JOC The Journal of Organic Chemistry

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Stereocontrolled Debenzylative Cycloetherification Reaction as a Route to Enantiopure *C*-Furanosides with Amino Substituents in the Side Chain

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Cite This: *J. Org. Chem.* 2020, 85, 3517−3526 Read Online

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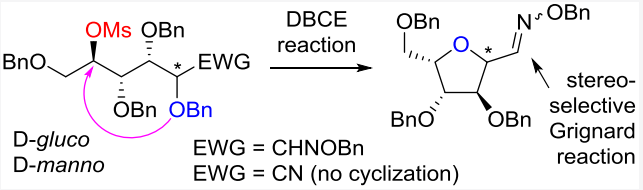
ABSTRACT: A highly efficient methodology of the preparation of synthetically important tetrahydrofuran derivatives with an amino substituent in the side chain is reported. This process is based on the stereocontrolled debenzylative cycloetherification (DBCE) reaction applied for chirons from the D-*gluco*- and D-*manno*-series and provides derivatives with new stereogenic centers. The influence of the electron-withdrawing group (EWG), present in the acyclic substrates with the mesyl leaving group, on the reactivity in the DBCE reaction was investigated both "in the flask" and by density functional theory (DFT) calculations. It was demonstrated that tetrahydrofuran derivatives with the benzoxime group (EWG = CHNOBn) are very good candidates for the subsequent highly stereoselective Grignard reaction.



INTRODUCTION

The evolution of the pharmaceutical industry entails intensive scientific research in the area of biologically active compounds. One of the most important types of such compounds are carbohydrates, which play an exclusive role due to their natural genesis, chirality, water solubility, etc.[1] Most carbohydrate derivatives have cyclic, usually pyranose, or furanose structures. Carbohydrates in the furanose form occur as building blocks in nucleic acids; therefore, many nucleoside analogs have been prepared for pharmaceutical investigation. Some of these compounds are used as commercial drugs, such as cytarabine, a medicament in leukemia chemotherapy,[2] or vidarabine, an antiviral drug with activity against herpes simplex and varicella zoster viruses.[3] The development and improvement of efficient synthetic methods for the preparation of such types of compounds are actually challenging for organic chemists.

Among different types of furanose carbohydrates, we focused our attention on *C*-furanosides.[4] They are present in biologically active, naturally occurring molecules among others in polyether antibiotics. For example, pyrazofurin, isolated from the culture filtrate of a strain of *Streptomyces candidus*, is effective against parasitic infections,[5] and (+)-Varitriol, isolated from the marine strain of the fungus Emericella Variecolor (M75-2), exhibits potent cytotoxicity against a variety of cancer cell lines.[6−8] Amino acid (**A**) has been incorporated as a scaffold into anticancer peptides, inhibiting growth of cancer cells.[4,9] A library of 10-α/β-D-arabinofuranosyl-undecenes (**B**) is a potential antimycobacterial agent, targeting enzymes involved in the biosynthesis of the cell wall of *Mycobacterium tuberculosis* (Figure 1).[4,10]

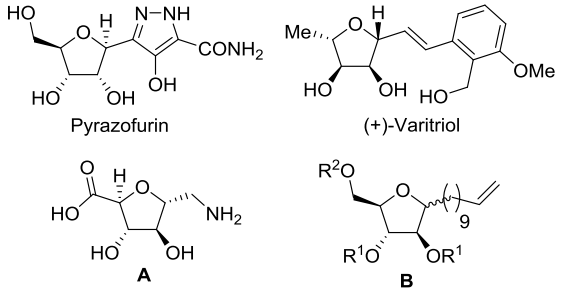


Figure 1. Examples of biologically active *C*-furanosides.

Typical methods of the synthesis of *C*-furanosides, which are based on the nucleophilic substitution reaction of the *O*-, *N*-, *S*-, or *Hal*-furanose derivatives by the corresponding *C*-nucleophiles, often yield a mixture of both anomers. The efficient preparation of the minor diastereomeric product can thus be problematic when this process is highly stereoselective.[4]

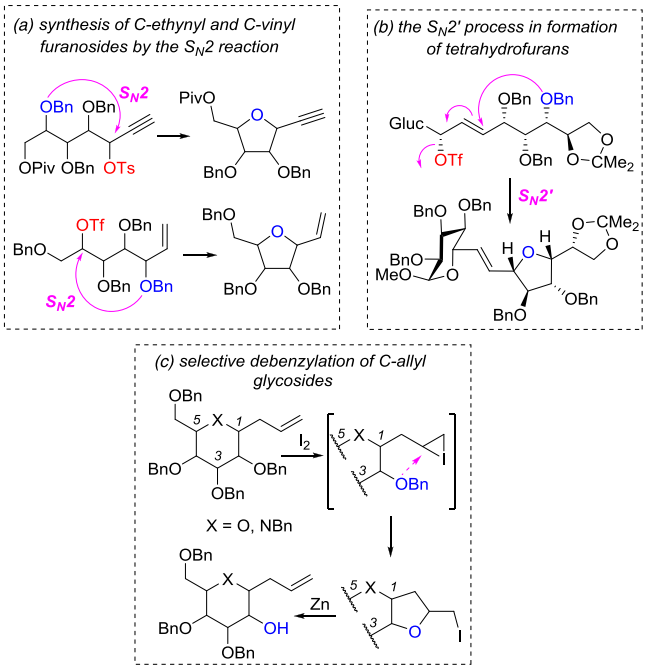
This problem can be overcome by a stereospecific cyclization of linear carbohydrates, i.e., the S_N2 reaction between the nucleophilic free hydroxyl group and the reactive sp^3-center located at the 1,5-position. Although this method is usually limited to compounds with one unprotected hydroxyl group and one leaving group (LG),[4] it can also be applied to

Received: December 2, 2019
Published: January 23, 2020

https://dx.doi.org/10.1021/acs.joc.9b03247
J. Org. Chem. 2020, 85, 3517−3526

fully protected linear derivatives containing a leaving group. The protected, such as a benzyl ether, oxygen function can also act as a nucleophile and attack the sp^3-carbon atom connected to the effective leaving group in the debenzylative cycloetherification (DBCE) process.[11−15] This methodology was successfully used for the preparation of *C*-ethynyl[13] and *C*-vinyl[14] furanosides as shown in Scheme 1a. During the synthesis of higher carbon sugars, we observed a similar rearrangement in which the protected oxygen nucleophile attacked the allylic analog in the S_N2' mode, which afforded the corresponding tetrahydrofuran derivative (Scheme 1b).[16] The process was also used for the selective deprotection of the 2-OH group in a fully benzylated *C*-allyl glycoside as reported recently by Blériot and co-workers (Scheme 1c).[17]

Scheme 1. Application of the DBCE Reaction in the Synthesis of *C*-Furanosides via the S_N2 (a) and S_N2' (b) Processes and in Selective Deprotection (c)

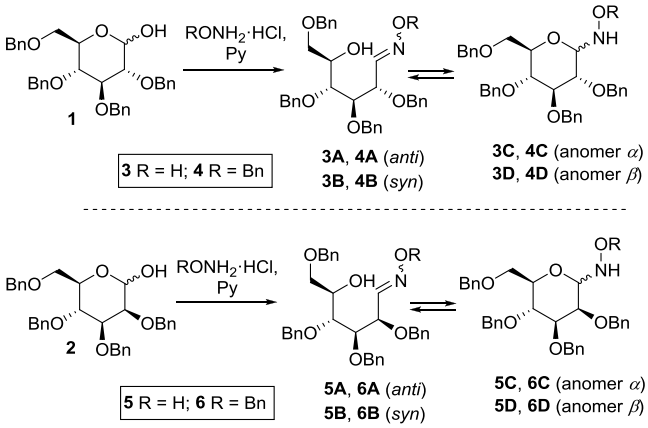


It seemed reasonable that such processes can be also adapted for the preparation of *C*-furanose derivatives containing the nitrile or oxime functionality attached directly to the 5-membered ring. The synthesis could be initiated from the corresponding linear carbohydrate derivatives containing the terminal nitrile or oxime groups; this concept is shown in Figure 2.

RESULTS AND DISCUSSION

Synthesis. We have initiated our syntheses of functionalized tetrahydrofurans from known tetra-*O*-benzylated derivatives of glucose and mannose (**1** and **2**, respectively).[18] These hexoses were converted, under standard conditions, either to oximes **3** and **5** (in 80−90% yield) or to protected oximes **4** and **6** (Scheme 2). Products **3**−**6** could exist in four dynamic isomeric forms: *anti*-oxime (**A**), *syn*-oxime (**B**), *α*-pyranoside (**C**), and *β*-pyranoside (**D**).

Scheme 2. Synthesis of Hydroxyoximes 3 and 5 and Benzoxyoximes 4 and 6



All synthesized compounds were fully characterized by the one- (^1H, ^{13}C) and two-dimensional (2D) ($^1H-^1H$ COSY and $^1H-^{13}C$ HSQC) NMR, elemental analysis, as well as high-resolution mass spectrometry (HRMS). Careful analysis of the NMR data of products **3**−**6** allowed us to detect the presence of isomers **A**, **B**, **C**, and **D**. The cyclic forms (C, D) were observed in the spectra of benzyloxy derivative **5** (corresponding signals from anomeric protons H^C-1 and H^D-1 were observed at δ = 5.05 and 4.32 ppm, respectively); the ratio of all isomers was assigned at **5A**/**5B**/**5C**/**5D** ≈ 5:1.25:1:1. In the spectra of analogous **3**, **4**, and **6**, only the *syn*- and *anti*-isomers were observed in each case in the ratio ∼1:4, respectively. In the ^1H NMR spectra of compounds **3**−**6**, the signals from H-1 are located at 7.44−7.56 ppm for *anti*-isomers **A** and at 6.88−6.93 ppm for *syn*-isomers **B**.

It is well documented that the mesylation of *ω*-hydroxy carbohydrate hydroxymes affords *ω*-methylatocarbohydrate nitriles.[19] Application of this reaction to compounds **3** and **4** allowed, as expected, the preparation of nitryl-methanesulfonates **7** and **8** (in 70 and 78% yields, respectively; Scheme 3). However, all attempts to convert these useful intermediates into tetrahydrofuran derivatives (**9** and **10**) failed. In all cases—including refluxing of substrates in different solvents (toluene, acetonitrile, 1,4-dioxane, pyridine) with or without a base (triethylamine, sodium acetate, potassium carbonate, pyridine) even for 7 days—only the starting material was isolated, which indicated that nitriles **7** and **8** are very inert under the debenzylative cycloetherification conditions leading to *C*-furanosides.

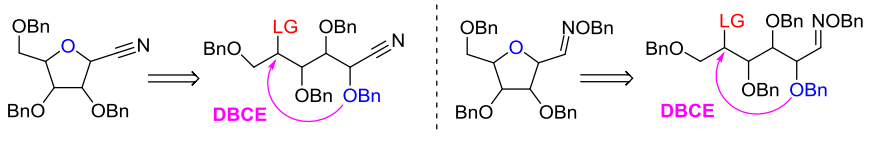


Figure 2. Retrosynthetic analysis to prepare *C*-nitrile- and *C*-benzoxime-furanosides.

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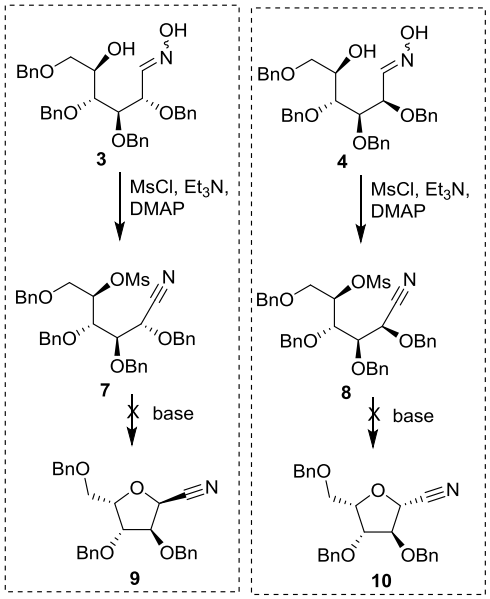
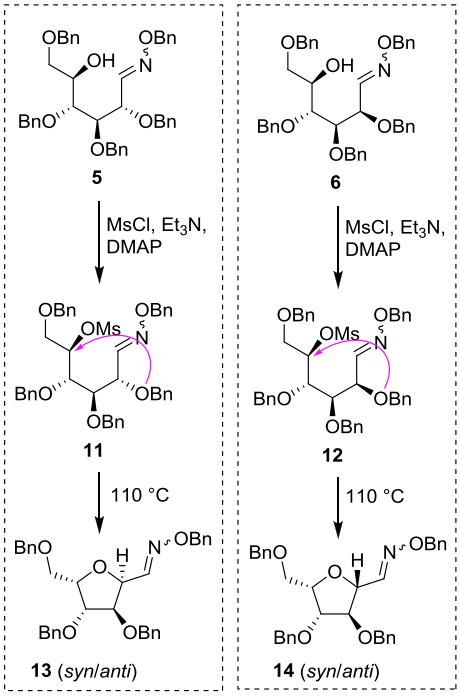
Scheme 3. Synthesis of Nitriles 7 and 8 and Unsuccessful Attempts of their Cyclization



However, much better results were obtained in the cyclization reaction of the protected oximes under analogous conditions. Mesylation of benzoximes **5** and **6** afforded compounds **11** and **12** in good yields (76 and 70%, respectively). Heating of these mesylates in toluene at reflux induced the desired cyclization and furnished furanosides **13** and **14** in very high yields (90 and 99%, respectively; Scheme 4).

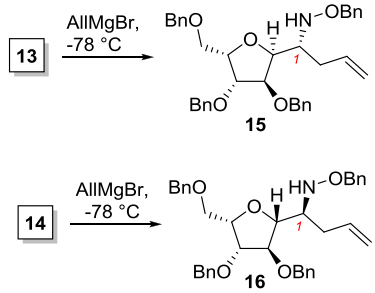
Because of the dynamic isomerization of the benzoxime group, compounds **13** and **14** were obtained as *syn*/*anti* pairs as can be judged from the NMR data (i.e., signals of the H-1 atom are located at δ = 6.97 and 7.56 ppm for *syn*-**13** and *anti*-**13** isomers, respectively, while in the case of *syn*/*anti*-**14**, the corresponding signals are located at δ = 6.82 and 7.47 ppm).

Scheme 4. Formation of Tetrahydrofurans 13 and 14



Since the benzoxime group is a good acceptor of nucleophilic species, its presence should allow the efficient preparation of a number of interesting amino derivatives. Therefore, we decided to test benzoximes **13** and **14** in the Grignard reaction. Indeed, reaction of both isomers with allylmagnesium bromide afforded the corresponding amines **15** and **16** in good yields (70 and 68%, respectively). It is worth mentioning that both reactions were highly stereoselective and only one stereoisomer was isolated in each case (Scheme 5).

Scheme 5. Grignard Reaction of Benzoximes 13 and 14 with Allylmagnesium Bromide



The configuration at the C-1 center in products **15** and **16** can be assigned with high probability by the conformation analysis, which is shown in Scheme 6. According to the Cram chelating model, the simultaneous coordination of magnesium to the benzoxime nitrogen and the α-endocyclic oxygen atoms of compounds **13** and **14** forms cyclic α-chelates **13A** and **14A**, respectively. In the case of intermediate **13A**, the attack of the allylic nucleophile should be favored from the Re side, giving product **15** with the *R*-configuration at the C-1 stereocenter. Meanwhile, α-chelate **14A** could be evidently attacked by the *C*-nucleophile from the Si side, leading to isomer **16** with the 1*S*-configuration. Such a predicted stereochemical outcome is in good agreement with that previously described for the addition reactions of nucleophiles with *C*-furanosyl carbaldehydes or their imines.[20]

Density Functional Theory (DFT) Calculation. To gain a better understanding of the different reactivities of the investigated mesylates vs nitriles, density functional theory (DFT) computational studies were performed for transformations **7** → **9** and **11** → **13**. Geometrical structures of substrates **7** and **11**, products **9** and **13**, intermediates **im-7,9** and **im-11,13**, as well as transition states **TS-7**, **TS-11**, **imTS-7,9**, and **imTS-11,13** (Figures 3 and 4) were optimized, and the relative Gibbs free energy (ΔG) values were calculated with the addition of the toluene solvent effect utilizing the solvation model based on density (SMD).

Comparison of the ΔG values of each component in both DBCE transformations clearly demonstrates that in the case of nitrile **7** (Figure 3), the transition energy barriers are higher than for benzoxime analog **11** (Figure 4). The relative Gibbs free energies for **TS-7** and **TS-11** were estimated as 35.7 and 30.7 kcal/mol, respectively, while the corresponding energies of transition states **imTS-7,9** and **imTS-11,13** were 37.3 and 35.3 kcal/mol. In addition, the intermediate product of the reaction **7** → **9** (**im-7,9**, ΔG = 26.36 kcal/mol) is less stable by approximately 5.5 kcal/mol than analogous **im-11,13** (ΔG = 20.84 kcal/mol). Moreover, the relative Gibbs free energy of

https://dx.doi.org/10.1021/acs.joc.9b03247
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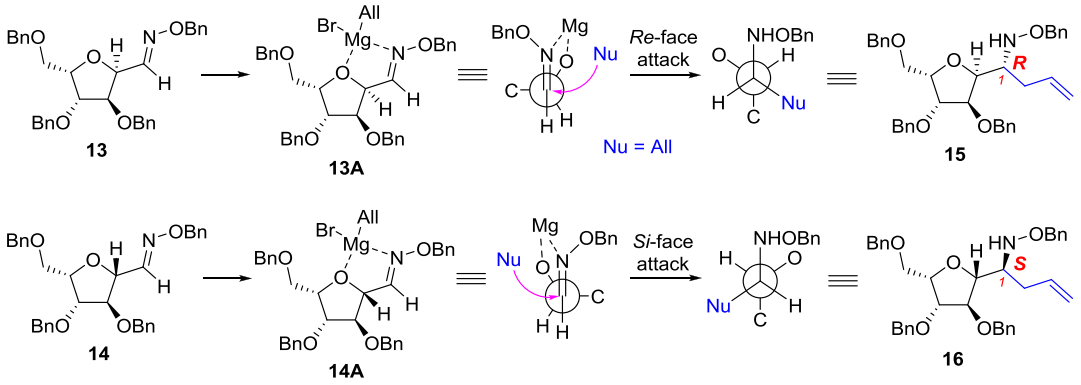
Scheme 6. Proposed Mechanism of the Grignard Reaction of Benzoximes 13 and 14 with Allylmagnesium Bromide



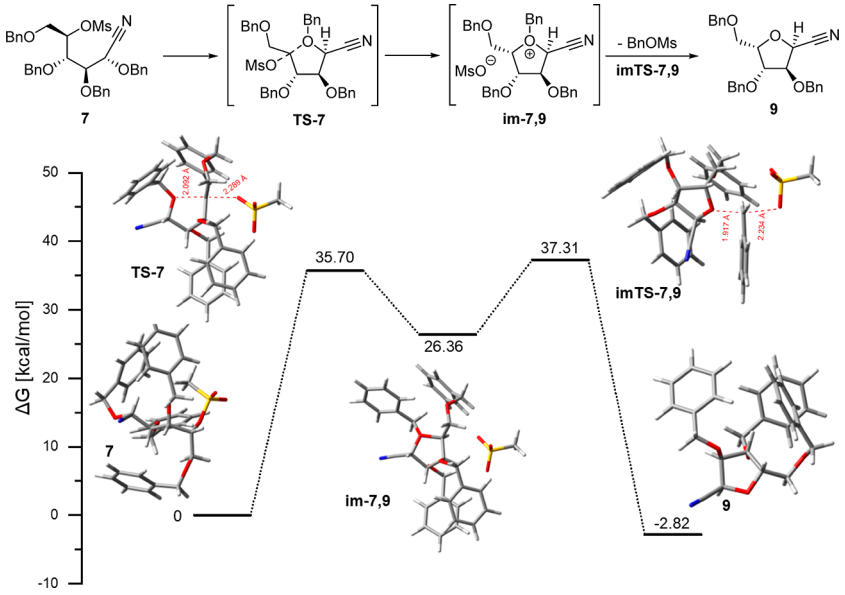


Figure 3. Gibbs free energy diagram of transformation of linear compounds **7** into *C*-furanoside **9**.

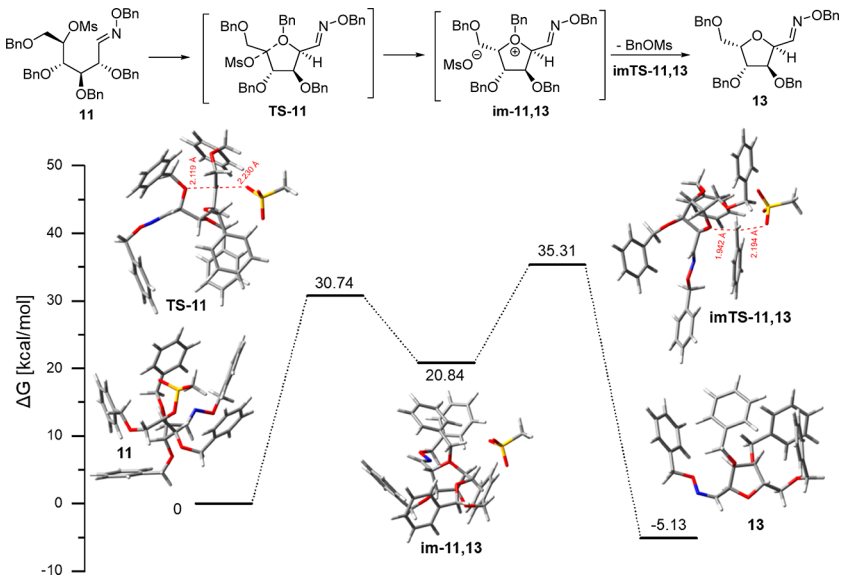


Figure 4. Gibbs free energy diagram of transformation of linear compounds **11** into *C*-furanoside **13**.

C-furanoside **11** (ΔG = −5.13 kcal/mol) is lower than the corresponding value of product **9** (ΔG = −2.82 kcal/mol). It can be unequivocally postulated that reaction **11** → **13** is thermochemically and kinetically more favorable than reaction

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7 → 9, which is in accordance with the results of the experiments in the flask but does not fully explain why we do not obtain the expected products in the reaction 7 → 9.

On the other hand, one of the key aspects that affects the course of these reactions is the electron density of the oxygen atom involved in the intramolecular S_N2 reaction. The presence of the highly electron-withdrawing nitrile group in close proximity to the "nucleophilic" oxygen atom in compound 7 induces the decrease of the electron density of this oxygen atom. We decided to illustrate the impact of the substituents by calculation of partial charges (Figures S1−S10 in the Supporting Information). Natural bond orbital (NBO) analysis was used to calculate the charges, as it gives much more reliable results than the default Mulliken method implemented in the Gaussian package. The partial charge on the oxygen atom involved in the cyclization reaction at each stage (except for the intermediate stage) of the transformation of compounds 11 into furanoside 13 is more negative than in the transformation of substrate 7 into product 9 (Table 1).

Table 1. NBO Atomic Charges on the Oxygen Atom Involved in the Intramolecular S_N2 Reaction

	reaction 7 → 9
structure	Bn−O−CH−CN
7	−0.582
TS-7	−0.566
im-7,9	−0.458
imTS-7,9	−0.524
9	−0.587 (oxygen from tetrahydrofuran ring)
	reaction 11 → 13
structure	Bn−O−CH−CH═N−O
11	−0.629
TS-11	−0.581
im-11,13	−0.456
imTS-11,13	−0.546
13	−0.608 (oxygen from tetrahydrofuran ring)

Indirectly, the electron density of the oxygen atom affects its nucleophilicity. Therefore, the calculated values of partial charges demonstrate that in the case of transformation 11 → 13, the nucleophilic strength of the reactive oxygen atom is definitely stronger than that in reaction 7 → 9. These theoretical results indicate the differences in reactivity of mesylates 7 and 11 and are in good correlation with the experimental data.

CONCLUSIONS

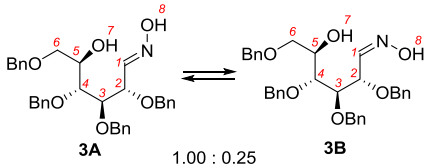
In conclusion, we have investigated the debenzylative cycloetherification reaction of 1,3,4,5-tetrakis(benzyloxy)-5-cyanopentan-2-yl methanesulfonates 7 and 8 and 2,3,4,6-tetrakis(benzyloxy)-5-hydroxyhexanal *O*-benzyl oximes 11 and 12. The compounds with the benzoxime group (11 and 12) are apparently more reactive in the DBCE reaction than the cyano-analogs (7 and 8). These differences in reactivity are caused by the stronger electron-withdrawing effect of the nitrile group on the nucleophilicity of the reactive oxygen atom at the α-position, in comparison with the corresponding influence of the benzoxime group. The experimental results were confirmed by DFT calculation. The obtained *C*-furanosides with the benzoxime group in the side chain (tetrahydrofurans 13 and 14) are good candidates for stereoselective modification in the Grignard reaction with allylmagnesium bromide.

EXPERIMENTAL SECTION

General. The NMR spectra were recorded with Varian VNMRS 500 MHz or Varian VNMRS 600 MHz spectrometers for solutions in $CDCl_3$ at 25 °C. The structures were assigned, whenever necessary, with the help of 2D correlation experiments (COSY, HSQC, HMBC). Chemical shifts were reported with reference to tetramethylsilane (TMS). Optical rotations were measured with a Jasco P 1020 polarimeter (sodium light) in chloroform at room temperature. Mass spectra were recorded with a Synapt G2-S HDMS (Waters Inc) mass spectrometer equipped with an electrospray ion source and a q-TOF-type mass analyzer. The instrument was controlled and recorded data were processed using the MassLynx V4.1 software package (Waters Inc). Thin-layer chromatography (TLC) was performed on silica gel plates coated with a fluorescent indicator. Column chromatography was performed on silica gel (Merck, 230−400 mesh). Organic solutions were dried over anhydrous $MgSO_4$.

Synthesis. *Synthesis of Compounds 3−6 (General Procedure A).* To a solution of alcohol 1 or 2 (200−230 mg, 0.37−0.43 mmol) in pyridine (8 mL), hydroxyammonium chloride or *O*-benzylhydroxylamine hydrochloride (2.5 equiv, 0.92−1.07 mmol) was added. The mixture was stirred for 3 h at room temperature (for $HONH_2$·HCl) or for 8 h at 55 °C (for $BnONH_2$·HCl). Then, pyridine was evaporated in vacuum, ethyl acetate (40 mL) was added, and the residue was washed with 1 M H_2SO_4 (15 mL), water (25 mL), and brine (15 mL). The organic phase was dried and concentrated. The products 3−6 were purified by flash chromatography (hexanes/ethyl acetate = 85:15, v/v).

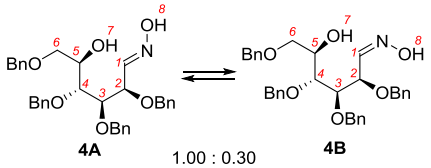
(2S,3R,4R,5R)-2,3,4,6-Tetrakis(benzyloxy)-5-hydroxyhexanal Oxime (3A + 3B).



This compound was obtained in 87% yield (193 mg) from 1 (215 mg, 0.40 mmol) and hydroxylammonium chloride (69 mg, 1.00 mmol) as an isomeric mixture in a 1.00:0.25 ratio; colorless oil. TLC (hexanes/AcOEt = 2:1): R_f = 0.60. $[\alpha]_D^{22}$ = +21.7. ^{1}H NMR (600 MHz): δ 8.36 (0.25H, br s, H^B-8), 7.97 (1H, br s, H^A-8), 7.44 (1H, d, $J_{1,2}$ = 8.0 Hz, H^A-1), 7.15−7.34 (25H, m, ArH), 6.92 (0.25H, d, $J_{1,2}$ = 7.3 Hz, H^B-1), 5.12 (0.25H, dd, $J_{2,1}$ = 7.3 Hz, $J_{2,3}$ = 5.0 Hz, H^B-2), 4.64−4.73 (2.50H, m, 2 × OC$\underline{H}^A_2$Ph, 2 × OC$\underline{H}^B_2$Ph), 4.58 (1H, *J* = 11.7 Hz, OC$\underline{H}^A_2$Ph), 4.55 (0.50H, *J* = 11.5 Hz, 2 × OC$\underline{H}^B_2$Ph), 4.41−4.51 (4.75H, m, 4 × OC$\underline{H}^A_2$Ph, 3 × OC$\underline{H}^B_2$Ph), 4.35 (0.25H, *J* = 11.7 Hz, OC$\underline{H}^B_2$Ph), 4.27 (1H, d, *J* = 11.7 Hz, OC$\underline{H}^A_2$Ph), 4.27 (1H, dd, $J_{2,1}$ = 8.0 Hz, $J_{2,3}$ = 6.3 Hz, H^A-2), 3.99−4.07 (2.50H, m, H^A-3, H^A-5, H^B-3, H^B-5), 3.78 (1H, dd, $J_{4,5}$ = 7.8 Hz, $J_{4,3}$ = 3.3 Hz, H^A-4), 3.75 (0.25H, dd, $J_{4,5}$ = 7.4 Hz, $J_{4,3}$ = 5.1 Hz, H^B-4), 3.62 (1H, dd, $J_{6,6'}$ = 9.6 Hz, $J_{6,5}$ = 3.4 Hz, H^A-6), 3.62 (0.25H, m, H^B-6), 3.57 (1H, dd, $J_{6',6}$ = 9.6 Hz, $J_{6',5}$ = 5.2 Hz, H^A-6′), 3.57 (0.25H, m, H^B-6′), 2.86 (0.25H, d, $J_{7,5}$ = 5.7 Hz, H^B-7), 2.75 (1H, d, $J_{7,5}$ = 5.9 Hz, H^A-7) ppm. ^{13}C NMR (150 MHz): δ 150.61 (C^B-1), 150.06 (C^A-1), 138.12, 137.93, 137.81, 137.59 (C_{quat}, 4 × C^A-Ph), 137.59−138.18 (C_{quat}, 4 × C^B-Ph), 127.55−128.41 (20 × C^A-Ph, 20 × C^B-Ph), 79.51 (C^A-3), 79.43 (C^B-3), 78.71 (C^B-4), 78.51 (C^A-4), 76.59 (C^A-2), 74.33, 74.00, 73.33, 70.60 (4 × O$\underline{C}^A$H$_2$Ph), 74.16, 74.06, 73.33, 71.69 (4 × O$\underline{C}^B$H$_2$Ph), 71.00 (C^A-6), 71.00 (C^B-6), 70.60 (C^B-2), 70.41 (C^B-5), 69.96 (C^A-5) ppm. HRMS (ESI-TOF) calcd for $C_{34}H_{37}NO_6Na$ [M + Na]$^+$: $C_{34}H_{37}NO_6Na$ [M + Na]$^+$: 578.2518, found: 578.2514. Analysis calcd for $C_{34}H_{37}NO_6$ (540.67): C, 73.49; H, 6.71; N, 2.52; found: C,73.42; H, 6.61; N, 2.35.

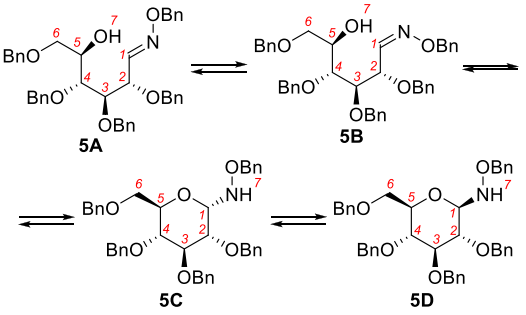
https://dx.doi.org/10.1021/acs.joc.9b03247
J. Org. Chem. 2020, 85, 3517−3526

*(2R,3R,4R,5R)-2,3,4,6-Tetrakis(benzyloxy)-5-hydroxyhexanal Oxime (**4A** + **4B**).*



This compound was obtained in 88% yield (209 mg) from **2** (230 mg, 0.43 mmol) and hydroxylammonium chloride (74 mg, 1.07 mmol) as an isomeric mixture in a 1.00:0.30 ratio; colorless oil. TLC (hexanes/AcOEt = 2:1): R_f = 0.50. ^{1}H NMR (600 MHz,): δ 7.85 (0.30H, br s, H^B-8), 7.52 (1H, br s, H^A-8), 7.44 (1H, d, J = 8.0 Hz, H^A-1), 7.36−7.15 (26H, m, ArH), 6.93 (0.30H, d, J = 7.2 Hz, H^B-1), 5.12 (0.30H, dd, $J_{2,1}$ = 7.2 Hz, $J_{2,3}$ = 5.2 Hz, H^B-2), 4.98 (0.3H, d, J = 11.4 Hz, OC$\underline{H}^B_2$Ph), 4.87 (0.3H, d, J = 10.7 Hz, OC$\underline{H}^B_2$Ph), 4.72 (0.3H, d, J = 11.3 Hz, OC$\underline{H}^B_2$Ph), 4.70 (1H, d, J = 11.3 Hz, OC$\underline{H}^A_2$Ph), 4.67 (1H, d, J = 11.3 Hz, OC$\underline{H}^A_2$Ph), 4.66 (0.3H, d, J = 11.3 Hz, OC$\underline{H}^B_2$Ph), 4.59 (1H, J = 11.7 Hz, OC$\underline{H}^A_2$Ph), 4.56 (0.3H, J = 11.7 Hz, 2 × OC$\underline{H}^B_2$Ph), 4.55 (0.3H, J = 11.2 Hz, 2 × OC$\underline{H}^B_2$Ph), 4.45−4.52 (3.3H, m, 3 × OC$\underline{H}^A_2$Ph, OC$\underline{H}^B_2$Ph), 4.43 (1H, J = 11.4 Hz, OC$\underline{H}^A_2$Ph), 4.36 (0.3H, J = 11.7 Hz, OC$\underline{H}^B_2$Ph), 4.29 (1H, d, J = 11.5 Hz, OC$\underline{H}^A_2$Ph), 4.27 (1H, dd, $J_{2,1}$ = 8.0 Hz, $J_{2,3}$ = 6.2 Hz, H^A-2), 4.02−4.06 (0.6H, m, H^B-3, H^B-5), 4.04 (1H, dd, $J_{3,2}$ = 6.2 Hz, $J_{3,4}$ = 3.2 Hz, H^A-3), 4.01 (1H, m, H^A-5), 3.78 (1H, dd, $J_{4,5}$ = 7.8 Hz, $J_{4,3}$ = 3.2 Hz, H^A-4), 3.75 (0.3H, dd, $J_{4,5}$ = 7.4 Hz, $J_{4,3}$ = 4.0 Hz, H^B-4), 3.63 (1H, dd, $J_{4,5}$ = 7.8 Hz, $J_{4,3}$ = 3.2 Hz, H^A-6), 3.62 (0.3H, m, H^B-6), 3.58 (1H, dd, $J_{4,5}$ = 7.8 Hz, $J_{4,3}$ = 3.2 Hz, H^A-6), 3.58 (0.3H, m, H^B-6), 2.78 (0.3H, d, $J_{7,5}$ = 5.8 Hz, H^B-7), 2.66 (1H, d, $J_{7,5}$ = 5.9 Hz, H^A-7) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, only the major isomer is quoted): δ 150.26 (C-1), 138.14, 137.96, 137.86, 137.61 (C$_{quat}$, 4 × C-Ph), 127.58−128.44 (20 × C-Ph), 79.48 (C-3), 78.52 (C-4), 76.59 (C-2), 74.33, 74.01, 73.36 (3 × O$\underline{C}$H$_2$Ph), 71.00 (C-6), 70.63 (O$\underline{C}$H$_2$Ph), 69.97 (C-5) ppm. HRMS (ESI-TOF) calcd for $C_{34}H_{37}NO_6Na$ [M + Na]$^+$: 578.2519, found: 578.2514. Analysis calcd for $C_{34}H_{37}NO_6$ (555.67): C, 73.49; H, 6.71; N, 2.52; found: C, 73.26; H, 6.73; N, 2.40.

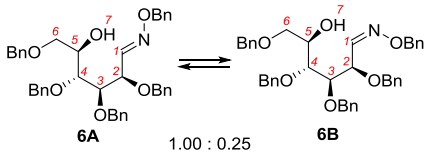
*(2S,3R,4R,5R)-2,3,4,6-Tetrakis(benzyloxy)-5-hydroxyhexanal O-benzyl Oxime (**5A** + **5B** + **5C** + **5D**).*



5A : **5B** : **5C** : **5D** = 1.00 : 0.25 : 0.20 : 0.20

This compound was obtained in 80% yield (199 mg) from **1** (208 mg, 0.38 mmol) and *O*-benzylhydroxylamine hydrochloride (154 mg, 0.96 mmol) as an isomeric mixture in a 1.00:0.25:0.20:0.20 ratio; yellowish oil. TLC (hexanes/AcOEt = 2:1): R_f = 0.70. ^{1}H NMR (600 MHz): δ 7.56 (1H, d, $J_{1,2}$ = 7.8 Hz, H^A-1), 7.06−7.43 (41.25H, m, ArH), 6.92 (0.25H, d, $J_{1,2}$ = 6.4 Hz, H^B-1), 6.15 (0.20H, s, H^C-7), 5.83 (0.20H, d, $J_{7,1}$ = 6.5 Hz, H^D-7), 5.09 (2H, s, OC$\underline{H}^A_2$Ph), 5.05 (0.20H, d, $J_{1,2}$ = 4.9 Hz, H^C-1), 5.03 (0.40H, s, OC$\underline{H}^{C/D}_2$Ph), 5.00 (0.20H, dd, $J_{2,1}$ = 6.4 Hz, $J_{2,3}$ = 4.1 Hz, H^B-2), 4.90 (0.20H, d, J = 11.0 Hz, OC$\underline{H}^{C/D}_2$Ph), 4.38−4.86 (13.90H, m, OC$\underline{H}^A_2$Ph, OC$\underline{H}^B_2$Ph, OC$\underline{H}^C_2$Ph, OC$\underline{H}^D_2$Ph), 4.36 (1H, dd, $J_{2,1}$ = 7.8 Hz, $J_{2,3}$ = 6.7 Hz, H^A-2), 4.32 (0.2H, dd, $J_{1,2}$ = 9.0 Hz, $J_{1,7}$ = 6.5 Hz, H^D-1), 4.14 (0.20H, m, H^D-5), 3.89−3.95 (1.70H, m, H^A-5, H^B-5, H^B-3, H^C-5), 3.89 (1H, dd, J = 6.6 Hz, J = 3.4 Hz, H^A-3), 3.77−3.84 (0.70H, m, H^C-4, H^B-4, H^B-6), 3.75 (0.25H, dd, $J_{6',6}$ = 10.8 Hz, $J_{6',5}$ = 3.8 Hz, H^B-6′), 3.65−3.73 (1.00H, m, H^C-2, H^D-3, H^C-6, H^C-6′, H^D-6), 3.69 (1H, dd, J = 7.2 Hz, J = 3.5 Hz, H^A-4), 3.62 (0.20H, dd, $J_{3,4}$ = 9.9 Hz, $J_{3,2}$ = 8.5 Hz, H^D-4), 3.47−3.59 (2.40H, m, H^C-3, H^A-6, H^A-6′, H^D-6′), 3.37 (0.20H, dd, $J_{2,1}$ = 9.0 Hz, $J_{2,3}$ = 8.5 Hz, H^D-2), 2.79 (0.25H, d, $J_{7,5}$ = 4.6 Hz, H^B-7), 2.63 (1H, d, $J_{7,5}$ = 5.6 Hz, H^A-7) ppm. ^{13}C NMR (150 MHz, only the major isomer is quoted): δ 148.90 (C-1), 136.12, 137.97, 137.92, 137.66, 137.62 (C$_{quat}$, 5 × C-Ph), 127.54−128.50 (25 × C-Ph), 79.46 (C-3), 77.70 (C-4), 76.84 (C-2), 75.93, 74.42, 73.45, 73.32, 71.26 (5 × O$\underline{C}$H$_2$Ph), 70.96 (C-6), 70.26 (C-5) ppm. HRMS (ESI-TOF) calcd for $C_{41}H_{43}NO_6Na$ [M + Na]$^+$: 668.2988, found: 668.2990. Analysis calcd for $C_{41}H_{43}NO_6$ (645.80): C, 76.25; H, 6.71; N, 2.17; found: C, 76.04; H, 6.72; N, 2.15.

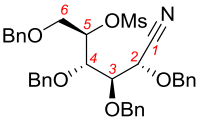
*(2R,3R,4R,5R)-2,3,4,6-Tetrakis(benzyloxy)-5-hydroxyhexanal O-benzyl Oxime (**6A** + **6B**).*



This compound was obtained in 90% yield (215 mg) from **2** (200 mg, 0.37 mmol) and *O*-benzylhydroxylamine hydrochloride (147 mg, 0.92 mmol) as an isomeric mixture in a 1.00:0.25 ratio; yellowish oil. TLC (hexanes/AcOEt = 2:1): R_f = 0.70. ^{1}H NMR (600 MHz): δ 7.46 (1H, d, $J_{1,2}$ = 8.1 Hz, H^A-1), 7.03−7.43 (31.25H, m, ArH), 6.88 (0.25H, d, $J_{1,2}$ = 7.3 Hz, H^B-1), 5.11 (1H, d, J = 12.0 Hz, OC$\underline{H}^A_2$Ph), 5.07 (1H, d, J = 12.0 Hz, OC$\underline{H}^A_2$Ph), 5.06−5.10 (0.75H, m, H^B-2, 2 × OC$\underline{H}^B_2$Ph), 4.68 (1H, d, J = 11.2 Hz, OC$\underline{H}^A_2$Ph), 4.67 (0.25, d, J = 11.4 Hz, OC$\underline{H}^B_2$Ph), 4.65 (1H, d, J = 11.2 Hz, OC$\underline{H}^A_2$Ph), 4.61 (0.25, d, J = 11.4 Hz, OC$\underline{H}^B_2$Ph), 4.53 (1H, d, J = 11.7 Hz, OC$\underline{H}^A_2$Ph), 4.44−4.50 (4.00H, m, 3 × OC$\underline{H}^A_2$Ph, 4 × OC$\underline{H}^B_2$Ph), 4.40 (1H, d, J = 11.4 Hz, OC$\underline{H}^A_2$Ph), 4.36 (0.25, d, J = 11.4 Hz, OC$\underline{H}^B_2$Ph), 4.30 (0.25, d, J = 11.7 Hz, OC$\underline{H}^B_2$Ph), 4.26 (1H, d, J = 11.7 Hz, OC$\underline{H}^A_2$Ph), 4.25 (1H, dd, $J_{2,1}$ = 8.1 Hz, $J_{2,3}$ = 6.3 Hz, H^A-2), 4.03 (1H, dd, $J_{3,2}$ = 6.3 Hz, $J_{3,4}$ = 3.1 Hz, H^A-3), 4.03 (0.25, m, H^B-5), 3.97−4.01 (1.25H, m, H^A-5, H^B-3), 3.75 (1H, dd, $J_{4,5}$ = 7.8 Hz, $J_{4,3}$ = 3.1 Hz, H^A-4), 3.71 (0.25, dd, $J_{4,5}$ = 7.6 Hz, $J_{4,3}$ = 4.0 Hz, H^B-4), 3.60 (1H, dd, $J_{6,6'}$ = 9.6 Hz, $J_{6,5}$ = 3.5 Hz, H^A-6), 3.56 (1H, dd, $J_{6',6}$ = 9.6 Hz, $J_{6',5}$ = 5.0 Hz, H^A-6′), 3.53−3.59 (0.50H, m, H^B-6, H^B-6′), 2.70 (0.25H, d, $J_{7,5}$ = 5.7 Hz, H^B-7), 2.56 (1H, d, $J_{7,5}$ = 6.1 Hz, H^A-7) ppm. ^{13}C NMR (150 MHz; only the major isomer is quoted): δ 148.99 (C-1), 138.18, 138.03, 137.90, 137.65, 137.49 (C$_{quat}$, 5 × C-Ph), 127.51−128.41 (25 × C-Ph), 79.50 (C-3), 78.51 (C-4), 76.54 (C-2), 76.01, 74.22, 73.92, 73.32 (4 × O$\underline{C}$H$_2$Ph), 70.96 (C-6), 70.41 (O$\underline{C}$H$_2$Ph), 69.93 (C-5) ppm. HRMS (ESI-TOF) calcd for $C_{41}H_{43}NO_6Na$ [M + Na]$^+$: 668.2988, found: 668.2985. Analysis calcd for $C_{41}H_{43}NO_6$ (645.80): C, 76.25; H, 6.71; N, 2.17; found: C, 76.12; H, 6.69; N, 2.17.

Synthesis of Mesylates 7, 8, 11, and 12 (General Procedure B). To a solution of compounds **3**−**6** (140−180 mg, 0.25−0.28 mmol) in CH_2Cl_2 (5 mL), DMAP (cat. amount ∼1.5 mg) and Et_3N (144−157 μL, 1.03−1.20 mmol) were added, and the mixture was stirred for 20 min at room temperature. Then, the mixture was cooled to −78 °C, and a solution of methanesulfonyl chloride (80−87 μL, 1.03−1.20 mmol) in CH_2Cl_2 (1 mL) was added dropwise. The mixture was stirred for 3 h at −78 °C and allowed to reach room temperature. Water (8 mL) was added, and the product was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic solutions were washed with brine (10 mL), dried, and concentrated, and the crude product was isolated by flash chromatography (hexanes/ethyl acetate = 85:15, v/v).

*(2R,3S,4R,5S)-1,3,4,5-Tetrakis(benzyloxy)-5-cyanopentan-2-yl Methanesulfonate (**7**).*



This compound was obtained in 70% yield (121 mg) from oxime **3** (156 mg, 0.28 mmol) as a white solid. TLC (hexanes/AcOEt = 3:1): R_f = 0.50. $[\alpha]_D^{22}$ = +35.5. ^{1}H NMR (600 MHz): δ 7.24−7.37 (20H, ArH), 4.94 (1H, ddd, $J_{5,6}$ = 6.8 Hz, $J_{5,4}$ = 4.3 Hz, $J_{5,6'}$ = 3.1 Hz, H-5),

https://dx.doi.org/10.1021/acs.joc.9b03247
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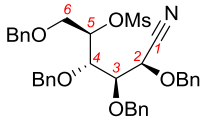
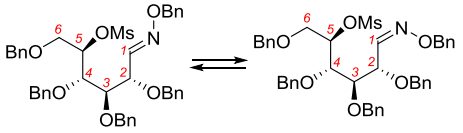
4.83 (1H, d, J = 11.4 Hz, OC$\underline{H}_2$Ph), 4.71 (1H, d, J = 11.2 Hz, OC$\underline{H}_2$Ph), 4.69 (1H, d, J = 11.2 Hz, OC$\underline{H}_2$Ph), 4.67 (1H, d, J = 11.0 Hz, OC$\underline{H}_2$Ph), 4.66 (1H, d, J = 11.0 Hz, OC$\underline{H}_2$Ph), 4.50 (1H, d, J = 11.4 Hz, OC$\underline{H}_2$Ph), 4.44 (1H, d, J = 11.4 Hz, OC$\underline{H}_2$Ph), 4.43 (1H, d, J = 11.4 Hz, OC$\underline{H}_2$Ph), 4.34 (1H, d, $J_{2,3}$ = 6.3 Hz, H-2), 4.16 (1H, dd, $J_{4,5}$ = 4.3 Hz, $J_{4,3}$ = 3.6 Hz, H-4), 3.95 (1H, dd, $J_{3,2}$ = 6.3 Hz, $J_{3,4}$ = 3.6 Hz, H-3), 3.89 (1H, dd, $J_{6',6}$ = 11.2 Hz, $J_{6',5}$ = 3.1 Hz, H-6′), 3.68 (1H, dd, $J_{6,6'}$ = 11.2 Hz, $J_{6,5}$ = 6.8 Hz, H-6), 2.91 (s, 3H, C$\underline{H}_3$) ppm. ^{13}C NMR (150 MHz): δ 137.27, 137.01, 136.99, 135.27 (C_{quat}, 4 × Ph), 127.85−128.72 (20 × C-Ph), 116.38 (C-1), 81.18 (C-5), 78.16 (C-4), 78.06 (C-3), 75.11, 74.98, 73.36, 72.94 (4 × O$\underline{C}$H$_2$Ph), 68.63 (C-6), 68.59 (C-2), 38.67 ($\underline{C}$H$_3$) ppm. HRMS (ESI-TOF) calcd for $C_{35}H_{37}NO_7SNa$ [M + Na]$^+$: 638.2188, found: 638.2179. Analysis calcd for $C_{35}H_{37}NO_7S$ (615.74): C, 68.27; H, 6.06; N, 2.27; found: C, 68.37; H, 6.18; N, 2.17.

*(2R,3S,4R,5R)-1,3,4,5-Tetrakis(benzyloxy)-5-cyanopentan-2-yl Methanesulfonate (**8**).*



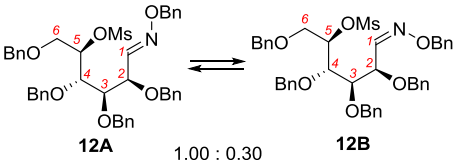
This compound was obtained in 78% yield (125 mg) from oxime **4** (144 mg, 0.26 mmol) as a white solid. TLC (hexanes/AcOEt = 2:1): R_f = 0.70. $[\alpha]_D^{22}$ = +30.8. ^{1}H NMR (600 MHz): δ 7.16−7.39 (20H, ArH), 4.96 (1H, ddd, $J_{5,6}$ = 7.0 Hz, $J_{5,4}$ = 3.6 Hz, $J_{5,6'}$ = 3.2 Hz, H-5), 4.93 (1H, d, J = 10.4 Hz, OC$\underline{H}_2$Ph), 4.78 (1H, d, J = 11.0 Hz, OC$\underline{H}_2$Ph), 4.68 (1H, d, J = 10.4 Hz, OC$\underline{H}_2$Ph), 4.65 (1H, d, J = 11.4 Hz, OC$\underline{H}_2$Ph), 4.47 (1H, d, J = 11.7 Hz, OC$\underline{H}_2$Ph), 4.45 (1H, d, J = 11.7 Hz, OC$\underline{H}_2$Ph), 4.38 (1H, d, J = 11.4 Hz, OC$\underline{H}_2$Ph), 4.34 (1H, d, J = 11.0 Hz, OC$\underline{H}_2$Ph), 4.33 (1H, d, $J_{2,3}$ = 6.8 Hz, H-2), 3.98 (1H, dd, $J_{3,2}$ = 6.8 Hz, $J_{3,4}$ = 3.4 Hz, H-3), 3.94 (1H, dd, $J_{4,5}$ = 3.6 Hz, $J_{4,3}$ = 3.4 Hz, H-4), 3.89 (1H, dd, $J_{6',6}$ = 11.3 Hz, $J_{6',5}$ = 3.2 Hz, H-6′), 3.76 (1H, dd, $J_{6,6'}$ = 11.3 Hz, $J_{6,5}$ = 7.0 Hz, H-6), 2.91 (s, 3H, C$\underline{H}_3$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 137.27, 136.88, 136.67, 135.26 (C_{quat}, 4 × Ph), 128.84 (2C-Ph), 128.66 (2C-Ph), 128.59 (C-Ph), 128.50 (2C-Ph), 128.47 (2C-Ph), 127.46 (2C-Ph), 128.43 (2C-Ph), 128.20 (C-Ph), 128.13 (2C-Ph), 128.08 (C-Ph), 127.98 (C-Ph), 127.81 (2C-Ph), 117.26 (C-1), 81.65 (C-5), 78.49 (C-3), 77.83 (C-4), 75.20, 74.07, 73.41, 72.45 (4 × O$\underline{C}$H$_2$Ph), 68.78 (C-6), 68.78 (C-2), 38.64 ($\underline{C}$H$_3$) ppm. HRMS (ESI-TOF) calcd for $C_{35}H_{37}NO_7SNa$ [M + Na]$^+$: 638.2188, found: 638.2187. Analysis calcd for $C_{35}H_{37}NO_7S$ (615.74): C, 68.27; H, 6.06; N, 2.27; found: C, 68.22; H, 6.06; N, 2.17.

*(2R,3S,4R,5S)-1,3,4,5-Tetrakis(benzyloxy)-6-((benzyloxy)imino)-hexan-2-yl Methanesulfonate (**11A** + **11B**).*



This compound was obtained in 76% yield (144 mg) from benzoxime **5** (169 mg, 0.26 mmol) as an isomeric mixture in a 1.00:0.30 ratio; colorless oil. TLC (hexanes/AcOEt = 2:1): R_f = 0.50. ^{1}H NMR (600 MHz): δ 7.50 (1H, d, $J_{1,2}$ = 7.8 Hz, H^A-1), 7.20−7.36 (32.5H, m, ArH), 6.94 (0.3H, d, $J_{1,2}$ = 6.4 Hz, H^B-1), 5.09 (2H, s, OC$\underline{H}_2^A$Ph), 5.02 (0.3H, d, J = 11.6 Hz, OC$\underline{H}^B_2$Ph), 5.00 (0.3H, d, J = 11.6 Hz, OC$\underline{H}^B_2$Ph), 4.96 (1H, ddd, $J_{5,6}$ = 7.5 Hz, $J_{5,4}$ = 3.5 Hz, $J_{5,6'}$ = 3.0 Hz, H^A-5), 4.92 (0.3H, ddd, $J_{5,6}$ = 7.6 Hz, $J_{5,6'}$ = 3.7 Hz, $J_{5,4}$ = 3.0 Hz, H^B-5), 4.87 (0.3H, dd, $J_{2,1}$ = 6.4 Hz, $J_{2,3}$ = 4.1 Hz, H^B-2), 4.68 (1.6H, m, OC$\underline{H}^A_2$Ph, OC$\underline{H}^B_2$Ph), 4.56−4.60 (3.6H, m, 3 × OC$\underline{H}^A_2$Ph, OC$\underline{H}^B_2$Ph), 4.52 (1H, d, J = 11.1 Hz, OC$\underline{H}^A_2$Ph), 4.51 (0.3H, d, J = 11.0 Hz, OC$\underline{H}^B_2$Ph), 4.37−4.44 (3.3H, m, 3 × OC$\underline{H}^A_2$Ph, OC$\underline{H}^B_2$Ph), 4.29 (1H, dd, $J_{2,1}$ = 7.8 Hz, $J_{2,3}$ = 6.2 Hz, H^A-2), 4.29 (0.6H, m, OC$\underline{H}^B_2$Ph), 4.13 (0.3H, dd, $J_{4,3}$ = 6.4 Hz, $J_{4,5}$ = 3.0 Hz, H^B-4), 4.02 (1H, dd, $J_{4,3}$ = 4.6 Hz, $J_{4,5}$ = 3.5 Hz, H^A-4), 3.86 (1H, dd, $J_{6',6}$ = 11.2 Hz, $J_{6',5}$ = 3.0 Hz, H^A-6′), 3.83 (0.3H, dd, $J_{3,4}$ = 6.4 Hz, $J_{3,2}$ = 4.1 Hz, H^B-3), 3.80 (1H, dd, $J_{3,2}$ = 6.2 Hz, $J_{3,4}$ = 4.6 Hz, H^A-3), 3.70 (1H, dd, $J_{6,6'}$ = 11.2 Hz, $J_{6,5}$ = 7.5 Hz, H^A-6), 3.68−3.72 (0.6H, m, H^B-6, H^B-6′), 2.87 (3H, s, C$\underline{H}^A_3$), 2.84 (0.9H, s, C$\underline{H}^B_3$) ppm. ^{13}C NMR (150 MHz): δ 150.84 (C^B-1), 148.36 (C^A-1), 136.96−137.93 (C_{quat}, 5 × C^A-Ph, 5 × C^B-Ph), 127.57−128.53 (25 × C^A-Ph, 25 × C^B-Ph), 82.64 (C^A-5), 82.25 (C^B-5), 79.75 (C^B-4), 79.50 (C^A-3), 79.44 (C^A-4), 78.79 (C^B-3), 76.52 (O$\underline{C}^B$H$_2$Ph), 76.39 (C^A-2), 75.96 (O$\underline{C}^A$H$_2$Ph), 74.97, 74.68 (2 × O$\underline{C}^B$H$_2$Ph), 74.59, 74.31, 73.26 (3 × O$\underline{C}^A$H$_2$Ph), 73.14, 72.29 (2 × O$\underline{C}^B$H$_2$Ph), 71.36 (O$\underline{C}^A$H$_2$Ph), 71.16 (C^B-2), 68.96 (C^A-6), 68.59 (C^B-6), 38.35 (C^{A}H$_3$), 38.35 (C^{B}H$_3$) ppm. HRMS (ESI-TOF) calcd for $C_{42}H_{45}NO_8SNa$ [M + Na]$^+$: 746.2764, found: 746.2758. Analysis calcd for $C_{42}H_{45}NO_8S$ (723.88): C, 69.69; H, 6.27; N, 1.93; found: C, 69.60; H, 6.19; N, 1.71.

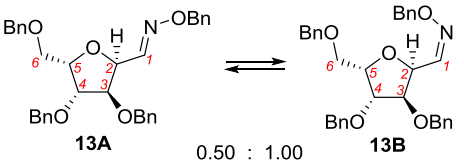
*(2R,3S,4R,5R)-1,3,4,5-Tetrakis(benzyloxy)-6-((benzyloxy)imino)-hexan-2-yl Methanesulfonate (**12A** + **12B**).*



This compound was obtained in 70% yield (141 mg) from benzoxime **6** (179 mg, 0.28 mmol) as an isomeric mixture in a 1.00:0.30 ratio; colorless oil. TLC (hexanes/AcOEt = 2:1): R_f = 0.50. (600 MHz): δ 7.47 (1H, d, $J_{1,2}$ = 8.1 Hz, H^A-1), 7.13−7.36 (32.5H, m, ArH), 6.87 (0.3H, d, $J_{1,2}$ = 7.2 Hz, H^B-1), 5.07−5.13 (2.6H, m, 2 × OC$\underline{H}^A_2$Ph, 2 × OC$\underline{H}^B_2$Ph), 4.99−5.05 (1.6H, m, H^A-5, H^B-5, H^B-2), 4.59−4.69 (3.9H, m, 3 × OC$\underline{H}^A_2$Ph, 3 × OC$\underline{H}^B_2$Ph), 4.48−4.55 (2.3H, m, 2 × OC$\underline{H}^A_2$Ph, OC$\underline{H}^B_2$Ph), 4.36−4.47 (2.9H, m, 2 × OC$\underline{H}^A_2$Ph, 3 × OC$\underline{H}^B_2$Ph), 4.29 (0.3H, d, J = 11.6 Hz, OC$\underline{H}^B_2$Ph), 4.26 (1H, d, J = 11.6 Hz, OC$\underline{H}^A_2$Ph), 4.19 (1H, dd, $J_{2,1}$ = 8.0 Hz, $J_{2,3}$ = 6.3 Hz, H^A-2), 4.03 (1H, dd, $J_{4,3}$ = 4.5 Hz, $J_{4,5}$ = 3.6 Hz, H^A-4), 4.01 (0.3H, dd, $J_{4,3}$ = 5.3 Hz, $J_{4,5}$ = 3.6 Hz, H^B-4), 3.83−3.87 (2.3H, m, H^A-3, H^A-6, H^B-3), 3.79 (0.3H, dd, $J_{6,6'}$ = 11.2 Hz, $J_{6,5}$ = 3.1 Hz, H^B-6), 3.75 (1H, dd, $J_{6',6}$ = 11.1, $J_{6',5}$ = 7.2 Hz, H^A-6′), 3.74 (0.3H, m, H^B-6′), 2.89 (3H, s, C$\underline{H}^A_3$), 2.86 (0.9H, s, C$\underline{H}^B_3$) ppm. ^{13}C NMR (150 MHz): δ 149.63 (C^B-1), 148.43 (C^A-1), 137.33−137.90 (C_{quat}, 5 × C^A-Ph, 5 × C^B-Ph), 127.62−128.42 (25 × C^A-Ph, 25 × C^B-Ph), 82.22 (C^A-5), 82.22 (C^B-5), 79.93 (C^B-4), 79.87 (C^A-4), 79.67 (C^A-3), 79.40 (C^B-3), 76.74 (C^A-2), 76.39 (O$\underline{C}^B$H$_2$Ph), 76.15 (O$\underline{C}^A$H$_2$Ph), 74.83 (O$\underline{C}^B$H$_2$Ph), 74.72, 74.43 (2 × O$\underline{C}^A$H$_2$Ph), 74.17 (O$\underline{C}^B$H$_2$Ph), 73.29 (O$\underline{C}^A$H$_2$Ph), 73.19, 71.76 (2 × O$\underline{C}^B$H$_2$Ph), 71.26 (C^B-2), 70.64 (O$\underline{C}^A$H$_2$Ph), 68.83 (C^A-6), 68.80 (C^B-6), 38.46 (C^{A}H$_3$), 38.46 (C^{B}H$_3$) ppm. HRMS (ESI-TOF) calcd for $C_{42}H_{45}NO_8SNa$ [M + Na]$^+$: 746.2764, found: 746.2740. Analysis calcd for $C_{42}H_{45}NO_8S$ (723.88): C, 69.69; H, 6.27; N, 1.93; found: C, 69.60; H, 6.19; N, 1.71.

Synthesis of Tetrahydrofurans 13 and 14 (General Procedure C). A solution of benzoxime **11** or **12** in toluene (10 mL) was boiled under reflux for 5 h and cooled to room temperature. The solvent was removed in vacuum, and the product was isolated by flash chromatography (hexanes/ethyl acetate = 85:15, v/v).

*3,4-Bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-carbaldehyde O-benzyl Oxime (**13A** + **13B**).*



This compound was obtained in 90% yield (71 mg) from **11** (106 mg, 0.146 mmol) as an isomeric mixture in a 0.50:1.00 ratio. TLC (hexanes/AcOEt = 2:1): R_f = 0.50. ^{1}H NMR (600 MHz): δ 7.56 (0.5H, d, $J_{1,2}$ = 7.8 Hz, H^A-1), 7.15−7.40 (30H, m, ArH), 6.97 (1H, d, $J_{1,2}$ = 4.3 Hz, H^B-1), 5.20 (1H, dd, $J_{2,1}$ = 4.3 Hz, $J_{2,3}$ = 4.0 Hz, H^B-2), 5.10 (2H, s, OC$\underline{H}^B_2$Ph), 5.10 (1.0H, s, OC$\underline{H}^A_2$Ph), 4.70 (0.5H, dd, $J_{2,1}$ = 7.8 Hz, $J_{2,3}$ = 4.2 Hz, H^A-2), 4.62 (1H, d, J = 12.0 Hz, OC$\underline{H}^B_2$Ph), 4.62 (0.5H, d, J = 12.0 Hz, OC$\underline{H}^A_2$Ph), 4.51 (1H, d, J = 12.0 Hz, OC$\underline{H}^B_2$Ph), 4.50 (0.5H, d, J = 12.0 Hz, OC$\underline{H}^A_2$Ph), 4.46

https://dx.doi.org/10.1021/acs.joc.9b03247
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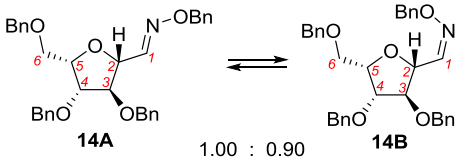
(1H, d, J = 12.2 Hz, OC$\underline{H}^{B}_{2}$Ph), 4.41−4.45 (3.0H, m, H^{A}-5, H^{B}-5, 3 × OC$\underline{H}^{A}_{2}$Ph), 4.33−4.40 (3.5H, m, 3 × OC$\underline{H}^{B}_{2}$Ph, OC$\underline{H}^{A}_{2}$Ph), 4.24 (1H, dd, $J_{3,2}$ = 4.0 Hz, $J_{3,4}$ = 1.1 Hz, H^{B}-3), 4.05 (0.5H, dd, $J_{3,2}$ = 4.2 Hz, $J_{3,4}$ = 1.5 Hz, H^{A}-3), 4.03 (0.5H, dd, $J_{4,5}$ = 3.8 Hz, $J_{4,3}$ = 1.5 Hz, H^{A}-4), 3.94 (1H, dd, $J_{4,5}$ = 3.7 Hz, $J_{4,3}$ = 1.1 Hz, H^{B}-4), 3.67−3.73 (3.0H, m, H^{A}-6, H^{A}-6′, H^{B}-6, H^{B}-6′) ppm. ^{13}C NMR (150 MHz): δ 151.13 (C^{B}-1), 148.42 (C^{A}-1), 138.14, 137.62, 137.53, 137.38 (C_{quat}, 4 × C^{A}-Ph), 138.14, 137.71, 137.70, 137.62 (C_{quat}, 4 × C^{B}-Ph), 127.58−128.44 (20 × C^{A}-Ph, 20 × C^{B}-Ph), 83.29 (C^{A}-3), 82.06 (C^{B}-3), 81.70 (C^{B}-4), 81.52 (C^{A}-4), 79.72 (C^{A}-5), 79.64 (C^{B}-5), 77.76 (C^{A}-2), 76.24 (O$\underline{C}^{B}$H$_2$Ph), 75.99 (C^{B}-2), 75.96, 73.48 (2 × O$\underline{C}^{A}$H$_2$Ph), 73.45, 72.32 (2 × O$\underline{C}^{B}$H$_2$Ph), 72.24, 72.21 (2 × O$\underline{C}^{A}$H$_2$Ph), 72.15 (O$\underline{C}^{B}$H$_2$Ph), 68.36 (C^{B}-6), 68.29 (C^{A}-6) ppm. HRMS (ESI-TOF) calcd for $C_{34}H_{35}NO_5Na$ $[M + Na]^+$: 560.2413, found: 560.2415. Analysis calcd for $C_{34}H_{35}NO_5$ (537.66): C, 75.95; H, 6.56; N, 2.61; found: C, 76.06; H, 6.58; N, 2.64.

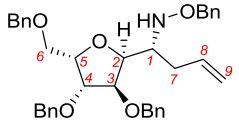
*3,4-Bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-carbaldehyde O-benzyl Oxime (**14A** + **14B**).*



This compound was obtained in 99% yield (81 mg) from **12** (110 mg, 0.152 mmol) as an isomeric mixture in a 1.00:0.90 ratio; colorless oil. TLC (hexanes/AcOEt = 3:1): R_f = 0.60. ^{1}H NMR (500 MHz): δ 7.47 (1H, d, $J_{1,2}$ = 7.0 Hz, H^{A}-1), 7.08−7.44 (38H, m, ArH), 6.82 (0.9H, d, $J_{1,2}$ = 4.5 Hz, H^{B}-1), 5.08−5.13 (2.9H, m, 2 × OC$\underline{H}^{A}_{2}$Ph, H^{B}-2), 5.07 (1.8H, s, 2 × OC$\underline{H}^{B}_{2}$Ph), 4.60 (1H, d, J = 12.0 Hz, OC$\underline{H}^{A}_{2}$Ph), 4.59 (0.9H, d, J = 12.0 Hz, OC$\underline{H}^{B}_{2}$Ph), 4.48−4.56 (5.7H, m, 2 × OC$\underline{H}^{A}_{2}$Ph, H^{A}-2, 3 × OC$\underline{H}^{B}_{2}$Ph), 4.44 (1H, d, J = 11.9 Hz, OC$\underline{H}^{A}_{2}$Ph), 4.41 (1H, d, J = 12.0 Hz, OC$\underline{H}^{A}_{2}$Ph), 4.36−4.39 (2.7H, m, H^{B}-5, 2 × OC$\underline{H}^{B}_{2}$Ph), 4.29 (1H, m, H^{A}-5), 4.26 (1H, d, J = 11.9 Hz, OC$\underline{H}^{A}_{2}$Ph), 4.08 (0.9H, br s, H^{B}-3), 4.06 (1H, dd, $J_{3,2}$ = 2.7 Hz, $J_{3,4}$ = 1.4 Hz, H^{A}-3), 4.00 (1H, dd, $J_{4,5}$ = 3.9 Hz, $J_{4,3}$ = 1.4 Hz, H^{A}-4), 3.90 (1H, br d, $J_{4,5}$ = 3.0 Hz, H^{B}-4), 3.69−3.77 (3.8H, m, H^{A}-6, H^{A}-6′, H^{B}-6, H^{B}-6′) ppm. ^{13}C NMR (150 MHz): δ 153.47 (C^{B}-1), 149.89 (C^{A}-1), 138.17, 138.09, 137.77, 137.59, 137.51, 137.38, 137.38, 137.36 (C_{quat}, 4 × C^{A}-Ph, 4 × C^{B}-Ph), 127.32−128.43 (20 × C^{A}-Ph, 20 × C^{B}-Ph), 85.18 (C^{A}-3), 84.62 (C^{B}-3), 82.28 (C^{A}-4), 81.04 (C^{B}-4), 81.00 (C^{A}-2), 80.70 (C^{B}-5), 80.39 (C^{A}-5), 78.22 (C^{B}-2), 76.49 (O$\underline{C}^{A}$H$_2$Ph), 76.04 (O$\underline{C}^{B}$H$_2$Ph), 73.45 (O$\underline{C}^{B}$H$_2$Ph), 73.38 (O$\underline{C}^{A}$H$_2$Ph), 71.72 (O$\underline{C}^{A}$H$_2$Ph), 71.64 (O$\underline{C}^{B}$H$_2$Ph), 71.51 (O$\underline{C}^{A}$H$_2$Ph), 71.42 (O$\underline{C}^{B}$H$_2$Ph), 68.48 (C^{B}-6), 68.29 (C^{A}-6) ppm. HRMS (ESI-TOF) calcd for $C_{34}H_{35}NO_5$ $[M + Na]^+$: 560.2413, found: 560.2407. Analysis calcd for $C_{34}H_{35}NO_5$ (537.66): C, 75.95; H, 6.56; N, 2.61; found: C, 75.82; H, 6.51; N, 2.61.

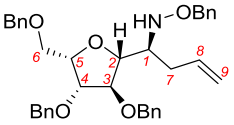
Synthesis of Compounds 15 and 16 (General Procedure D). A solution of imine **13** or **14** (45 mg, 0.084 mmol) in dry toluene (4 mL) was cooled at −78 °C, and a 1.0 M solution of allylmagnesium bromide in diethyl ether (250 μL) was added. The mixture was stirred for 30 min at −78 °C and allowed to reach room temperature. Water (10 mL) was added, and the crude product was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried, and concentrated, and the residue was purified by flash chromatography (hexanes/ethyl acetate = 90:10, v/v).

*O-Benzyl-N-((R)-1-((2S,3R,4R,5S)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)but-3-en-1-yl)-hydroxylamine (**15**).*



This compound was obtained in 70% yield (34 mg) from **13** as a colorless oil. TLC (hexanes/AcOEt = 2:1): R_f = 0.50. $[\alpha]_D^{22}$ = +16.8. ^{1}H NMR (600 MHz): δ 7.20−7.36 (20H, m, ArH), 6.24 (1H, br s, NH), 5.89 (1H, m, H-8), 5.00 (1H, dd, $J_{9,8}$ = 10.6 Hz, $J_{9,9'}$ = 1.6 Hz, H-9), 4.97 (1H, dd, $J_{9',8}$ = 17.4 Hz, $J_{9',9}$ = 1.6 Hz, H-9′), 4.71 (2H, s, 2H, OC$\underline{H}_2$Ph), 4.58 (1H, d, J = 11.9 Hz, OC$\underline{H}_2$Ph), 4.54 (2H, s, 2H, OC$\underline{H}_2$Ph), 4.52 (1H, d, J = 11.9 Hz, OC$\underline{H}_2$Ph), 4.48 (1H, d, J = 11.7 Hz, OC$\underline{H}_2$Ph), 4.34 (1H, ddd, $J_{5,6}$ = 6.7 Hz, $J_{5,6'}$ = 6.2 Hz, $J_{5,4}$ = 3.8 Hz, H-5), 4.30 (1H, d, J = 11.6 Hz, OC$\underline{H}_2$Ph), 4.13 (1H, dd, $J_{2,1}$ = 9.6 Hz, $J_{2,3}$ = 3.5 Hz, H-2), 4.06 (1H, d, $J_{4,5}$ = 3.8 Hz, H-4), 3.85 (1H, d, $J_{3,2}$ = 3.5 Hz, H-3), 3.73 (1H, dd, $J_{6,6'}$ = 9.7 Hz, $J_{6,5}$ = 6.7 Hz, H-6), 3.66 (1H, dd, $J_{6',6}$ = 9.7 Hz, $J_{6',5}$ = 6.2 Hz, H-6′), 3.25 (1H, ddd, $J_{1,2}$ = 9.6 Hz, $J_{1,7}$ = 7.5 Hz, $J_{1,7'}$ = 4.3 Hz, H-1), 2.27 (1H, m, H-7), 2.15 (1H, m, H-7′) ppm. ^{13}C NMR (150 MHz): δ 138.27, 138.16, 137.95, 137.45 (C_{quat}, 4 × Ph), 136.03 (C-8) 128.45 (2C-Ph), 128.40 (2C-Ph), 128.34 (2C-Ph), 128.30 (2C-Ph), 128.23 (2C-Ph), 127.88 (C-Ph), 127.86 (C-Ph), 127.80 (2C-Ph), 127.71 (2C-Ph), 127.67 (2C-Ph), 127.57 (C-Ph), 127.55 (C-Ph), 116.21 (C-9), 81.13 (C-3), 80.83 (C-4), 79.18 (C-2), 78.97 (C-5), 76.57, 73.46, 72.47, 71.61 (4 × O$\underline{C}$H$_2$Ph), 68.27 (C-6), 59.72 (C-1), 33.05 (C-7) ppm. HRMS (ESI-TOF) calcd for $C_{37}H_{42}NO_5$ $[M + H]^+$: 580.3063, found: 580.3055. Analysis calcd for $C_{37}H_{41}NO_5$ (579.74): C, 76.66; H, 7.13; N, 2.42; found: C, 76.86; H, 7.19; N, 2.29.

*O-Benzyl-N-((S)-1-((2R,3R,4R,5S)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)but-3-en-1-yl)-hydroxylamine (**16**).*



This compound was obtained in 68% yield (33 mg) from **14** as a colorless oil. TLC (hexanes/AcOEt = 2:1): R_f = 0.50. $[\alpha]_D^{22}$ = +27.3. ^{1}H NMR (500 MHz): δ 7.20−7.36 (20H, m, ArH), 6.09 (1H, s, NH), 5.84 (1H, m, H-8), 5.01−5.06 (2H, m, H-9, H-9′), 4.65 (1H, d, J = 12.2 Hz, OC$\underline{H}_2$Ph), 4.54 (1H, d, J = 11.8 Hz, OC$\underline{H}_2$Ph), 4.58 (1H, d, J = 12.0 Hz, OC$\underline{H}_2$Ph), 4.52 (1H, d, J = 12.0 Hz, OC$\underline{H}_2$Ph), 4.51 (1H, d, J = 12.0 Hz, OC$\underline{H}_2$Ph), 4.49 (1H, d, J = 12.2 Hz, OC$\underline{H}_2$Ph), 4.43 (1H, d, J = 11.8 Hz, OC$\underline{H}_2$Ph), 4.42 (1H, d, J = 12.0 Hz, OC$\underline{H}_2$Ph), 4.21 (1H, ddd, $J_{5,6}$ = 5.9 Hz, $J_{5,6'}$ = 6.0 Hz, $J_{5,4}$ = 3.8 Hz, H-5), 4.01 (1H, d, $J_{3,2}$ = 3.4 Hz, H-3), 3.98 (1H, $J_{2,1}$ = 6.8 Hz, $J_{2,3}$ = 3.4 Hz, H-2), 3.95 (1H, d, $J_{4,5}$ = 3.8 Hz, H-4), 3.76 (1H, dd, $J_{6,6'}$ = 9.9 Hz, $J_{6,5}$ = 5.9 Hz, H-6), 3.70 (1H, dd, $J_{6',6}$ = 9.9 Hz, $J_{6',5}$ = 6.0 Hz, H-6′), 3.05 (1H, ddd, $J_{1,7}$ = 7.2 Hz, $J_{1,2}$ = 6.8 Hz, $J_{1,7'}$ = 5.3 Hz, H-1), 2.29 (1H, m, H-7), 2.24 (1H, m, H-7′) ppm. ^{13}C NMR (125 MHz): δ 138.20, 138.06, 137.90, 137.76 (C_{quat}, 4 × Ph), 135.97 (C-8) 128.43 (2C-Ph), 128.41 (2C-Ph), 128.34 (2C-Ph), 128.32 (2C-Ph), 128.23 (2C-Ph), 127.82 (C-Ph), 127.77 (2C-Ph), 127.74 (C-Ph), 127.65 (2C-Ph), 127.58 (4C-Ph), 116.73 (C-9), 83.68 (C-3), 83.59 (C-2), 82.31 (C-4), 79.88 (C-5), 76.38, 73.39, 71.60, 71.60 (4 × O$\underline{C}$H$_2$Ph), 68.09 (C-6), 62.06 (C-1), 33.24 (C-7) ppm. HRMS (ESI-TOF) calcd for $C_{37}H_{41}NO_5$ $[M + H]^+$: 580.3063, found: 580.3060. Analysis calcd for $C_{37}H_{41}NO_5$ (579.74): C, 76.66; H, 7.13; N, 2.42; found: C, 76.79; H, 7.24; N, 2.33.

DFT Calculations. All calculations were performed using a four-step approach: (1) conformational search using the Spartan′18 Parallel Suite[21] at the MMFF level of theory; (2) all structures obtained in the previous step were optimized using MOPAC2016[22] with the PM7 semiempirical method; (3) all structures from step 2 with energy <22 kJ/mol (with reference to the lowest energy conformer) were optimized using the Gaussian 16 program[23] at the m062x/6-31+g(d) level of theory; and (4) for all structures from step 3 with energy <22 kJ/mol, vibrational frequency calculations were carried out at the same level of theory as of the optimization theory. Each conformer contribution to Gibbs free energy was calculated according to a Boltzmann distribution. The SMD implicit solvent model was used to simulate the toluene environment (radii = bondi, surface = SAS).

https://dx.doi.org/10.1021/acs.joc.9b03247
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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b03247.

NBO charge distributions of compounds **7**, **9**, **11**, and **13**; transition states **TS-7**, **TS-11**, **7,9**, and **11,13**; intermediates **im-7,9** and **im-11,13**; Cartesian coordinates of calculated structures; NMR spectra of all synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the financial support from Institute of Organic Chemistry of the Polish Academy of Sciences. The calculation research was supported in part by the PLGrid Infrastructure.

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J. Org. Chem. 2020, 85, 3517−3526