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An iodocyclization approach toward diastereoselective synthesis of highly functionalized tetrasubstituted tetrahydrofurans with 2,5-*trans* and 2,5-*cis* relationships from pyranoside derived acyclic oximes☆

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Abstract—An efficient method to obtain novel tetrasubstituted tetrahydrofurans with C2 and C5 substitution in *trans*- and *cis*-relative configurations has been reported.

1. Introduction

The stereoselective synthesis of highly functionalized tetrahydrofuran (THF) derivatives have received much attention in recent years owing to their widespread occurrence in various natural products as structural units[1] and also their presence in many biologically active compounds,[2] such as renealtins A and B,[1a] asitrocin, 2,4-*cis*- and *trans*-asitrocinones,[1b] and donnaienin.[1e] A polysubstituted THF segment is also found in trilobatin B **I**, a lignan from the liverwort *Bazzania trilobata* (Fig. 1).[3] A few literature reports on unnatural tetrasubstituted tetrahydrofurans (THFs) **II**–**IV**, which have been used for the development of high-affinity ligands and photoaffinity labels for the D-fructose transporter GLUT5[4] and more interestingly compound **V** exhibiting in vitro microbial activity on cultures of *Mycobacterium tuberculosis*[5] are noteworthy (Fig. 1). The densely substituted chiral THFs can offer a high degree of structural diversity and may be used as intermediates for the synthesis of various biodynamic compounds. Therefore, an easy access to a synthetic approach capable of targeting chiral substituted THFs is required. With this in mind, many synthetic strategies have been developed to obtain these compounds and the natural products themselves.[6] Several literature methods have been reported with regards to the construction of 2,5-disubstituted THFs, while reports toward the synthesis of tri- and tetra-substituted tetrahydrofurans are few.[7,8] We have recently reported new and convenient approaches for the stereoselective synthesis of highly functionalized trisubstituted THFs starting from commercially available glycals.[9,10]

Our interest in the synthesis of substituted tetrahydrofurans motivated us to develop a new synthetic route to afford stereochemically pure isomers of appropriately functionalized tetrasubstituted THFs as novel privileged scaffolds. These will be further elaborated upon to a wide variety of new chemical libraries of unnatural THFs from a biological point of view.

Realizing the importance of the above mentioned polyfunctionalized THFs, we envisaged a new oxime substituted THF scaffold **1** containing various diversification sites that allow amenability of the product transformation to biologically interesting molecules. The retrosynthetic strategy to obtain **1** is depicted in Scheme 1. It is worth noting that the direct iodocyclization of aldehyde **1b′**, which to the major extent exists in hemiacetal furanoid form is not possible. Therefore, we decided to use oxime ether **1c**, a key intermediate in this study that on iodocyclization involving participation of C2 benzyloxy oxygen atom could afford a stereodiversified THF-oxime of type **1** as a building block for library development. Another explicit reason to use the oxime ether rather than alternatives in this study

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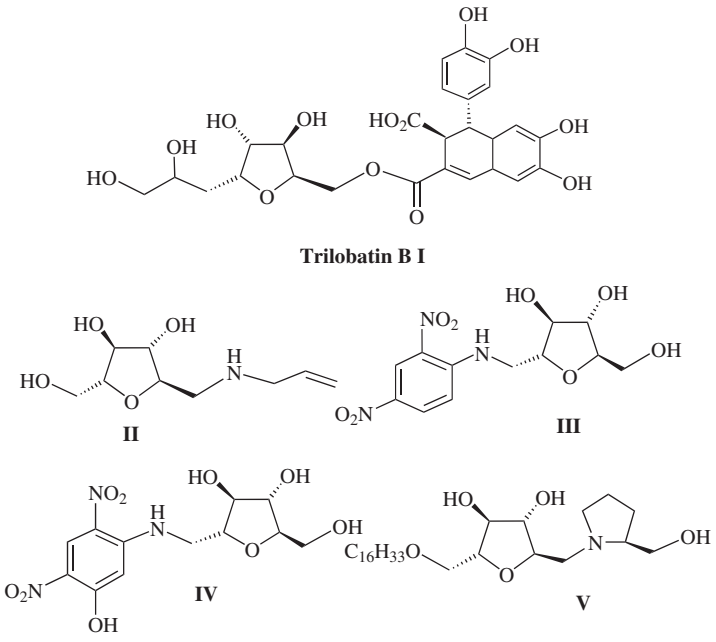
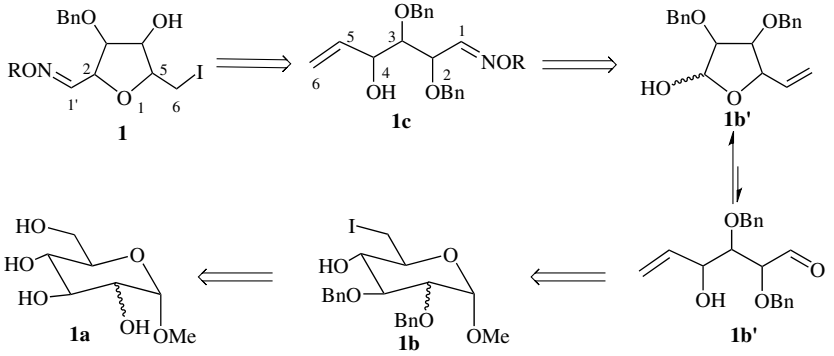


Figure 1.



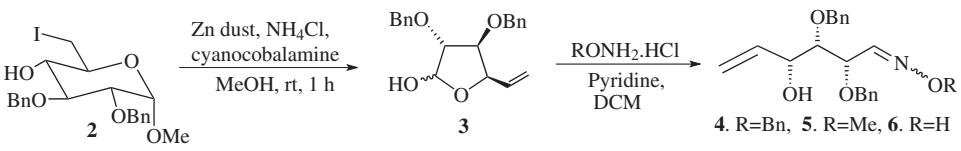
Scheme 1.

was its facile transformation to various functionalities such as aldehydes,[11] amines,[12] nitriles,[13] and amides.[14] The representative analogues of **1c** can be obtained from methyl α,D-glycopyranoside **1a**.

Although the cyclization of oxime ethers toward the synthesis of aminocyclitols is known in the literature,[15] to the best of our knowledge, the iodocyclization of the sugar derived oxime ethers of type **1c** to their corresponding THFs has not yet been reported. Herein, we report the full results of iodocyclization of oximes **4**, **5**, **6**, and **16** to obtain new tetrasubstituted THFs **7a**–**d**, **8a**–**c**, **9a**,**b**, and **17a**,**b**, respectively.

2. Results and discussion

Methyl 6-deoxy-6-iodo-2,3-di-*O*-benzyl-α,D-glucopyranoside **2** was prepared from methyl α,D-glucopyranoside.[16] Compound **2** on treatment with Zn dust in MeOH in the presence of a catalytic amount of cyanocobalamine[17] yielded cyclic hemiacetal **3** (an α- and β-mixture). Hemiacetal **3** on refluxing with *O*-benzylhydroxylamine hydrochloride[13] in DCM (Scheme 2) furnished an inseparable mixture of *E*- and *Z*-isomers of oxime **4** in an 84:16 ratio, as determined by ^{1}H NMR spectra, in very good yield (Table 1, compound **4**).



Scheme 2.

Table 1. Oxime derivatives **4–6** via Scheme 2

Compound	Reaction condition	Ratio[a] (*E*:*Z*)	Yield (%)
4	Reflux, 5 h	84:16	86
5	Reflux, 3.5 h	80:20	81
6	rt, 24 h	75:25	52

[a] Ratio of *E*/*Z* isomers of oximes was determined by ^{1}H NMR.[13]

Table 2. THF derivative **7–9** via Scheme 3

Compound	Yield of each isomer[a] (%)			
	a	**b**	**c**	**d**
7	46	29	12	2
8	40	27	9	NI
9	50 (**a**+**b**)		—	—

NI = not isolable.

[a] The geometry of each isomeric oxime was determined on the basis of chemical shift of H1′ and its $J_{1',2}$ value.[13]

To obtain the desired THF, oxime **4** was subjected to an iodocyclization reaction[18] (Scheme 3). In this process, a mixture of four stereoisomers was formed. The chromatographic purification of this mixture resulted in the separation of all four isomers **7a–d** in 2–46% yield (Table 2). The 1D and 2D NMR experiments of the major isomer showed the formation of a tetrasubstituted THF skeleton but its stereochemical outcome could not be analyzed due to the appearance of overlapping signals for H_4 and H_5 at δ 4.47 ppm in ^{1}H NMR spectra. Therefore, in order to establish its stereostructure completely, it was derivatized to its acetyl analogue.

Here, in its ^{1}H NMR spectra the signals for H_4 and H_5 became separated and appeared at δ 5.44 ppm ($J_{4,5} = 3.63$ Hz) and 4.65–4.60 ppm (multiplet), respectively. The NOE and NOESY experiments allowed its identification as **10** (Fig. 2). The transannular NOE experiment[19] of **10** showed that both H_4 and H_5 were *trans* to H_2. The ^{1}H NMR spectra of **10** showing coupling between H_4 and H_5 ($J_{4,5} = 3.63$ Hz) with no coupling between H_3 and H_4 ($J_{3,4} = 0.00$ Hz) provided adequate evidence for the pseudoequatorial dispositions of H_3 and H_4 suggesting the torsion angle closer to 90° between them (Fig. 2).[20]

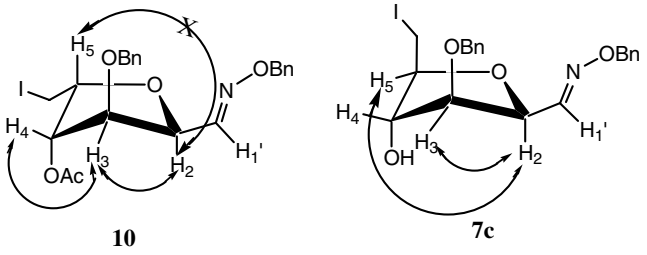
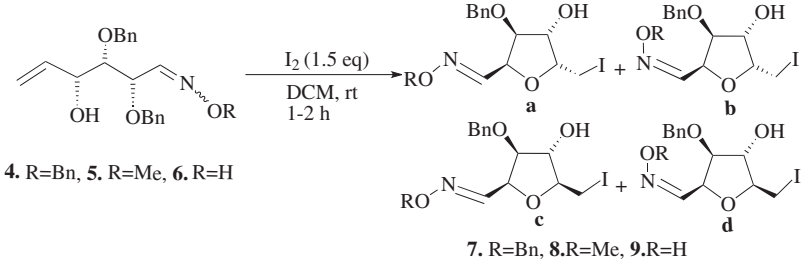


Figure 2. NOE correlations.

Thus, after establishing the stereostructure of **10**, the major isomer was identified as THF **7a** (2,5-*trans*). The NOE and NOESY experiments for compound **7c** showed the *cis* relationship between H_2 and H_5. Its ^{1}H NMR spectra showed the appearance of a triplet at δ 4.29 ppm due to proton H_4 ($J_{4,3} = J_{4,5} = 2.97$ Hz) and a double doublet at δ 4.02 ppm due to H_3 ($J_{3,2} = 5.10$ Hz, $J_{3,4} = 2.85$ Hz), clearly indicating the pseudoequatorial orientation of H_3, H_4, and H_5 and pseudoaxial orientation of H_2, and thereby showing a slight distortion in the ring structure due to unfavorable 1,3-steric interaction between CH_2I at C_5 and OBn at C_3. It can be argued here that based on NOE experiments and coupling constants between the vicinal protons as illustrated above, the H_3–H_4 torsion angle[20] is greater than 90° and therefore, the stereostructure of this isomer could be assigned as **7c** (Fig. 2). The NMR spectra of the remaining THF isomers **7b** (2,5-*trans*) and **7d**, (2,5-*cis*) showed that they adopt similar structures. Furthermore, the stereochemical results obtained in iodocyclization of oxime **4** revealed that both **7a** and **7c** were obtained from the *E*-isomer, whereas **7b** and **7d** were derived from its *Z*-isomer.

It can be presumed that the predominant formation of diastereoisomer **7a** over **7c** was due to the more favored disposition of the iodine π complex at one side of the double bond than the other side.[21] While the steric crowding near the *si* (upper) face of the double bond in oxime **4** favors the *re* (bottom) face attack of iodine on the double bond resulting in **7a** as the major isomer (46%), the poor yield of **7c** (12%) in this process was attributed to the *si* face attack of the iodine on it (Fig. 3). The same argument can be applied for the better yield of **7b** (29%) as compared to **7d** (2%), both obtained from the *Z*-isomer of oxime **4**.

Encouraged by these results, we performed similar experiments under identical conditions using *O*-methylhydroxylamine hydrochloride and hydroxylamine hydrochloride, respectively, with a view to test their efficacy toward the iodocyclization reaction. The formation of four THF



4. R=Bn, **5.** R=Me, **6.** R=H

7. R=Bn, **8.**R=Me, **9.**R=H

Scheme 3.

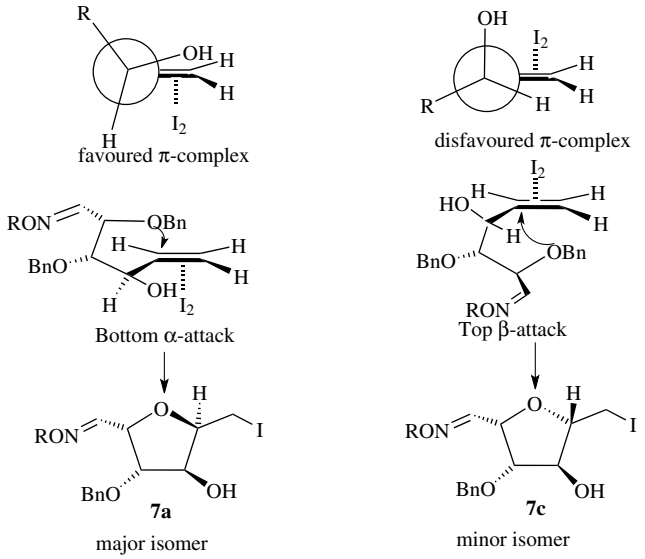


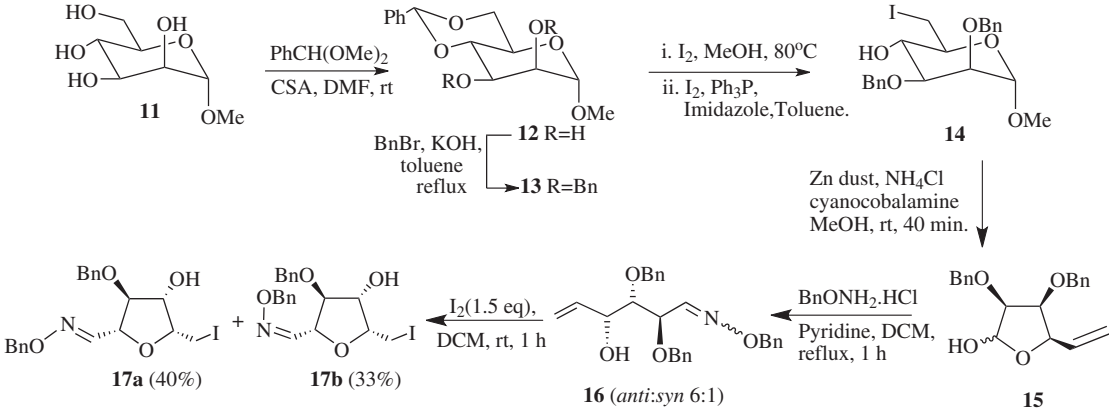
Figure 3.

isomers in the case of *O*-methylhydroxylamine hydrochloride was also noticed in the crude ^{1}H NMR spectra of **8**. Three isomers were separated by the column chromatography of the crude product mixture but the fourth isomer could not be isolated from this series as its yield was negligible. These isomers were identified as **8a**–**c** by their detailed spectral analyses and also based on the identification of **7a**–**d**.

However, when hydroxylamine hydrochloride was used the results were different when compared to substituted hydroxyl amines. Here an inseparable mixture of *E*- and *Z*-isomers (75:25) of oxime **6** was isolated in 52% yield. Its iodocyclization furnished only two isolable diastereoisomers of THF derivative **9**. These two isomers were separated by column chromatography (from TLC) but subsequently isomerized into a mixture of two diastereoisomers during evaporation of their chromatographic eluents and identified as **9a** and **9b** (Tables 1 and 2).

These results clearly indicated that the iodocyclization of oximes **4**–**6** involved the participation of the C2 benzyloxy oxygen atom to furnish the 2,5-*trans* THF scaffold as major isomers. In order to synthesize the 2,5-*cis* THFs we required a methyl α,D-glycopyranoside whose stereochemistry at C2 should be opposite to that of methyl α,D-glucopyranoside. Therefore, we identified the commercially available methyl α,D-mannopyranoside **11** as a suitable starting material in this endeavor. Adopting similar experimental protocols as described above to obtain THFs **7**–**9** from their respective oxime derivatives, the iodocyclization of oxime **16** derived from **11** furnished chromatographically pure 2,5-*cis* THF derivatives **17a** and **17b** (Scheme 4). Their stereostructures were established by the combined use of 1D and 2D NMR experiments.

Here the exclusive formation of 2,5-*cis* THF **17** from the oxime **16** might be due to high diastereofacial selectivity in electrophilic addition of iodine on the C5–C6 double bond in **16** to form π complex. On the other hand, the preferential formation of 2,5-*trans* THFs **7a** and **7b**, **8a** and **8b**, and **9a** and **9b** over their *cis*-isomers may be attributed to the moderate facial selectivity in the process of the iodocyclization of oximes **4**–**6** (Fig. 4).[22]



Scheme 4.

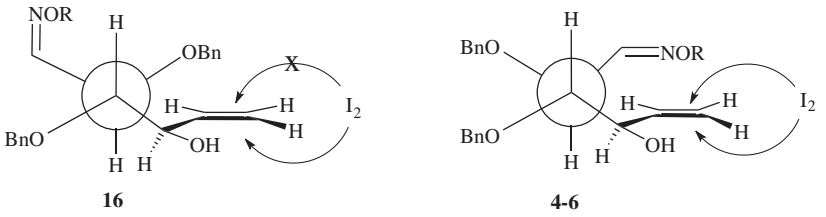


Figure 4.

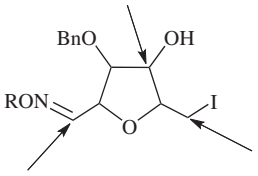


Figure 5. Sites of diversification.

Moreover, in all the cases, iodocyclization of inseparable *E*- and *Z*-oxime isomers predominantly resulted 4,5-*cis* THF derivatives. These results suggested that no significant differences should be expected between the iodocyclization of each oxime isomer.[13]

3. Conclusion

In conclusion, we have developed an efficient method to obtain densely functionalized, stereochemically pure tetrasubstituted 2,5-*trans*-**7a** and **7b**, **8a** and **8b**, and **9a** and **9b** and 2,5-*cis*-**17a** and **17b** THF derivatives as novel scaffolds. Here we successfully isolated all these THF isomers and established their stereostructure, which was not the case in the earlier report on intramolecular cyclization reactions of sugar derived γ-hydroxyalkenes.[8e] The production of a mixture is potentially problematic in such applications, but in this study, each isomeric THF was separated from the mixture and therefore, access to all isomers in the discovery phase can be advantageous. All these THFs with an appropriate orientation of functional groups and three points of diversification (Fig. 5) can generate chemical libraries for a broad spectrum of biological screening.

4. Experimental

4.1. General

Organic solvents were dried by standard methods. The oxime derivatives **4**–**6** and **16** were synthesized in the laboratory. All the products were characterized by ^{1}H, ^{13}C, two-dimensional homonuclear COSY (correlation spectroscopy), heteronuclear single quantum coherence (HSQC), heteronuclear multiple bond correlation spectroscopy (HMBC), IR, ESI-MS, and elemental analysis (C, H, N). Analytical TLC was performed using 2.5 × 5 cm plates coated with a 0.25 mm thickness of silica gel (60F-254), and visualization was accomplished with $CeSO_4$ or 10% H_2SO_4/EtOH and subsequent charring over hot plate. Column chromatography was performed using silica gel (60–120 and 100–200 mesh). NMR spectra were recorded on Bruker Avance DPX 200FT, Bruker Robotics, and Bruker DRX 300 Spectrometers at 200, 300 MHz (^{1}H) and 50, 75 MHz (^{13}C). Experiments were recorded in $CDCl_3$ and CD_3OD at 25 °C. 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. For ^{13}C NMR reference $CDCl_3$ appeared at 77.16 ppm. IR spectra were recorded on Perkin–Elmer 881 and FTIR-8210 PC Shimadzu Spectrophotometers. Mass spectra were recorded on a JEOL JMS-600H high resolution spectrometer using EI mode at 70 eV. Optical rotations were determined on an Autopol III polarimeter using a 1 dm cell at 28 °C in chloroform and methanol as the solvents; concentrations mentioned are in g/100 mL.

4.1.1. (3*R*,4*S*,5*R*) 3,4-Bis(benzyloxy)-5-vinyl-tetrahydrofuran-2-ol 3. To a magnetically stirred suspension of Zn dust (1.36 g, 20.79 mmol) and NH_4Cl (1.11 g, 20.76 mmol) in dry methanol (35 mL) was added cyanocobalamine (10 mg, 0.007 mmol) and allowed to stir for 10 min. After that, a solution of **2** (1.0 g, 2.07 mmol) in dry methanol was added and the resulting solution was further stirred till the disappearance of starting material (TLC control, 1 h). The reaction mixture was filtered through a Celite bed. The filtrate was evaporated under reduced pressure. The residue obtained was dissolved in ethyl acetate (25 mL) and washed with a mixture of brine and water (1:1 v/v, 10 mL each). The organic layer was dried over Na_2SO_4 and concentrated to give **3**, which was purified by column chromatography to obtain a colorless oil (diasteromeric mixture, 572 mg, 85%). Eluent for column chromatography: EtOAc/hexane (1/9, v/v); R_f 0.55 (1/1, EtOAc/hexane); ^{1}H NMR (300 MHz) δ 7.38–7.22 (m, 10H), 6.12–5.92 (m, 1H), 5.51–5.24 (m, 3H), 4.65 (dd, $J = 3.33$, 8.22 Hz, 1H), 4.60–4.46 (m, 4H), 4.00–3.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5 (Ar q*C*), 134.6 (=CH), 134.0 (=CH), 129.2, 129.1, 129.0, 128.9, 128.7, 128.6, 128.5, 128.3, 128.2 (Ar*C*), 119.3 (=CH_2), 119.1 (=CH_2), 101.6 (CH anomeric), 96.5 (CH anomeric), 85.5 (CH), 83.9 (CH), 83.2 (CH), 82.3 (CH), 80.5 (CH), 80.1 (CH), 73.7(CH_2), 73.2 (CH_2), 72.8 (CH_2), 72.5 (CH_2); IR (neat, cm^{-1}) 3378, 3021, 2931, 2365, 1710, 1657, 1523, 1217, 1050; mass (ESI-MS) *m*/*z* 326; found 344 $[M+NH_4]^{+\cdot}$, 326 $[M]^{+\cdot}$, 309 $[M-OH]^{+\cdot}$; EI-HRMS: calcd for $C_{20}H_{22}O_4$: 326.1518, measured 326.1539.

4.1.2. (2*S*,3*S*,4*R*) 2,3-Bis(benzyloxy)-4-hydroxy hex-5-enal *O*-benzyl oxime 4. To a solution of **3** (500 mg, 1.53 mmol) in dry DCM (15 mL) were added *O*-benzylhydroxylamine hydrochloride (612 mg, 2.5 equiv), pyridine (0.4 mL) and this reaction mixture allowed to reflux. After completion of the reaction (TLC control, 5 h), saturated aqueous solution of $NaHCO_3$ was added to neutralize the reaction mixture. The organic layer was separated, dried over Na_2SO_4, and evaporated to dryness under reduced pressure to an oily product mixture that was subjected to column chromatography to obtain **4** (inseparable mixture of *E*- and *Z*-isomers, 86%) as a colorless oil. Eluent for column chromatography: EtOAc/hexane (2/23, v/v); R_f 0.45 (1/4, EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, $J =$ 7.95 Hz, 1H, H-1, *E*-isomer), 7.39–7.28 (m, 10H, 10ArH), 5.83 (ddd, $J = 5.67$, 10.50, 17.13 Hz, 1H, H-5), 5.27 (dt, $J = 1.44$, 17.25 Hz, 1H, H-6a), 5.18–5.14 (m, 3H, H-6b and NOCH_2Ph), 4.77–4.35 (m, 4H, 2 × CH_2Ph), 4.32 (br s, 1H, H-4), 4.22 (dd, $J = 5.34$, 7.92 Hz, 1H, H-2), 3.55 (dd, $J = 3.96$, 5.31 Hz, 1H, H-3), 2.45 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0 (HC=N), 149.6 (HC=N), 138.3 (=CH), 138.0 (Ar q*C*), 137.9 (Ar q*C*), 137.8 (=CH), 137.7 (Ar q*C*), 128.9, 128.8, 128.7, 128.6, 128.4, 128.4, 128.3 (Ar*C*), 117.4 (=CH_2), 116.9 (=CH_2), 82.8 (CH), 82.4 (CH), 77.3 (CH), 76.9 (CH_2), 76.5 (CH_2), 75.4 (CH_2), 75.1 (CH_2), 72.8 (CH), 72.7 (CH), 72.6

(CH_2), 72.3 (CH), 71.7 (CH_2); IR (neat, cm^{-1}) 3447, 3065, 3032, 2926, 1597, 1496, 1455, 1210, 1073, 1020; mass (ESI-MS) m/z 431; found 432 $[M+1]^{+\cdot}$, 454 $[M+Na]^{+\cdot}$. Elemental Anal. Calcd for $C_{27}H_{29}NO_4$: C, 73.6; H, 6.9; N, 3.2. Found: C, 73.1; H, 6.6; N, 3.6.

4.1.3. (2*S*,3*S*,4*R*) 2,3-Bis(benzyloxy)-4-hydroxy hex-5-enal *O*-methyl oxime 5. To a solution of **3** (1.0 g, 3.07 mmol) in dry DCM (30 mL) were added *O*-methylhydroxylamine hydrochloride (641 mg, 2.5 equiv), pyridine (0.8 mL) after which this reaction mixture was allowed to reflux. After completion of reaction (TLC control, 3.5 h), saturated aqueous solution of $NaHCO_3$ was added to neutralize the reaction mixture. The organic layer was separated, dried over Na_2SO_4, and evaporated to dryness under reduced pressure to an oily product mixture that was purified by column chromatography to yield **5** (inseparable mixture of *E* and *Z* isomers, 880 mg, 81%), colorless oil. Eluent for column chromatography: EtOAc/hexane (2/23, v/v); R_f 0.56 (1:4 EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, $J = 8.01$ Hz, 1H, H-1, *E*-isomer), 7.36–7.24 (m, 10H, ArH), 5.93–5.82 (m, 1H, H-5), 5.32 (dt, $J = 1.29$, 17.22 Hz, 1H, H-6a), 5.19 (dt, $J = 1.20$, 10.50 Hz, 1H, H-6b), 4.80 (d, $J = 11.28$ Hz, 1H, CH_2Ph), 4.69 (d, $J = 10.32$ Hz, 1H, CH_2Ph), 4.65 (d, $J = 9.87$ Hz, 1H, CH_2Ph), 4.46 (d, $J = 11.71$ Hz, 1H, CH_2Ph), 4.36 (br s, 1H, H-4), 4.26 (dd, $J = 5.37$, 7.95 Hz, 1H, H-2), 3.92 (s, 3H, CH_3), 3.58 (dd, $J = 3.93$, 5.22 Hz, 1H, H-3), ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3 (CH=N), 148.9 (CH=N), 138.4 (=CH), 138.3 (Ar q*C*), 138.1 (Ar q*C*), 137.8 (=CH), 128.9, 128.8, 128.7, 128.5, 128.4 (Ar C), 117.4, 117.0 (=CH_2), 82.9 (CH), 82.4 (CH), 77.5 (CH), 75.5 (CH_2), 75.2 (CH_2), 72.9 (CH), 72.8 (CH_2), 72.3 (CH), 71.9 (CH_2), 62.7 (CH_3), 62.4 (CH_3); IR (neat, cm^{-1}) 3465, 3035, 2936, 1597, 1455, 1351, 1210, 1042; mass (ESI-MS) m/z 355. Found: 378 $[M+Na]^{+\cdot}$, 357 $[M+2]^{+\cdot}$; 356 $[M+1]^{+\cdot}$; 316, 254, 181, 91. Elemental Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.9; H, 7.1; N, 3.9. Found: C, 70.6; H, 7.4; N, 4.1.

4.1.4. (2*S*,3*S*,4*R*) 2,3-Bis(benzyloxy)-4-hydroxy hex-5-enal oxime 6. To a solution of **3** (1.02 g, 3.13 mmol) in dry DCM (30 mL) were added hydroxylamine hydrochloride (544 mg, 2.5 equiv) and pyridine (0.8 mL) after which this reaction mixture was stirred at room temperature. After completion of reaction (TLC control, 24 h), saturated aqueous solution of $NaHCO_3$ was added to neutralize the reaction mixture. The organic layer was separated, dried over Na_2SO_4, and evaporated to dryness under reduced pressure to obtain an oily product mixture. This on column chromatographic purification furnished **6** (inseparable mixture of *E*- and *Z*-isomers, 556 mg, 52%) as a colorless solid (mp 68–71 °C). Eluent for column chromatography: EtOAc/hexane (7/43, v/v); R_f 0.43 (3:7 EtOAc/hexane, v/v); ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (br s, 1H, =N–O*H*), 7.55 (d, $J = 7.86$ Hz, 1H, H-1), 7.35–7.31 (m, 10H, ArH), 5.84 (ddd, $J = 5.58$, 10.59, 16.92 Hz, 1H, H-5), 5.31 (dt, $J = 1.38$, 15.87 Hz, 1H, H-6a), 5.19 (dt, $J = 1.20$, 10.50 Hz, 1H, H-6b), 4.79 (d, $J = 11.25$ Hz, 1H, CH_2Ph), 4.68 (d, $J = 8.76$ Hz, 1H, CH_2Ph), 4.64 (d, $J = 8.28$ Hz, 1H, CH_2Ph), 4.45 (d, $J = 11.73$ Hz, 1H, CH_2Ph), 4.36 (br s, 1H, H-4), 4.28 (dd, $J = 5.73$, 7.86 Hz, 1H, H-2), 3.59 (dd, $J = 3.63$, 5.64 Hz, 1H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2 (HC=N), 150.4 (HC=N), 138.3 (=CH), 138.2 (Ar q*C*), 138.0 (Ar q*C*), 137.8 (=CH), 128.9, 128.8, 128.6, 128.5, 128.4 (Ar*C*), 117.4 (=CH_2), 116.9 (=CH_2), 82.8 (CH), 82.4 (CH), 77.6 (CH), 75.6 (CH_2), 75.4 (CH_2), 72.9 (CH_2), 72.8 (CH) 72.6 (CH), 72.3 (CH), 72.0 (CH_2); IR (KBr, cm^{-1}): 3228, 2926, 1600, 1456, 1397, 1350, 1124, 1068, 1031; mass (ESI-MS) m/z 341. Found: 343 $[M+2]^{+\cdot}$, 342 $[M+1]^{+\cdot}$; EI-HRMS: calcd for $C_{20}H_{23}O_4N$: 341.1627, measured 341.1617.

4.1.5. General procedure for the synthesis of THF derivative. To a stirred solution of oxime (0.7 mmol) in dry DCM (20 mL), iodine (266 mg, 1.5 equiv) was added portionwise and the reaction mixture was allowed to stir at room temperature. After completion of the reaction (TLC control, 1–2 h), 10% aqueous $Na_2S_2O_3$ was added to neutralize the excess iodine. The organic layer was separated, dried over Na_2SO_4, and concentrated to dryness to furnish a mixture of products that was subjected to purification by column chromatography to obtain **7a**–**d**.

4.1.6. (1′*E*,2*S*,3*R*,4*S*,5*R*) 3-Benzyloxy-4-hydroxy-5-iodomethyl tetrahydrofuran-2-carbaldehyde *O*-benzyl oxime 7a. Yield 46%, a colorless solid (mp 76–78 °C), eluent for column chromatography: EtOAc/hexane (3/47, v/v); $[\alpha]_D = +29.4$ (*c* 0.18, $CHCl_3$); R_f 0.42 (1/4 EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, $J = 7.68$ Hz, 1H, H-1′), 7.35–7.25 (m, 10-H, 10ArH), 5.09 (s, 2H, NOCH_2Ph), 4.79 (dd, $J = 3.90$, 7.62 Hz, 1H, H-2), 4.59–4.45 (m, 4H, CH_2Ph, H-4, H-5), 4.02 (d, $J = 3.63$ Hz, 1H, H-3), 3.26–3.20 (m, 2H, H-6), 2.05 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5 (HC=N), 137.9 (Ar q*C*), 137.8 (Ar q*C*), 129.1, 129.0, 128.8, 128.6, 128.5, 128.1 (Ar*C*), 86.3 (CH), 82.0 (CH), 79.5 (CH), 76.7 (CH_2), 75.3 (CH), 73.1 (CH_2), 1.1 (CH_2I); IR (neat, cm^{-1}) 3448 , 2933, 2873, 1596, 1496, 1455, 1257, 1081, 1035; mass (ESI-MS) m/z 467; found 468 $[M+1]^{+\cdot}$, 461, 340 $[M-I]^{+\cdot}$; EI-HRMS: calcd for $C_{20}H_{22}NO_4I$: 467.0594, measured 467.0610.

4.1.7. (1′*E*,2*S*,3*R*,4*S*,5*R*) 3-Benzyloxy-4-acetyloxy-5-iodomethyl tetrahydrofuran-2-carbaldehyde *O*-benzyl oxime 10. Yield 72%, colorless oil, eluent for column chromatography: EtOAc/hexane (1/24, v/v); $[\alpha]_D = +156.8$ (*c* 0.19, $CHCl_3$) R_f 0.47 (1/9, EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, $J = 7.74$ Hz, 1H, H-1′), 7.36–7.18 (m, 10H, ArH), 5.44 (d, $J = 3.63$ Hz, 1H, H-4), 5.09 (s, 2H, NOCH_2Ph), 4.76 (d, $J = 12.12$ Hz, 1H, CH_2Ph), 4.68 (dd, $J = 4.11$, 7.71 Hz, 1H, H-2), 4.65–4.60 (m, 1H, H-5), 4.57 (d, $J = 12.09$ Hz, 1H, CH_2Ph), 4.04 (d, $J = 4.08$ Hz, 1H, H-3), 3.29–3.15 (m, 2H, H-6), 2.10 (s, 3H, COCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3 (*C*OMe), 147.9 (HC=N), 137.9 (Ar q*C*), 137.7 (Ar q*C*), 129.0, 128.9, 128.7, 128.6, 128.5, 128.3 (Ar*C*), 84.1 (CH), 80.6 (CH), 79.6 (CH), 76.7 (CH_2), 76.6(CH), 72.8 (CH_2), 21.3 (CH_3), −0.3 (CH_2I); IR (neat, cm^{-1}) 3032, 2922, 1744, 1596, 1496, 1454, 1371, 1230, 1065, 1032; mass (ESI-MS) m/z 509; found 511 $[M+2]^{+\cdot}$, 510 $[M+1]^{+\cdot}$, 382 $[M-I]^{+\cdot}$.

4.1.8. (1′*Z*,2*S*,3*R*,4*S*,5*R*) 3-Benzyloxy-4-hydroxy-5-iodomethyl tetrahydrofuran-2-carbaldehyde *O*-benzyl oxime 7b. Yield 29%, colorless oil, eluent for column chromato-

graphy: EtOAc/hexane (3/47, v/v); $[\alpha]_D = +141.25$ (*c* 0.16, $CHCl_3$); R_f 0.56 (1/4, EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.21 (m, 10H, ArH), 6.91 (d, $J = 4.26$ Hz, 1H, H-1′), 5.30 (t, $J = 3.99$, 4.08 Hz, 1H, H-2), 5.10 (s, 2H, NOCH_2Ph), 4.50–4.44 (m, 3H, CH_2Ph, H-5), 4.39 (br s, 1H, H-4), 4.26 (d, $J = 3.75$ Hz, 1H, H-3), 3.26–3.23 (m, 2H, H-6), 1.98 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2 (HC=N), 138.1 (Ar q*C*), 129.1, 129.0, 128.9, 128.7, 128.6, 128.4, 128.2 (Ar*C*), 85.4 (CH), 81.9 (CH), 77.7 (CH), 77.0 (CH_2), 75.3 (CH), 73.1 (CH_2), 1.0 (CH_2I); IR (neat, cm^{-1}) 3433, 2928, 1596, 1496, 1455, 1209, 1088, 1026; mass (ESI-MS) *m*/*z* 467; found 468 $[M+1]^{+\cdot}$, 454, 432, 340 $[M-I]^{+\cdot}$.

4.1.9. (1′*E*,2*S*,3*R*,4*S*,5*S*) 3-Benzyloxy-4-hydroxy-5-iodomethyl tetrahydrofuran-2-carbaldehyde *O*-benzyl oxime 7c. Yield 12%, a colorless solid (mp 68–70 °C), eluent for column chromatography: EtOAc/hexane (3/47, v/v); $[\alpha]_D = -7.5$ (*c* 0.16, $CHCl_3$); R_f 0.31 (1/4 EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, $J = 7.71$ Hz, 1H, H-1′), 7.37–7.24 (m, 10H, ArH), 5.11 (s, 2H, NOCH_2Ph), 4.72 (dd, $J = 5.07$, 7.74 Hz, 1H, H-2), 4.52 (s, 2H, CH_2Ph), 4.29 (t, $J = 2.97$, 1H, H-4), 4.02 (dd, $J = 2.85$, 5.10 Hz, 1H, H-3), 3.93 (ddd, $J = 3.63$, 5.61, 9.12 Hz, 1H, H-5), 3.37–3.26 (m, 2H, H-6), 2.12 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4 (HC=N), 137.8 (Ar q*C*), 137.7 (Ar q*C*), 129.1, 129.0, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 127.9 (Ar*C*), 86.2 (CH), 85.3 (CH), 79.4 (CH), 79.1 (CH), 76.7 (CH_2), 73.0 (CH_2), 6.6 (CH_2I); IR (neat, cm^{-1}) 3409, 3029, 2925, 1610, 1495, 1455, 1364, 1216, 1074, 1024; mass (ESI-MS) *m*/*z* 467; found 468 $[M+1]^{+\cdot}$, 432, 340 $[M-I]^{+\cdot}$; EI-HRMS: calcd for $C_{20}H_{22}NO_4I$: 467.0594, measured 467.0548.

4.1.10. (1′*Z*,2*S*,3*R*,4*S*,5*S*) 3-Benzyloxy-4-hydroxy-5-iodomethyl tetrahydrofuran-2-carbaldehyde *O*-benzyl oxime 7d. Yield 2%, colorless oil, eluent for column chromatography: EtOAc/hexane (3/47, v/v); $[\alpha]_D = +114.0$ (*c* 0.05, $CHCl_3$); R_f 0.47 (1/4 EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.27 (m, 10H, ArH), 6.93(d, $J = 4.38$ Hz, 1H, H-1′), 5.18 (t, $J = 4.32$ Hz, 1H, H-2), 5.11 (s, 2H, NOCH_2Ph), 4.46 (s, 2H, CH_2Ph), 4.29 (br s, 1H, H-4), 4.17 (dd, $J = 1.32$, 4.26 Hz, 1H, H-3), 4.01–3.95 (m, 1H, H-5), 3.34–3.30 (m, 2H, H-6), 1.83 (br s, 1H, OH); ^{13}C NMR (75 MHz) δ 150.3 (HC=N), 138.1 (Ar q*C*), 129.0, 128.8, 128.6, 128.5, 128.3 (Ar q*C*), 86.5 (CH), 85.8 (CH), 79.8 (CH), 77.8 (CH), 77.1 (CH_2), 73.2 (CH_2), 6.1 (CH_2I); IR (neat, cm^{-1}) 3448, 3019, 2928, 1645, 1457, 1368, 1218, 1080, 1033; mass (ESI-MS) *m*/*z* 467; found 468 $[M+1]^{+\cdot}$, 454, 432, 340 $[M-I]^{+\cdot}$.

4.1.11. (1′*E*,2*S*,3*R*,4*S*,5*R*)-3-Benzyloxy-4-hydroxy-5-iodomethyl tetrahydrofuran-2-carbaldehyde *O*-methyl oxime 8a. Yield 40%, a colorless solid (mp 59–62 °C), eluent for column chromatography: EtOAc/toluene (1/19, v/v); $[\alpha]_D = +60.0$ (*c* 0.28, $CHCl_3$); R_f 0.45 (1/4 EtOAc/toluene); ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, $J = 7.65$ Hz, 1H, H-1′), 7.41–7.28 (m, 5H, ArH), 4.81 (dd, $J = 3.87$, 7.62 Hz, 1H, H-2), 4.67–4.56 (m, 2H, OCH_2Ph), 4.53–4.48 (m, 2H, H-4, H-5), 4.08 (d, $J = 3.63$ Hz, 1H, H-3), 3.89 (s, 3H, OCH_3), 3.30–3.27 (m, 2H, H-6), 2.02 (br s, 1H, OH), ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8 (HC=N), 137.8 (Ar q*C*), 129.6, 129.1, 128.6, 128.3, 128.1 (Ar*C*), 86.3 (CH), 82.0 (CH), 79.5 (CH), 75.3 (CH), 73.1 (CH_2), 62.4 (CH_3), 1.1 (CH_2I); IR (KBr, cm^{-1}) 3421, 2937, 2820, 1594, 1458, 1385, 1351, 1276, 1108, 1033; mass (ESI-MS) *m*/*z* 391; found 393 $[M+2]^{+\cdot}$, 392 $[M+1]^{+\cdot}$, 264 $[M-I]^{+\cdot}$; EI-HRMS: calcd for $C_{14}H_{18}NO_4I$: 391.0281, measured 391.0266.

4.1.12. (1′*Z*,2*S*,3*R*,4*S*,5*R*)-3-Benzyloxy-4-hydroxy-5-iodomethyltetrahydrofuran-2-carbaldehyde *O*-methyl oxime 8b. Yield 27%, colorless oil, eluent for column chromatography: EtOAc/toluene (1/19, v/v); $[\alpha]_D = +69.8$ (*c* 0.41, $CHCl_3$); R_f 0.58 (1/4 EtOAc/toluene); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.28 (m, 5H, ArH), 6.89 (d, $J = 4.38$ Hz, 1H, H-1′), 5.26 (t, $J = 4.14$, 4.08 Hz, 1H, H-2), 4.58 (d, $J = 2.4$ Hz, 1H, CH_2Ph), 4.53–4.47 (m, 1H, H-5), 4.43 (br s, 1H, H-4), 4.28 (d, $J = 3.84$ Hz, 1H, H-3), 3.88 (s, 3H, OCH_3), 3.30–3.27 (m, 2H, H-6), 2.07 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6 (HC=N), 138.1 (Ar q*C*), 129.0, 128.8, 128.7, 128.5, 128.3 (Ar*C*), 85.2 (CH), 81.9 (CH), 77.4 (CH), 75.3 (CH), 73.1 (CH_2), 62.6 (CH_3), 1.02 (CH_2I); IR (Neat, cm^{-1}) 3434, 2933, 2820, 1596, 1457, 1384, 1352, 1209, 1077, 1044; mass (ESI-MS) *m*/*z* 391; found 393 $[M+2]^{+\cdot}$, 392 $[M+1]^{+\cdot}$, 264 $[M-I]^{+\cdot}$.

4.1.13. (1′*E*,2*S*,3*R*,4*S*,5*S*)-3-Benzyloxy-4-hydroxy-5-iodomethyl tetrahydrofuran-2-carbaldehyde *O*-methyl oxime 8c. Yield 9%, colorless oil, eluent for column chromatography: EtOAc/toluene (1/19, v/v); $[\alpha]_D = -11.1$ (*c* 0.18, $CHCl_3$); R_f 0.36 (1/4, EtOAc/toluene); ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, $J = 7.80$ Hz, 1H, H-1′), 7.39–7.28 (m, 5H, ArH), 4.71 (dd, $J = 5.01$, 7.80 Hz, 1H, H-2), 4.57 (s, 2H, OCH_2Ph), 4.32 (t, $J = 2.85$ Hz, 1H, H-4), 4.05 (dd, $J = 2.64$, 4.95 Hz, 1H, H-3), 3.95 (ddd, $J = 3.51$, 5.61, 8.82 Hz, 1H, H-5), 3.88 (s, 3H, OCH_3), 3.39–3.28 (m, 2H, H-6), 2.30 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7 (HC=N), 137.8 (Ar q*C*), 129.2, 128.6, 128.4 (Ar*C*), 86.3 (CH), 85.5 (CH), 79.4 (CH), 79.2 (CH), 73.0 (CH_2), 62.4 (CH_3), 6.7 (CH_2I); IR (KBr, cm^{-1}) 3437, 2926, 2856, 1595, 1458, 1382, 1351, 1040; mass (ESI-MS) *m*/*z* 391; found 393 $[M+2]^{+\cdot}$, 392 $[M+1]^{+\cdot}$, 264 $[M-I]^{+\cdot}$; EI-HRMS: calcd for $C_{14}H_{18}O_4NI$: 391.0281, measured 391.0231.

4.1.14. Mixture of 1′*E*- and 1′*Z*-(2*S*,3*R*,4*S*,5*R*) 3-benzyloxy-4-hydroxy-5-iodomethyl tetrahydrofuran-2-carbaldehyde oximes 9a and 9b. Yield 50%, colorless oil, eluent for column chromatography: EtOAc/toluene (2/23, v/v); R_f 0.34, 0.55 (3/7, EtOAc/toluene); ^1H (300 MHz, $CDCl_3$): δ 7.82 (br s, 0.7H, =N–O*H*), 7.52 (d, $J = 7.47$ Hz, 0.63H, H-1′, *E*-isomer), 7.39–7.28 (m, 5H, ArH), 6.94 (d, $J = 4.32$ Hz, 0.37H, H-1′, *Z*-isomer), 5.35 (t, $J = 4.05$ Hz, 0.5H, H-2, *Z*-isomer), 4.81 (dd, $J = 3.96$, 7.53 Hz, 0.7H, H-2, *E*-isomer), 4.61–4.57 (m, 2H, CH_2Ph), 4.54–4.43 (m, 2H, H-4, H-5), 4.34 (d, $J = 3.69$ Hz, 0.56H, H-3, *Z*-isomer), 4.07 (d, $J = 3.96$ Hz, 0.73H, H-3, *E*-isomer), 3.30–3.25 (m, 2H, H-6); ^{13}C (75 MHz, $CDCl_3$) δ 151.9 (HC=N), 149.5 (HC=N), 138.1 (Ar q*C*), 137.8 (Ar q*C*), 129.2, 129.0, 128.7, 128.5, 128.3, 128.2 (Ar*C*), 86.3 (CH), 85.4 (CH), 82.1 (CH), 81.9 (CH), 79.5 (CH), 77.1 (CH), 75.4 (CH) 75.3 (CH), 73.3 (CH_2), 73.1 (CH_2), 0.9 (CH_2I); IR (neat, cm^{-1}) 3414, 2926, 1596, 1459, 1383, 1352, 1094; mass (ESI-MS) *m*/*z*

377; found 378 $[M+1]^{+\cdot}$, 250 $[M-I]^{+\cdot}$; EI-HRMS: calcd for $C_{13}H_{16}O_4NI$: 377.0124, measured 377.0165.

4.1.15. Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside 12. To a solution of methyl α,D-mannopyranoside **11** (5.0 g, 25.8 mmol) in DMF (40 mL) were added benzaldehyde dimethylacetal (4.6 mL, 1.2 equiv) and camphorsulfonic acid (0.60 g, 2.58 mmol). The reaction mixture was allowed to stir at room temperature until completion of the reaction (TLC control, 24 h). Later, the reaction mixture was neutralized with triethylamine and DMF was evaporated under reduced pressure. The residue obtained was purified by column chromatography to give **12** (3.48 g, 48%) as a white solid. Eluent for column chromatography: EtOAc/hexane (1/1, v/v); $[\alpha]_D = +74.5$ (*c* 2.1, MeOH); R_f 0.48 (EtOAc); ^{1}H NMR (300 MHz, CD_3OD+$CDCl_3$) δ 7.53–7.49 (m, 2H), 7.40–7.35 (m, 3H), 5.61 (s, 1H), 4.71 (s, 1H), 4.27–4.22 (m, 4H), 3.96–3.93 (m, 2H), 3.41 (s, 3H), 2.01 (s, 0.8H); ^{13}C NMR (75 MHz, CD_3OD+$CDCl_3$) δ 137.2 (Ar q*C*), 128.7, 127.8, 126.0 (Ar*C*), 101.9 (CH), 101.8 (CH), 78.6 (CH), 70.7 (CH), 68.5 (CH_2), 67.9 (CH), 63.2 (CH), 54.5 (CH_3); IR (KBr, cm^{-1}) 3455, 3007, 2937, 2903, 1653, 1459, 1218, 1128, 1028; mass (ESI-MS) *m*/*z* 282; found 300 $[M+NH_4]^{+\cdot}$.

4.1.16. Methyl-2,3-di-*O*-benzyl-4,6-benzylidene-α,D-mannopyranoside 13. To a solution of **12** (1.30 g, 4.61 mmol) in dry toluene (16 mL) were added KOH (1.08 g, 19.3 mmol) and benzyl bromide (2.30 mL, 19.3 mmol) in succession. This reaction was then allowed to reflux until its completion (TLC control, 1 h). The reaction mixture was diluted with toluene (60 mL) and washed with water. The organic layer was evaporated to an oil. The oil was twice dissolved in toluene and the solvent was evaporated to dryness. The residue obtained was purified by column chromatography to give **13** (1.46 g, 69%) as a colorless oil. Eluent for column chromatography: EtOAc/hexane (1/9, v/v); $[\alpha]_D = +32.8$ (*c* 0.35, $CHCl_3$); R_f 0.46 (1/4, EtOAc/hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45–7.17 (m, 15H, ArH), 5.57 (s, 1H), 4.78–4.69 (m, 4H), 4.61 (d, $J = 3.69$ Hz, 1H), 4.22–4.13 (m, 2H), 3.86 (dt, $J = 3.22$ Hz, 2H), 3.77–3.68 (m, 2H), 3.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9 (Ar q*C*), 138.3 (Ar q*C*), 137.9 (Ar q*C*), 128.9, 128.5, 128.4, 128.3, 128.2, 127.9, 127.6, 126.2 (Ar*C*), 101.6 (CH), 100.6 (CH), 79.3 (CH), 76.5 (CH), 76.4 (CH), 73.7 (CH_2), 73.2 (CH_2), 69.0 (CH_2), 64.2 (CH), 54.9 (CH_3); IR (neat, cm^{-1}) 3064, 3033, 2917, 1606, 1455, 1376, 1210, 1125, 1058; mass (ESI-MS) *m*/*z* 462; found 463 $[M+1]^{+\cdot}$, 431 $[M-OMe]^{+\cdot}$.

4.1.17. Methyl-2,3-di-*O*-benzyl 6-deoxy-6-iodo-α,D-mannopyranoside 14. To a solution of **13** (1.35 g, 2.92 mmol) in dry methanol (36 mL) was added iodine (274 mg, 1.08 mmol) and the reaction mixture was heated at 80 °C. After the disappearance of **13**, the reaction mixture was cooled to rt, 10% aqueous $Na_2S_2O_3$ solution was added to it and the solution was evaporated to an oil, which was subsequently dissolved in water and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated to an oil (1.14 g), which was further used without purification. The oil (1.14 g) was dissolved in toluene (35 mL) and to this solution I_2 (1.15 g, 4.53 mmol), triphenylphosphine (1.12 g, 4.27 mmol), and imidazole (612 mg, 8.99 mmol) were added. The resultant reaction mixture was stirred at 50 °C till the disappearance of the starting material (TLC control, 1 h). The reaction mixture was cooled to room temperature, diluted with methanol, and the solvent was removed under reduced pressure. To the residue obtained was added 10% aqueous $Na_2S_2O_3$ solution (30 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was dried and evaporated to dryness. The Ph_3PO was precipitated with anhydrous diethyl ether. The resulting solution was decanted and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography to give **14** (1.2 g, 85% from **13**) as a colorless oil, eluent for column chromatography: EtOAc/toluene (1/24, v/v); $[\alpha]_D = -2.8$ (*c* 0.25, $CHCl_3$); R_f 0.57 (1/4, EtOAc/toluene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.28 (m, 10H), 4.80 (d, $J = 1.5$ Hz, 1H), 4.67–4.38 (m, 4H, 2 × CH_2Ph), 3.84 (br d, $J = 8.58$ Hz, 1H), 3.79 (dd, $J = 1.92$, 2.97 Hz, 1H) 3.68–3.62 (m, 2H), 3.52 (td, $J = 2.04$, 8.76 Hz, 1H), 3.41 (s, 3H), 3.33–3.26 (m, 1H), 2.33 (d, $J = 1.59$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1 (Ar q*C*), 137.9 (Ar q*C*), 128.7, 128.5, 128.1, 127.9 (Ar*C*), 99.3 (CH), 79.5 (CH), 73.8 (CH), 72.8 (CH_2), 72.2 (CH), 71.7 (CH_2), 70.6 (CH), 55.3 (CH_3), 6.7 (CH_2); IR (neat, cm^{-1}) 3447, 3033, 2925, 1654, 1458, 1201, 1120, 1071; mass (ESI-MS) *m*/*z* 484; found 502 $[M+NH_4]^{+\cdot}$, 342 $[M-I-Me]^{+\cdot}$, 279, 181.

4.1.18. (3*S*,4*S*,5*R*)-3,4-Bis(benzyloxy)-5-vinyl-tetrahydrofuran-2-ol 15. To a stirred suspension of Zn dust (1.35 g, 20.65 mmol) and NH_4Cl (1.10 g, 20.56 mmol) in dry methanol (35 mL) was added a catalytic amount of cyanocobalamine (10 mg, 0.007 mmol) and the resulting mixture was allowed to stir for 10 min. To the stirring mixture, methanolic solution of **14** (980 mg, 2.02 mmol) was added and the stirring was continued until the disappearance of the starting material (TLC control, 30 min.). The reaction mixture was filtered through a Celite bed and the filtrate was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (25 mL) and washed with a mixture of brine and water (1:1 v/v, 10 mL each). The organic layer was dried over Na_2SO_4 and concentrated to an oil, which after column chromatographic purification yield **15** (diastereomeric mixture, 510 mg, 77%) as a colorless oil. Eluent for column chromatography: EtOAc/toluene (3/47, v/v); R_f 0.43 (1/1, EtOAc/toluene); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37–7.32 (m, 10H, ArH), 6.17–5.99 (m, 1H), 5.42–5.25 (m, 3H), 4.79–4.57 (m, 4H), 4.37–4.26 (m, 1H), 4.04 (t, $J = 3.88$ Hz, 1H), 3.92 (t, $J = 4.20$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2 (Ar q*C*), 138.0 (Ar q*C*), 137.6 (Ar q*C*), 137.5 (Ar q*C*), 134.9 (=CH), 134.7 (=CH), 128.6, 128.5, 128.4, 128.1, 127.9, 127.8, 127.7 (Ar*C*), 118.7 (=CH_2), 100.2 (CH), 95.8 (CH), 83.6 (CH), 81.3 (CH), 81.1 (CH), 79.3 (CH), 79.2 (CH), 78.9 (CH), 74.0 (CH_2), 73.1 (CH_2), 72.6 (CH_2), 72.1 (CH_2); IR (neat, cm^{-1}) 3459, 3031, 2926, 2367, 1743, 1651, 1508, 1456, 1245, 1145, 1091, 1036; mass (ESI-MS) *m*/*z* 326; found 349 $[M+NH_4]^{+\cdot}$, 326 $[M]^{+\cdot}$, 309, 291.

4.1.19. (2*R*,3*S*,4*R*) 2,3-Bis(benzyloxy)-4-hydroxy hex-5-enal *O*-benzyl oxime 16. To a solution of **15** (380 mg, 1.17 mmol) in dry DCM (12 mL) were added *O*-benzyl-

hydroxylamine hydrochloride (466 mg, 2.92 mmol) and pyridine (0.3 mL) and this reaction mixture was allowed to reflux. After completion of the reaction (TLC control, 1 h), saturated aqueous solution of $NaHCO_3$ was added to neutralize the reaction mixture. The organic layer was separated, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The residue obtained was purified by column chromatography to obtain **16** (inseparable mixture of *E*- and *Z*-isomers, 485 mg 97%). Colorless oil, eluent for column chromatography: EtOAc/toluene (3/97, v/v); R_f 0.61 (3/7, EtOAc/toluene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, $J = 8.01$ Hz, 1H, H-1, *E*-isomer), 7.36–7.23 (m, 10H, ArH), 5.88 (ddd, $J = 5.34$, 10.56, 17.25 Hz, 1H, H-5), 5.31 (dt, $J = 1.53$, 17.28 Hz, 1H, H-6a), 5.20 (dt, $J = 1.44$, 10.38 Hz, 1H, H-6b), 5.13 (s, 2H, NOCH_2Ph), 4.71–4.33 (m, 4H, 2 × CH_2Ph), 4.24 (br dd, $J = 5.1$, 10.05 Hz, 1H, H-4), 4.15 (dd, $J = 6.15$, 7.95 Hz, 1H, H-2), 3.62 (dd, $J = 4.71$, 6.09 Hz, 1H, H-3), 2.68 (d, $J = 6.9$ Hz, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3 (HC=N), 148.7 (HC=N), 137.7 (Ar q*C*), 137.6 (Ar q*C*), 137.4 (Ar q*C*), 137.3 (=CH), 137.0 (=CH), 128.6, 128.4, 128.3, 128.2, 128.1, 128.0 (Ar*C*), 117.4 (=CH_2), 117.0 (=CH_2), 82.3 (CH), 81.7 (CH), 76.9 (CH), 76.6 (CH_2), 76.3 (CH_2), 74.4 (CH_2), 73.8 (CH_2), 72.4 (CH_2), 72.2 (CH), 72.0 (CH), 71.8 (CH), 71.3 (CH_2); IR (KBr, cm^{-1}) 3469, 3065, 3032, 2923, 2366, 1636, 1454, 1366, 1207, 1077; mass (ESI-MS) *m*/*z* 431; found 454 $[M+Na]^{+\cdot}$, 432 $[M+1]^{+\cdot}$.

4.1.20. (1′*E*,2*R*,3*R*,4*S*,5*R*) 3-Benzyloxy-4-hydroxy-5-iodomethyl tetrahydrofuran-2-carbaldehyde *O*-benzyl oxime 17a. Yield 40%, a white solid (mp 82–84 °C), eluent for column chromatography: EtOAc/toluene (1/49, v/v); $[\alpha]_D = +61.9$ (*c* 0.36, $CHCl_3$); R_f 0.63 (1/4 EtOAc/toluene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, $J = 6.45$ Hz, 1H, H-1′), 7.37–7.25 (m, 10H, ArH), 5.01 (s, 2H, NOCH_2Ph), 4.63 (dd, $J = 1.95$, 6.33 Hz, 1H, H-2), 4.60 (d, $J = 11.31$ Hz, 1H, CH_2Ph), 4.54 (d, $J = 11.85$ Hz, 1H, CH_2Ph), 4.38–4.32 (m, 2H, H-4 and H-5), 4.04 (d, $J = 1.38$ Hz, 1H, H-3), 3.24 (d, $J = 7.14$ Hz, 2H, H-6), 2.18 (d, $J = 5.97$ Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7 (HC=N), 137.3 (Ar q*C*), 137.2 (Ar q*C*), 128.7, 128.6, 128.5, 128.2, 127.9 (Ar*C*), 87.6 (CH), 82.6 (CH), 81.6 (CH), 76.4 (CH_2), 75.7 (CH), 72.0 (CH_2), 0.05 (CH_2); IR (KBr, cm^{-1}) 3548, 3029, 2921, 2364, 1629, 1454, 1387, 1235, 1081, 1021; mass (ESI-MS) *m*/*z* 467; found 468 $[M+1]^{+\cdot}$, 454, 432, 340 $[M-I]^{+\cdot}$.

4.1.21. (1′*Z*,2*R*,3*R*,4*S*,5*R*) 3-Benzyloxy-4-hydroxy-5-iodomethyl tetrahydrofuran-2-carbaldehyde *O*-benzyl oxime 17b. Yield 33%, colorless oil. Eluent for column chromatography: EtOAc/toluene (1/49, v/v); $[\alpha]_D = -47.3$ (*c* 0.26, $CHCl_3$); R_f 0.48 (1/4 EtOAc/toluene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.25 (m, 8H, ArH), 7.16–7.13 (m, 2H, ArH), 6.82 (d, $J = 4.62$ Hz, 1H, H-1′), 5.20 (dd, $J = 0.45$, 4.26 Hz, 1H, H-2), 5.11 (s, 2H, NOCH_2Ph), 4.57 (d, $J = 12.12$ Hz, 1H, CH_2Ph), 4.42–4.36 (m, 2H, CH_2Ph, H-5), 4.32 (br s, 1H, H-4), 4.01 (s, 1H, H-3), 3.29 (d, $J = 7.65$ Hz, 2H, H-6), 1.82 (d, $J = 3.9$ Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9 (HC=N), 137.7 (Ar q*C*), 137.3 (Ar q*C*), 128.6, 128.5, 128.3, 127.9, 127.6 (Ar*C*), 88.1 (CH), 82.5 (CH), 79.5 (CH), 76.8 (CH_2) 74.7 (CH), 71.7 (CH_2), 0.1 (CH_2); IR (neat, cm^{-1}) 3430, 3064, 3033, 2925, 1603, 1455, 1365, 1091, 1024; mass (ESI-MS) *m*/*z* 467; found 468 $[M+1]^{+\cdot}$, 454, 432, 340 $[M-I]^{+\cdot}$.

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22. The two Newman projections shown in Figure 4 representing oximes **16** and **4**–**6** are the most probable conformations for iodocyclization. In the case of the mannose derived oxime **16** the one face of C=C bond was crowded by OBn at C-2 rendering preferential electrophilic attack by iodine on the opposite face of the double bond whereas the formation of I_2-π complex in the case of **4**–**6** was possible on both the sides of the double bond. Our explanation on facial selectivity in the process of iodocyclization of oxime ethers is based on an earlier report by Chamberlin et al.[21b]