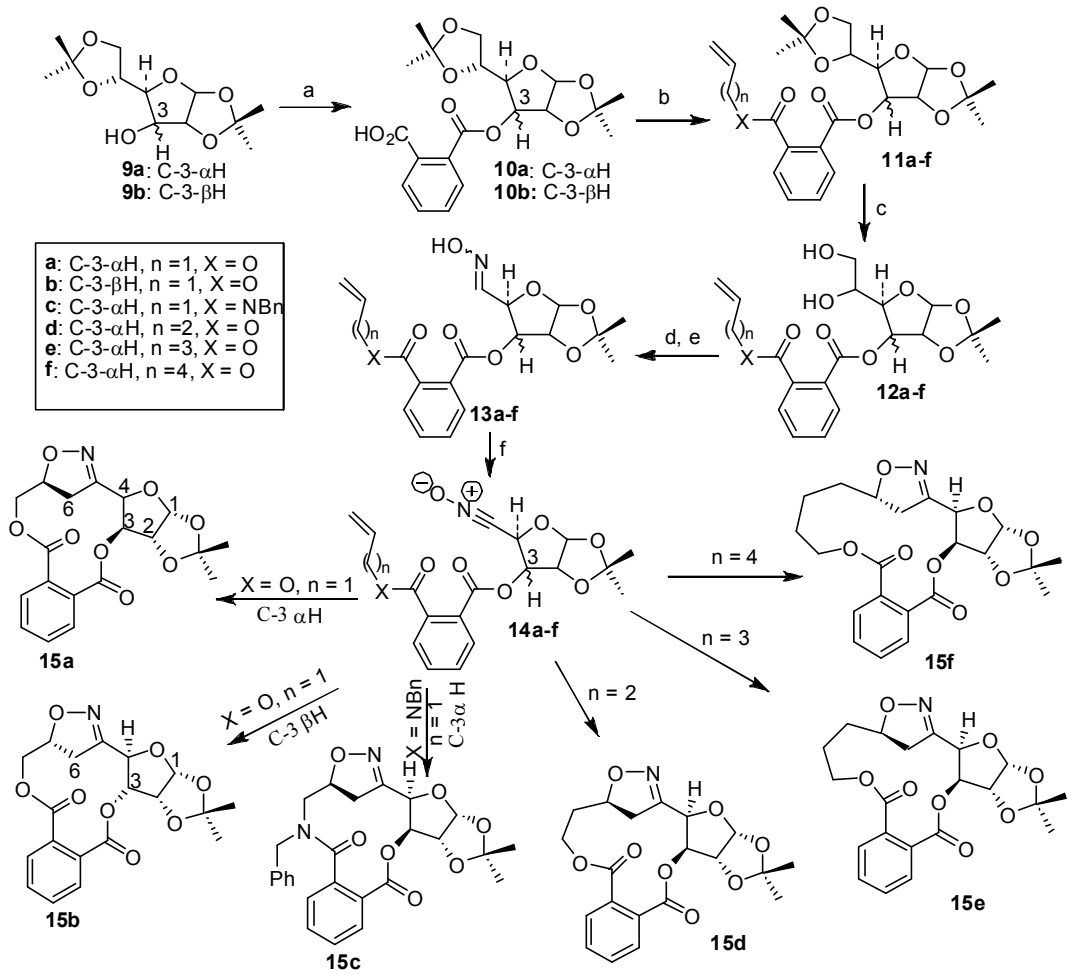
On removal of the tether group leads to exclusive formation of the bridged isoxazoline derivative **2.** Of course possibility for the formation of isoxazoline fused macrolide **8** (Scheme 2) cannot be ruled out. The ring size of the core macrolide is dependent on the value of "n", i.e. the number of intervening carbon atom(s) between olefin and the tether phthalate. To the best of our knowledge, the synthesis of chiral macro-heterocycles via phthalate tethered nitrile oxide cycloaddition and subsequent transformation to higher amino sugar remained unexplored. In this communication paper we describe the synthesis of 12-15 member enantiopure macrocycles based on intramolecular nitrile oxide cycloaddition (INOC) of phthalate tethered carbohydrate substrate and the subsequent transformation into amino sugar derivative.

The phatalate tethered carbohydrate scaffolds **11a-f** (Scheme 3) were synthesized in two steps starting from 1,2:5,6-di-*O*-isopropylidene glucofuranoside (**9a**) or 1,2:5,6-di-*O*-isopropy-lidene allofuranoside (**9b**). The monocarboxylic acid **10a** and **10b** were synthesized through the reaction between **9a** or **9b** with phthalic anhydride in the presence of pyridine in DMF at 110 °C (Scheme 2). Alkylation of monocarboxylic acid **10a** or **10b** with allyl bromide in the presence of anhydrous K_2CO_3 in DMF afforded **11a, b**, whereas higher analogues **11d-f** were achieved from **10a** using 4-bromo butene, 5-bromo pentene and 6-bromo hexene respectively. Compound **11c** was synthesized through the amidation of **10a** with *N*-allyl-*N*-benzyl amine using coupling agent EDCI and activator HOBt. The oxime derivatives **13a-f** were obtained through sequential transformation of **11a-f** involving selective removal[15] of 5,6-acetonide moiety to corresponding diols **12a-f** and sodium metaperiodate mediated oxidative carbon-carbon bond cleavage[16] of the diols (**12a-f**) to aldehydes followed by treatment of hydroxylamine hydrochloride in the presence of pyridine in ethanol.[7d] The oxime derivatives **13a-f** were found as a mixture of *syn* and *anti*-isomers as revealed by NMR spectra, while ^{1}H and ^{13}C NMR spectrum of **11c**, **12c** and **13c** were found to be more complex due to the presence of tertiary amide moiety (rotomers).

The bridged isoxazoline **15a** was afforded exclusively via the INOC of the nitrile oxide **14a** on treatment of oxime **13a** with 4% NaOCl and Et_3N in dichloromethane[17] as evident from the ^{1}H and ^{13}NMR spectral analyses. Completion of the cycloaddition reaction was monitored by disappearance of the ^{1}H NMR signal of the olefinic proton through analyses of the reaction mixture containing product **15a**. The presence of the bridged $-CH_2-$ group in the isoxazoline **15a** was established by the appearance of two protons multiplet at δ 3.34–3.14 ppm in the ^{1}H NMR spectrum as well as a high field methylene (confirmed by DEPT experiment) carbon signal at δ 36.6. The down field quaternary carbon peak at δ 154.6 in the ^{13}C NMR spectrum of **15a** confirm the presence of C=N. The structure of **15a** was further corroborated by DEPT, ^{1}H-^{1}H COSY and NOESY experiments. In the NOESY spectrum no co-relations were found between either bridgehead proton, or bridged methylene protons with other pre-existing carbohydrate chiral centers. It is possible only if the orientation protons those are located at C-3/C-4 (these protons are α-oriented) and methylene group are opposite to each other. Finally the β-orientation of bridged methylene group was established by the single crystal X-ray diffraction analyses (panel A, Figure 1).[18a]

A change in the stereochemistry at C-3 of the carbohydrate backbone did not influence changing the regioselectivity in the INOC of **14b**, which was derived from oxime **13b** on treatment of aqueous NaOCl. The ^{1}H NMR pattern of **15b** has shown close similarity to that of **15a**. The bridged isoxazoline structure of **15b** was consistent with the appearance of two sets of doublet of doublets at δ 3.35 (J = 17.4, 11.4 Hz) and δ 3.00 (J = 17.4, 3.0 Hz) in the proton NMR spectrum as well as a high field $-CH_2-$ peak at δ 38.3 and a quaternary carbon peak (C=N) at δ 154.4 in the ^{13}C NMR spectrum. The stereochemistry of the newly formed chiral center was established by NOESY experiment. A distinct cross peaks between C_3-H and C_6-H_A and C_6-H_B strongly supported the α-orientation of bridged methylene moiety in **15b**. These two observations revealed that the configuration at C-3 of the carbohydrate backbone had no effect in the controlling of regioselectivity in the cycloaddition process. The macrocycles **15a** and **15b** are diastereomeric because they were resulted from the cycloaddition of two epimeric nitrile oxides **14a** and **14b**.

In order to investigate whether a change of allyl ester by allyl amide could bring about any change in the regioselectivity of the



Scheme 3: Reagents and condition: [a]phthalic anhydride, Py; [b]alkenyl DMAP, DCMfor **11c,** 61-66% (two steps); [c]75% aqueous acetic acid, rt or Py, ethanol, reflux, 79-83% (two steps); [f] 4% NaOCl (aq.)-DCM, rt, overnight, bromide, K_2CO_3, DMF for **11a-b, d-f** and N-allylbenzylamine, EDCI, HOBt, HBIm.TFA, water, 70 °C, 1h, 83-89%; [d]$NaIO_4$, water-MeOH; [e]$NH_2OH.HCl$, 52-61%.

cycloaddition, we have synthesized oxime **13c** from **10a** via coupling with *N*-allyl benzyl amine using EDCI, selective cleavage of 5,6-isopropylidene followed by oxidative cleavage to aldehyde and oxime formation with hydroxyl amine hydrochloride (Scheme 3). The resulting oxime**13c** was subjected to react with NaOCl solution for the generation of nitrile oxide **14c**, which again gave rise to 12-membered bridged isoxazoline **15c** exclusively. The ^{1}H and ^{13}C NMR spectrum of **15c** exhibits all the characteristics features of bridged isoxazoline observed for **15a** and **15b**. Appearance of two sets of double doublets at δ 3.89 (*J* = 18.6, 3.0 Hz) and 3.30 (*J* = 18.6, 12.0 Hz) in the proton NMR spectrum and a methylene carbon signal at δ 38.4 as well as quaternary carbon signal (C=N) at δ 158.0 was a clear indication of the bridged isoxazoline nature of **15c**. Like the NOESY experiments of **15a**, here again we could not see any cross peaks, which could correlate either the bridgehead proton of bridged methylene protons with the protons of carbohydrate chiral centers at C-3 and C-4 (with respect to sugar skeleton) thus the configuration of bridged methylene is assigned as β-oriented. Due to the amorphous nature of the cycloadduct **15c** it was not possible to study the structure by single crystal X-ray diffraction experiment. The yield (58-61%) found in these cycloadducts **15a-*cis*** quite impressive considering the sizes of the 12-memberd macrocyclic ring. It is worthy to mention that in all cases reactions are highly regio- and diastereoselective in nature, because a single product was isolated in each case.

After developing successful cyclisation approach for 12-membered macrocycles based on phthalate strategy, we turned our attention to higher homologues of these macrocycles through the chain elongation of the alkenyl moiety. Thus sugar derived substrate **11d-f** were synthesized using higher homologue of allyl bromide as alkylating agent with subsequent selective de-protection, oxidative cleavage and oxime formation to obtain **13d-f** (Scheme 3). The in situ generated sugar-based nitrile oxides **14d-f** underwent smooth cyclisation to 13 to 15-membered bridged isoxazoline macrocycles **15d-f** in a regio- and diastereoselective manner. The presence of bridged methylene (-CH_2-) in **15d-f** was established due to appearance of two sets of doublets with a very large coupling constant (J_{gem}>16 Hz) in the ^{1}H NMR and very high

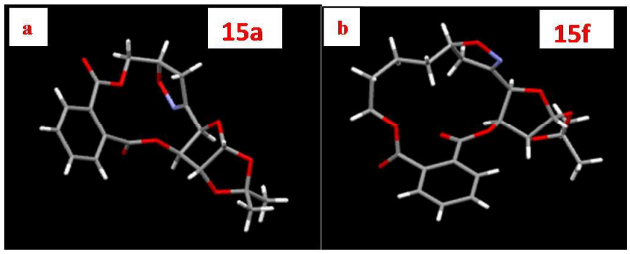
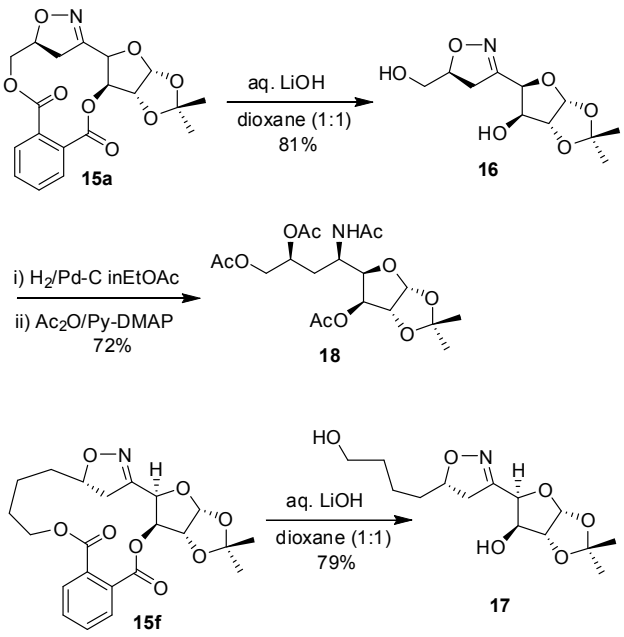


Figure 1 Single crystal X-ray structures of **15a** and **15f**

field methylene carbon signal in the ^{13}C NMR spectrum of the cycloadduct. The stereochemistry of the newly formed chiral center i.e. the orientation of bridged methylene group of the amorphous compound **15d-e** was established by NOESY experiment in a similar way that of **15a** and **15c**. But the stereochemistry of the bridged methylene in **15f** was established as α-oriented on the basis of NOE experiment which is actually opposite to that of **15a** and **15c-e**. Strong NOE was found between protons of bridged $-CH_2-$ and the α-oriented protons in C-3 and C-4. Finally the structure of **15f** was confirmed by single crystal X-ray analyses (panel B, Figure 1).[18b] At present the reason behind this observation is unknown to us but, one possibility could be the flexibility of the longer alkenyl chain that changes the orientation of dipolarophile.



Scheme 4 Easy accesses to valuable bridged isoxazoline and higher amino sugars

One of the important features of this macro cyclization strategy is that the rigid phthalate template can be removed from the macrocycles by base catalyzed hydrolysis to achieve the corresponding isoxazoline diols of biological importance. Thus, on treatment of **15a** and **15f** separately with aq. LiOH in water-dioxane at room temperature afforded the desired diols**16** and **17**in 81% and 79% yield respectively (Scheme 4). The isoxazoline moiety bearingdiol**16** is a potential candidate for higher amino sugar because isoxazoline ring can easily be cleaved under reductive conditions[19] to afford the corresponding amino–alcohol. Thus hydrogenolysis of **16** with H_2-Pd/C in ethyl acetate followed by acetylation with acetic anhydride-pyridine in the presence of catalytic amount of DMAP furnished tetraacetate **18** (Scheme 4) with 72% yield as single isomer.

In conclusion, the phthalate tethered INOC strategy described here presents a novel method for the synthesis of 12 to 15-membered chiral macrocycles having bridged isoxazoline moiety in a highly regio- and diastereoselective manner. The ring size and the stereochemistry of the newly created chiral center were established especially by 2D-NMR as well as X-ray crystallographic analyses of **15a** and **15f**. Removal of phthalate template and cleavage of isoxazoline ring provided an access to higher deoxy amino sugar of biological and pharmaceutical interest. The results from this innovative strategy open up a new avenue towards easy access to valuable chiral macrocycles of different ring sizes and higher amino sugars. Studies on the synthesis and DFT studies of large ring macro-heterocycles by varying the position of alkene with other heteroatoms are underway and will be reported in due course.

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18 (a) Crystallographic data for **15a** have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication number CCDC 1418502; (b) CCDC deposition number of **15f** is 1418503. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: (+44)-1223-336-033.

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