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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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Abstract

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 DFT calculations. It was demonstrated that tetrahydrofuran derivatives with benzoxime group (EWG = CHNOBn) are very good candidates for the subsequent highly stereoselective Grignard reaction.

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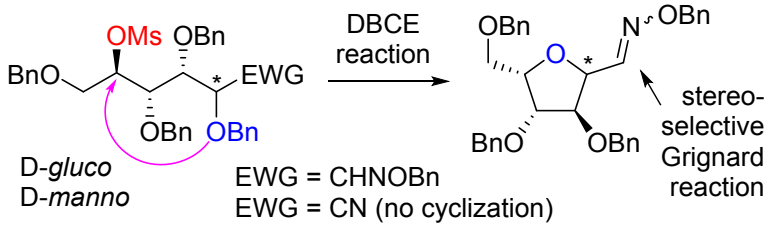


INTRODUCTION

The evolution of 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 of 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 *i.e.* cytarabine, a medicament in leukemia chemotherapy[2] or vidarabine, an antiviral drug with the activity against *herpes simplex* and *varicella zoster* viruses.[3] The development and improvement of the efficient

synthetic methods for the preparation of such type of compounds are actual challenge 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 marine strain of the fungus Emericella Variecolor (M75-2), exhibit potent cytotoxicity against a variety of cancer cell lines.[6,7,8] 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**) are potential antimycobacterial agents, targeting enzymes involved in the biosynthesis of the cell wall of *Mycobacterium tuberculosis* (Figure 1).[4,10]

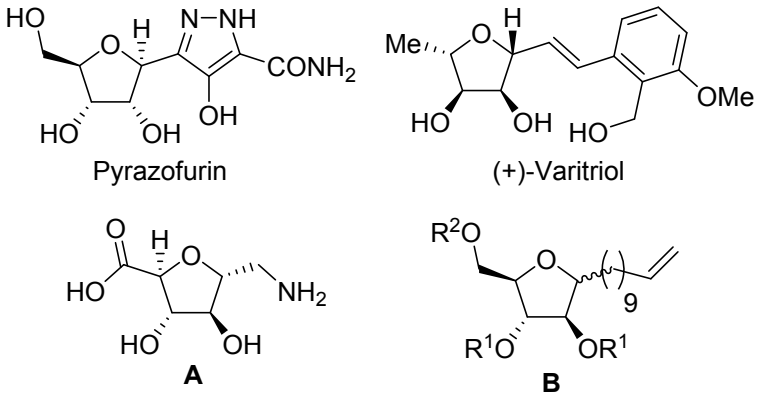
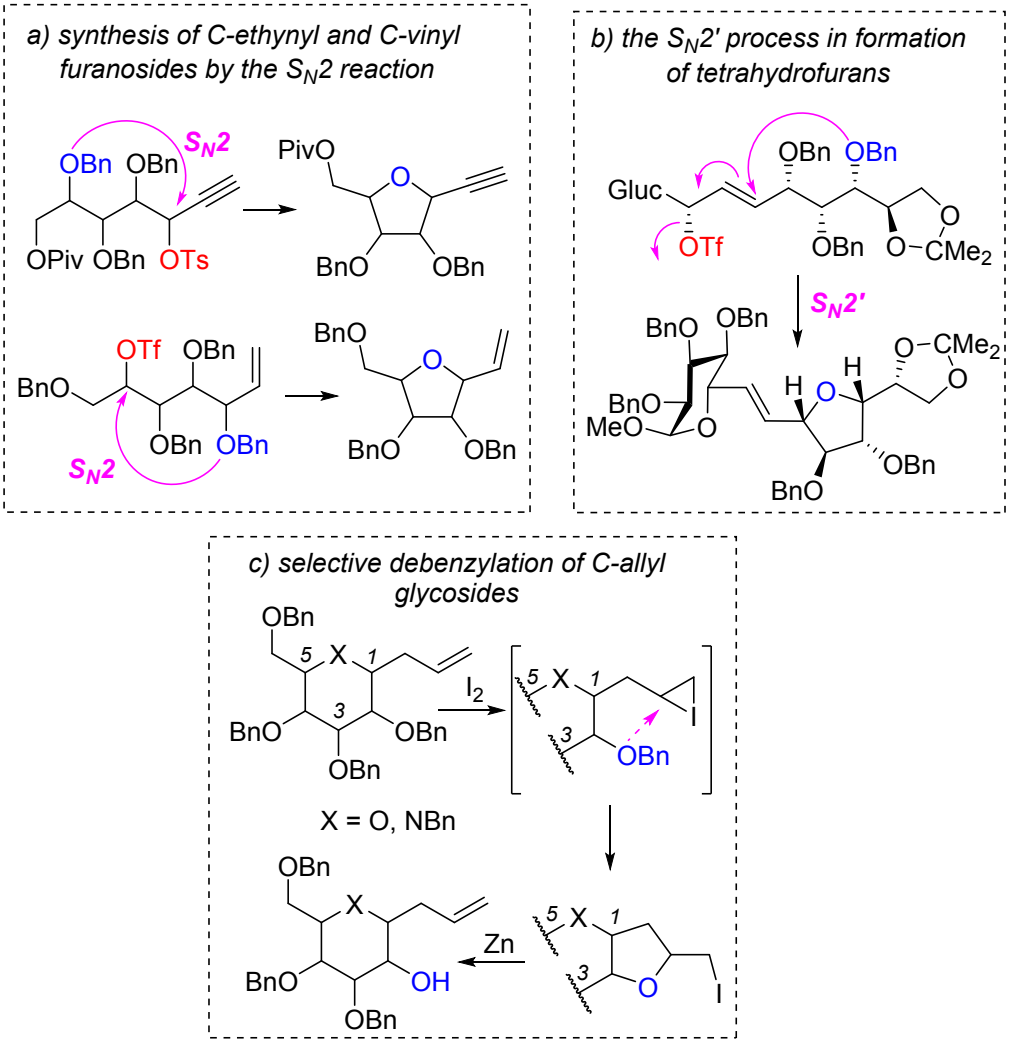


Figure 1. Examples of biologically active *C*-furanosides.

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 to each other. Although this method is usually limited to compounds with one unprotected hydroxyl group and one leaving group (LG),[4] it can be applied also to fully protected linear derivatives containing a leaving group. The protected, as a benzyl ether, oxygen function can also act as a nucleophile and attack the sp^3-carbon atom connected with the effective leaving group in debenzylative cycloetherification (DBCE) process.[11,12,13,14,15] 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 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 Bleriot and co-workers (Scheme 1c).[17]



Scheme 1. Application of DBCE reaction in the synthesis of *C*-furanosides *via* the S_N2 (1a) and S_N2' (1b) processes and in selective deprotection (1c).

It seemed reasonable that such process 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.

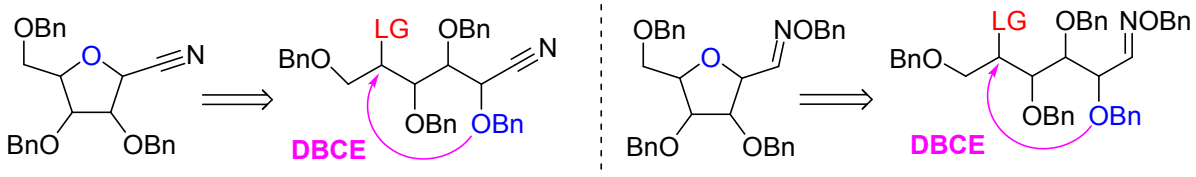
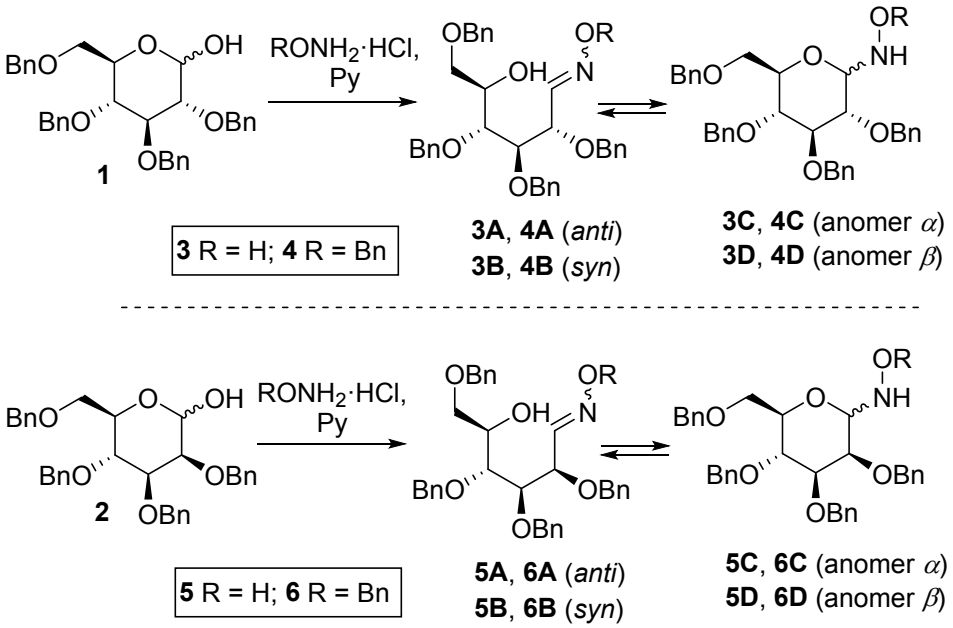


Figure 2. Retrosynthetic analysis to prepare *C*-nitrile- and *C*-benzoxime-furanosides

RESULTS AND DISCUSSION

Synthesis

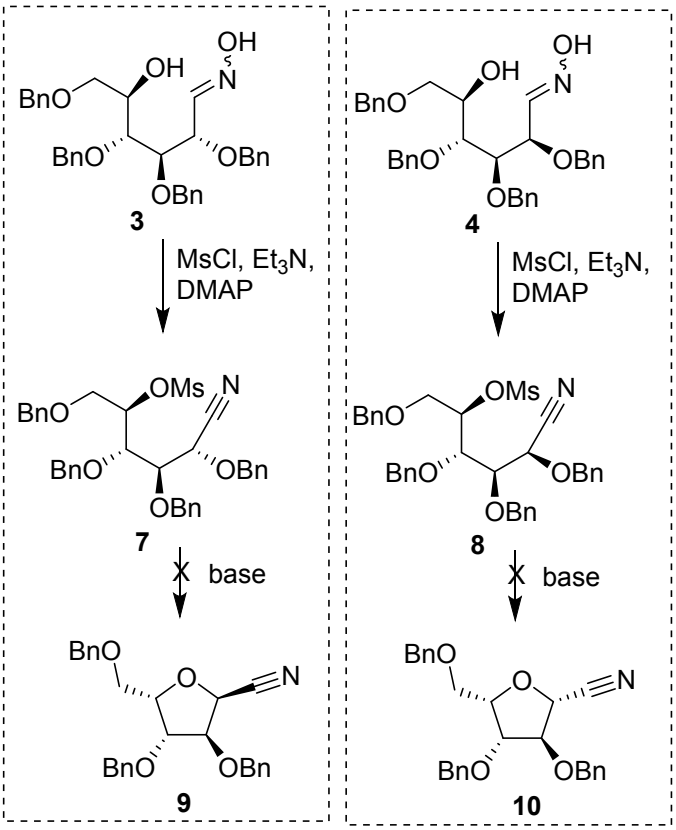
We have initiated our syntheses of functionalized tetrahydrofurans from known tetra-*O*-benzylated derivatives of glucose and mannose (**1** and **2** respectively).[18] These hexoses were converted, under the standard conditions, either to oximes **3**, **5** (in 80–90% yield) or protected oximes **4**, **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**,**5** and benzoxyoximes **4**,**6**.

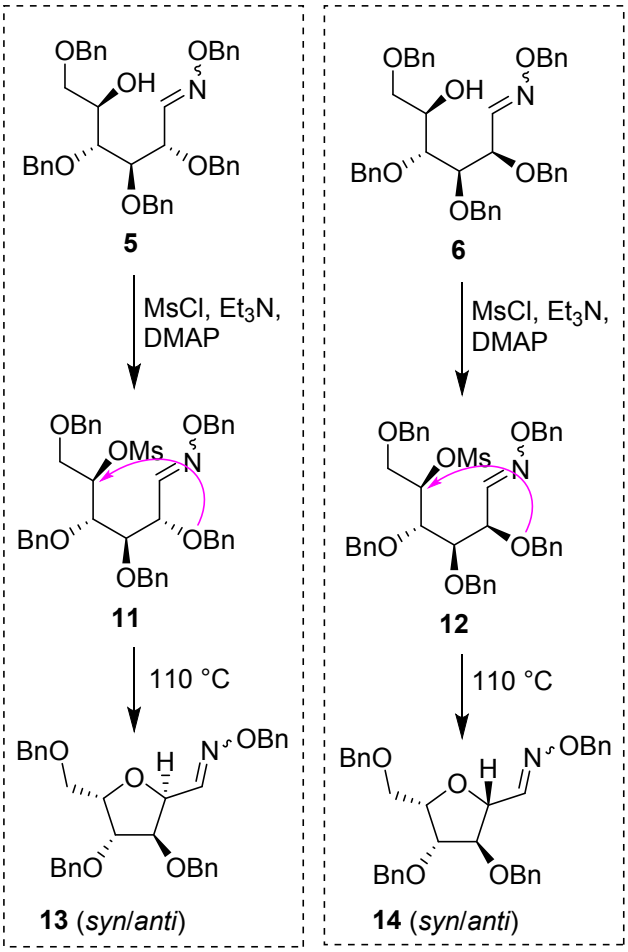
All synthesized compounds were fully characterized by the one- (^{1}H, ^{13}C) and two-dimensional (^{1}H–^{1}H COSY, and ^{1}H–^{13}C HSQC) NMR, elemental analysis, as well as high-resolution mass spectrometry (HRMS). Careful analysis of the NMR data of products **3–6** allowed us to detect the presence of isomers A, B, C, 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 ^{1}H 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 hydroximes 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% yield, 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.



Scheme 3. Synthesis of nitriles **7** and **8** and unsuccessful attempts of their cyclization.

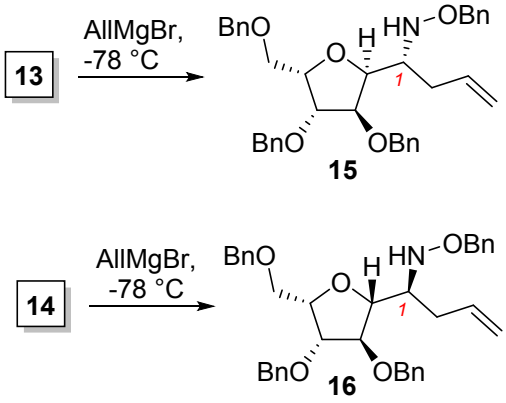
However, much better results were obtained in the cyclization reaction of the protected oximes under analogous conditions. Mesylation of benzoximes **5** and **6** afforded compounds **11** and **12** in good yields (76% and 70%, respectively). Heating of these mesylates in toluene at reflux induced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



Scheme 4. Formation of tetrahydrofurans **13** and **14**.

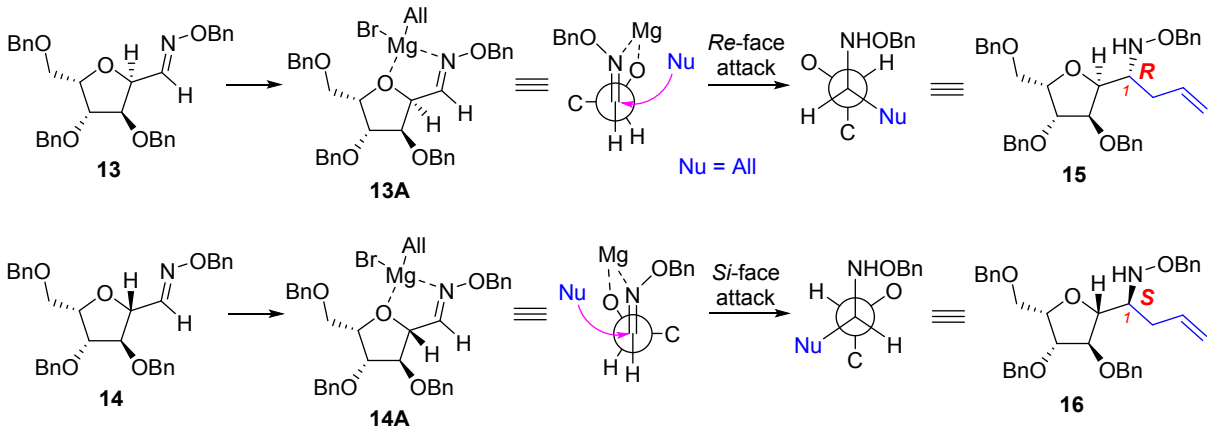
Because of the dynamic isomerization of the benzoxime group, compounds **13** and **14** were obtained as *syn*/*anti* pairs as can be judged from the NMR data (*i.e.* signals of the H-1 atom are located at δ = 6.97 and 7.56 ppm for *syn*-**13** and *anti*-**13** isomers, respectively; while in the case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

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 to mention 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 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 isomer **16** with the 1*S*-configuration. Such 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]



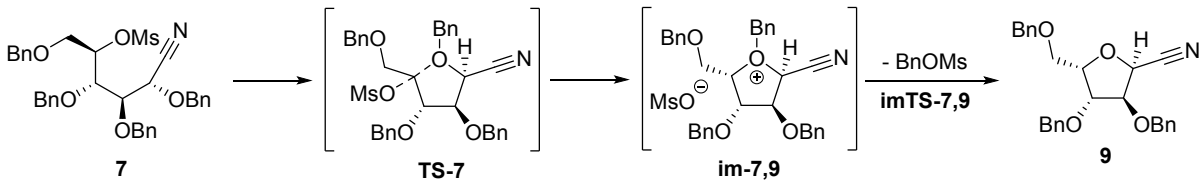
Scheme 6. Proposed mechanism of Grignard reaction of benzoximes **13** and **14** with allylmagnesium bromide.

DFT calculation

To gain better understanding of the different reactivity of the investigated mesylates vs nitriles, the 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 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 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 kcal/mol and 30.7 kcal/mol, respectively, while the corresponding energies of transition states **imTS-7,9** and **imTS-11,13** were 37.3 kcal/mol 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 *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 **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**.



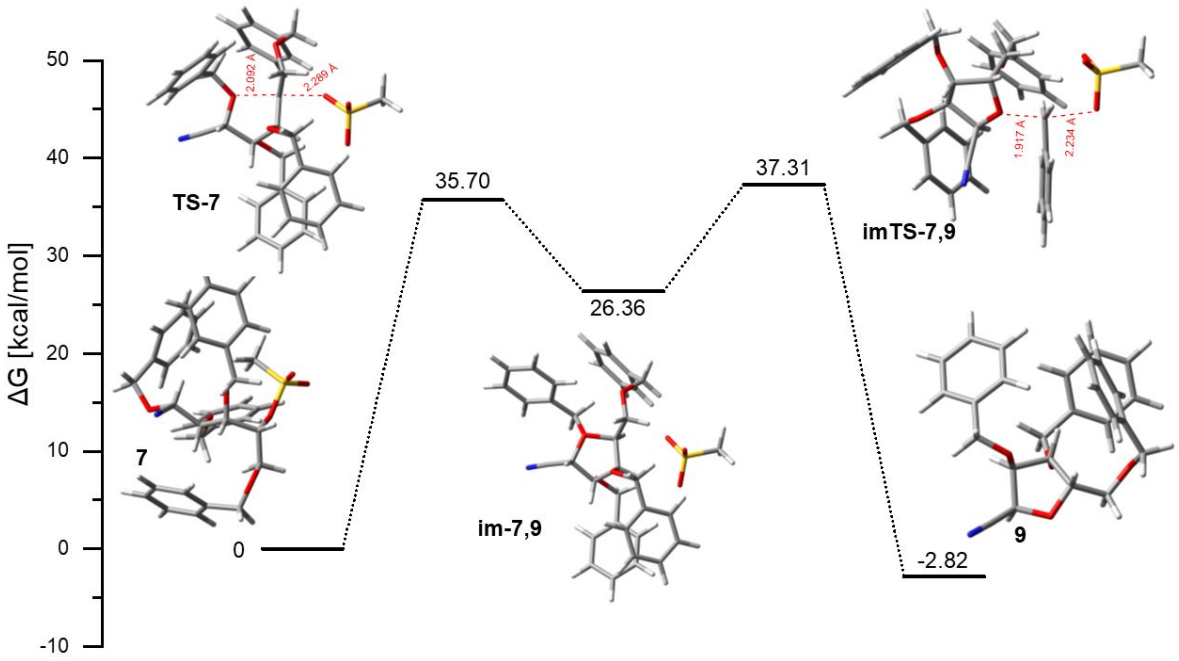


Figure 3. Gibbs free energy diagram of transformation of linear compounds **7** into *C*-furanoside **9**.

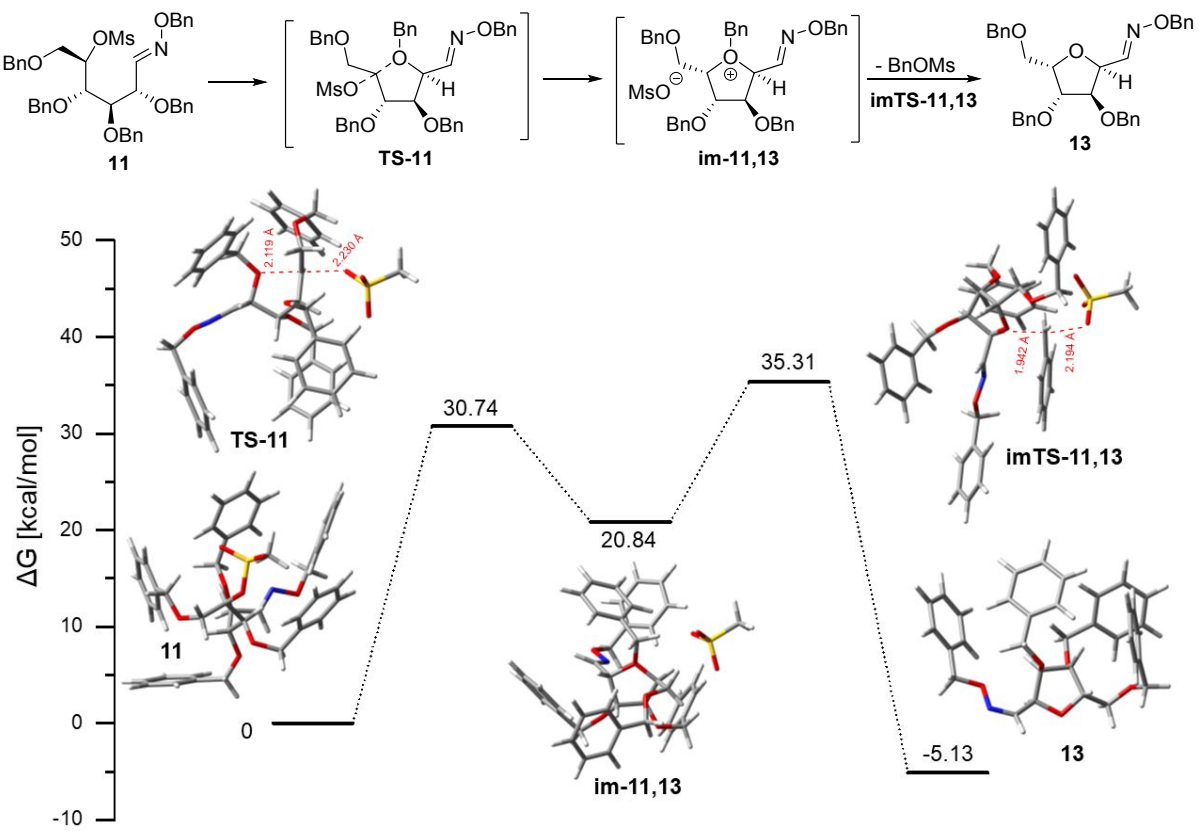


Figure 4. Gibbs free energy diagram of transformation of linear compounds **11** into *C*-furanoside **13**.

On the other hand, one of the key aspects that affect the course of these reactions is the electron density on the oxygen atom involved in the intramolecular S_N2 reaction. Presence of the highly electron-withdrawing nitrile group in close proximity of the "nucleophilic" oxygen atom in compound **7** induces the decrease of the electron density at 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 Gaussian package. The partial charge on the oxygen atom involved in the cyclization reaction at each stage (except for 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). Indirectly, the electron density at the oxygen atom affects its nucleophilicity. Therefore, the calculated values of partial charges demonstrate, that in the case of transformation **11→13** 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.

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)

CONCLUSIONS

In conclusion, we have investigated the debenzylative cycloetherification reaction of 1,3,4,5-tetrakis(benzyloxy)-5-cyanopentan-2-yl methanesulfonates **7**, **8** and 2,3,4,6-tetrakis (benzyloxy)-5-hydroxyhexanal *O*-benzyl oximes **11**, **12**. The compounds with benzoxime group (**11** and **12**) are apparently more reactive in the DBCE reaction than the cyano-analogs (**7** and **8**). These differences in the 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, comparatively with the corresponding influence of the benzoxime group. The experimental results were confirmed by DFT calculation. The obtained *C*-furanosides with benzoxime group in the side chain (tetrahydrofurans **13** and **14**) are good candidates for stereoselective modification in 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 help of the 2D correlation experiments (COSY, HSQC, HMBC). Chemical shifts were reported with reference to TMS. Optical rotations were measured with a Jasco P 1020 polarimeter (sodium light) in chloroform at room temp. Mass spectra were recorded with Synapt G2-S HDMS (*Waters Inc*) mass spectrometer equipped with an electrospray ion source and q-TOF type mass

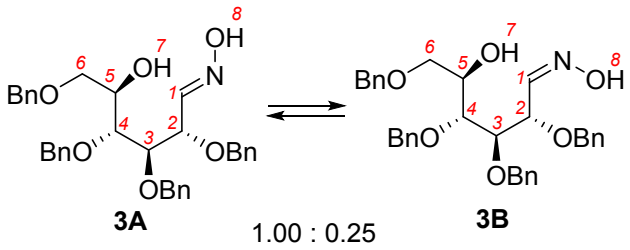
analyzer. The instrument was controlled and recorded data were processed using *MassLynx V4.1* software package (*Waters Inc*). Thin layer chromatography (TLC) was performed on silica gel plates coated with fluorescent indicator. Column chromatography was performed on silica gel (Merck, 230-400 mesh). 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), hydroxy-ammonium 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 $HONH_2{\cdot}HCl$) or for 8 hours at 55ºC (for $BnONH_2{\cdot}HCl$). 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), 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).

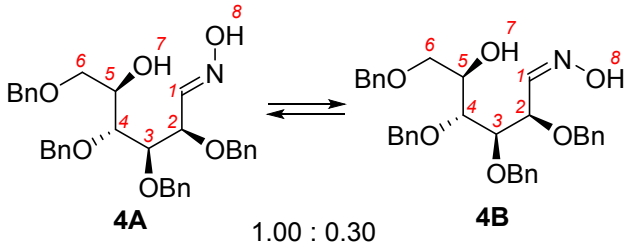
(2*S*,3*R*,4*R*,5*R*)-2,3,4,6-tetrakis(benzyloxy)-5-hydroxyhexanal oxime (3A + 3B).



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 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.

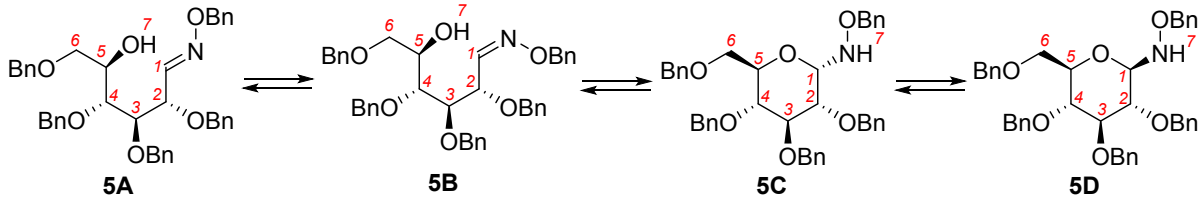
(2*R*,3*R*,4*R*,5*R*)-2,3,4,6-tetrakis(benzyloxy)-5-hydroxyhexanal oxime (4A + 4B).



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 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 major isomer 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.

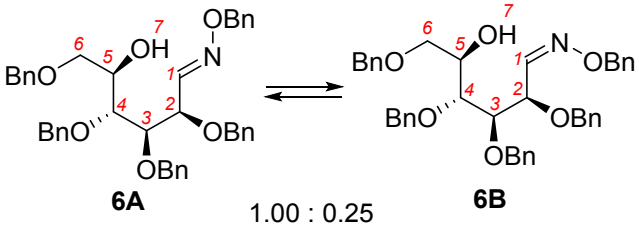
(2*S*,3*R*,4*R*,5*R*)-2,3,4,6-tetrakis(benzyloxy)-5-hydroxyhexanal *O*-benzyl oxime (5A + 5B + 5C + 5D).



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 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 major isomer 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.

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



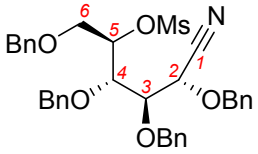
This compound was obtained in 90% yield (215 mg) from **2** (200 mg, 0.37 mmol) and *O*-benzylhydroxylamine hydrochloride (147 mg, 0.92 mmol) as an isomeric mixture in 1.00:0.25 ratio; yellowish oil. TLC (hexanes/AcOEt = 2:1): R_f = 0.70. ^{1}H NMR (600 MHz): δ 7.46 (1H, d, $J_{1,2}$ = 8.1 Hz, H^A-1), 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 major isomer 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, 12 (General procedure B).

To a solution of compound **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 ºC 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 hours at -78 ºC and allowed to reach room temperature. Water (8 mL) was added and the product was extracted with CH_2Cl_2 (3 × 10 mL).

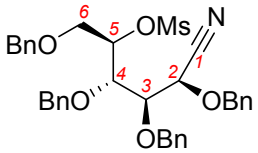
The combined organic solutions were washed with brine (10 mL), dried, concentrated, and the crude product was isoated by flash chromatography (hexanes/ethyl acetate = 85:15, v/v).

(2*R*,3*S*,4*R*,5*S*)-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), 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.

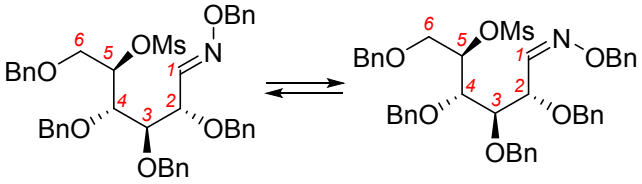
(2*R*,3*S*,4*R*,5*R*)-1,3,4,5-tetrakis(benzyloxy)-5-cyanopentan-2-yl methanesulfonate (8).



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<u>*C*</u>H_2Ph), 68.78 (C-6), 68.78 (C-2), 38.64 (<u>*C*</u>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.

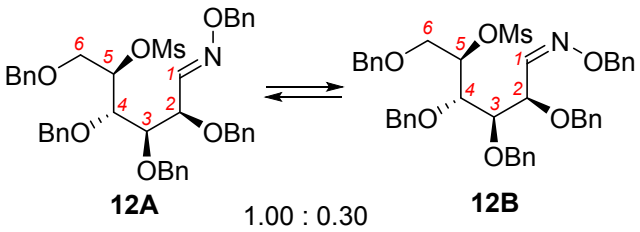
(2*R*,3*S*,4*R*,5*S*)-1,3,4,5-tetrakis(benzyloxy)-6-((benzyloxy)imino)hexan-2-yl methanesulfonate (11A + 11B).



This compound was obtained in 76% yield (144 mg) from benzoxime **5** (169 mg, 0.26 mmol) as an isomeric mixture in 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<u>*H*^{A}</u>$_2$Ph), 5.02 (0.3H, d, *J* = 11.6 Hz, OC<u>*H*^{B}</u>$_2$Ph), 5.00 (0.3H, d, *J* = 11.6 Hz, OC<u>*H*^{B}</u>$_2$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<u>*H*^{A}</u>$_2$Ph, OC<u>*H*^{B}</u>$_2$Ph), 4.56–4.60 (3.6H, m, 3 × OC<u>*H*^{A}</u>$_2$Ph, OC<u>*H*^{B}</u>$_2$Ph), 4.52 (1H, d, *J* = 11.1 Hz, OC<u>*H*^{A}</u>$_2$Ph), 4.51 (0.3H, d, *J* = 11.0 Hz, OC<u>*H*^{B}</u>$_2$Ph), 4.37–4.44 (3.3H, m, 3 × OC<u>*H*^{A}</u>$_2$Ph, OC<u>*H*^{B}</u>$_2$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<u>*H*^{B}</u>$_2$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<u>*H*^{A}</u>$_3$), 2.84 (0.9H, s, C<u>*H*^{B}</u>$_3$) 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<u>*C*^{B}</u>H_2Ph), 76.39 (C^A-2), 75.96 (O<u>*C*^{A}</u>H_2Ph), 74.97, 74.68 (2 × O<u>*C*^{B}</u>H_2Ph), 74.59, 74.31, 73.26 (3 × O<u>*C*^{A}</u>H_2Ph), 73.14, 72.29 (2 × O<u>*C*^{B}</u>H_2Ph), 71.36 (O<u>*C*^{A}</u>H_2Ph), 71.16 (C^B-2), 68.96 (C^A-6), 68.59 (C^B-6), 38.35 (C^AH_3), 38.35 (C^BH_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.

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

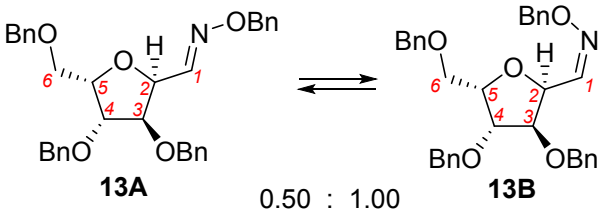


This compound was obtained in 70% yield (141 mg) from benzoxime **6** (179 mg, 0.28 mmol) as an isomeric mixture in 1.00:0.30 ratio; Colorless oil. TLC (hexanes/AcOEt = 2:1): R_f = 0.50. (600 MHz): δ 7.47 (1H, d, $J_{1,2}$ = 8.1 Hz, H^A-1), 7.13–7.36 (32.5H, m, ArH), 6.87 (0.3H, d, $J_{1,2}$ = 7.2 Hz, 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).

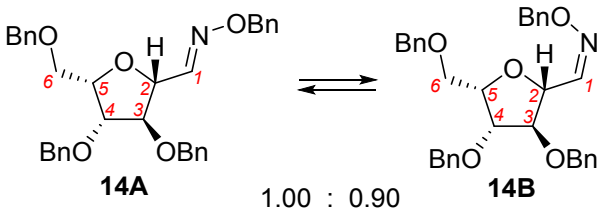
A solution of benzoxime **11** or **12** in toluene (10 mL) was boiled under reflux for 5 h, cooled to room temp. The solvent was removed in vacuum and the product was isolated by flash chromatography (hexanes/ethyl acetate = 85:15, v/v).

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



This compound was obtained in 90% yield (71 mg) **11** (106 mg, 0.146 mmol) as an isomeric mixture in 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 (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)



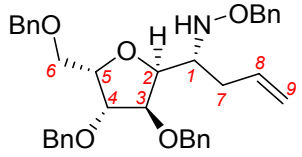
This compound was obtained in 99% yield (81 mg) from **12** (110 mg, 0.152 mmol) as an isomeric mixture in 1.00:0.90 ratio; colorless oil. TLC (hexanes/AcOEt = 3:1): $R_f = 0.60$. ^{1}H NMR (500 MHz): δ 7.47 (1H, d, $J_{1,2}$ = 7.0 Hz, H^A-1), 7.08–7.44 (38H, m, ArH), 6.82 (0.9H, d, $J_{1,2}$ = 4.5 Hz, 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 -78 ºC and a 1.0M solution of allylmagnesium bromide in diethyl ether (250 µL) was added. The mixture was stirred for 30 min at -78 ºC 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), brine (5 mL), dried, concentrated, and the residue was purified by flash chromatography (hexanes/ethyl acetate = 90:10, v/v).

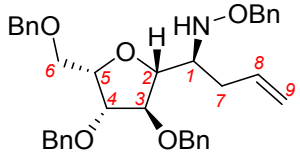
***O*-Benzyl-*N*-((*R*)-1-((2*S*,3*R*,4*R*,5*S*)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)but-3-en-1-yl)hydroxylamine (15).**



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<u>C</u>H_2Ph), 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-((2*R*,3*R*,4*R*,5*S*)-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<u>H_2</u>Ph), 4.54 (1H, d, *J* = 11.8 Hz, OC<u>H_2</u>Ph), 4.58 (1H, d, *J* = 12.0 Hz, OC<u>H_2</u>Ph), 4.52 (1H, d, *J* = 12.0 Hz, OC<u>H_2</u>Ph), 4.51 (1H, d, *J* = 12.0 Hz, OC<u>H_2</u>Ph), 4.49 (1H, d, *J* = 12.2 Hz, OC<u>H_2</u>Ph), 4.43 (1H, d, *J* = 11.8 Hz, OC<u>H_2</u>Ph), 4.42 (1H, d, *J* = 12.0 Hz, OC<u>H_2</u>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<u>C</u>H_2Ph), 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 steps approach: 1) Conformational search using the Spartan'18 Parallel Suite[21] at MMFF level of theory. 2) All structures obtained in previous step were optimized using MOPAC2016[22] with 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 m062x/6-31+g(d) level of theory. 4) For all structures from step 3 with energy < 22 kJ/mol vibrational frequency calculations was carried out at the same level of theory as of optimization theory. Each conformer contribution to Gibbs free energy was calculated according to a Boltzmann distribution. SMD implicit solvent model was used to simulate the toluene environment (Radii=Bondi, Surface=SAS).

Key words

Debenzylative cycloetherification, S_N2 reaction, *C*-furanoside, *O*-functionalized tetrahydrofuran, stereocontrolled synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge *via* the Internet at http://pubs.acs.org at DOI:

NBO charges distribution of compound **7**, **9**, **11**, **13**, transition states **TS-7**, **TS-11**, **imTS-7,9**, **imTS-11,13**, intermediates **im-7,9**, **im-11,13**; cartesian coordinates of calculated structures; NMR spectra of all synthesized compounds (PDF)

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References

(1) Wong, C.-H. (Ed.) *Carbohydrate-based Drug Discovery*, Wiley-VCH, 2003.
(2) Wei, A. H.; Strickland Jr, S. A.; Hou, J. Z.; Fiedler, W.; Tara, L.; Walter, R. B.; Enjeti, A.; Tiong, I. S.; Savona, M.; Lee, S.; Chyla, B.; Popovic, R.; Salem, A. H.; Agarwal, S.; Xu, T.; Fakouhi, K. M.; Humerickhouse, R.; Hong, W.-J.; Hayslip, J.; Roboz, G. J. Venetoclax Combined With Low-Dose Cytarabine for Previously Untreated Patients With Acute Myeloid Leukemia: Results From a Phase Ib/II Study. *J. Clin. Oncol.* **2019**, *37*, 1277-1284.
(3) Suzuki, M.; Okuda, T.; Shirak, K.; Synergistic Antiviral Activity of Acyclovir and Vidarabine Against Herpes Simplex Virus Types 1 and 2 and Varicella-Zoster Virus. *Antiviral Research* **2006**, *72*, 157-161.
(4) Goekjian, P.; Haudrechy, A.; Menhour, B.; Coiffier, C. *C-Furanosides: Synthesis and Stereochemistry*, Elsevier, **2017**.
(5) Meza-Avina, M. E.; Wei, L.; Liu, Y.; Poduch, E.; Bello, A. M.; Mishra, R. K.; Pai, E. F.; Kotra, L. P. Structural Determinants for the Inhibitory Ligands of Orotidine-5′-monophosphate Decarboxylase. *Bioorg. Med. Chem.* **2010**, *18*, 4032–4041.
(6) Malmstrom, J.; Christophersen, C.; Barrero, A. F.; Oltra, J. E.; Justicia, J.; Rosales, A. Bioactive Metabolites from a Marine-Derived Strain of the Fungus Emericella Variecolor. *J. Nat. Prod.* **2002**, *65*, 364–367.
(7) Mayer, A. M. S.; Gustafson, K. R. Marine Pharmacology in 2001–2: Antitumour and Cytotoxic Compounds. *Eur. J. Cancer* **2004**, *40*, 2676–2704.
(8) Kumar, V.; Shaw, A. K. First Total Synthesis of (+)-Varitriol. *J. Org. Chem.* **2008**, *73*, 7526–7531.
(9) Prasad, S.; Chakraborty, T. K.; Mathur, A.; Jaggi, M.; Kunwar, A. C.; Mukherjee, R.; Burman, A. C. Novel Peptides Comprising Furanoid Sugars Amino Acids for the Treatment of Cancer. US Patent US 2005/0032707A1, 2005.
(10) Chepuri, R. V.; Sarkar, D.; Patil, R. S.; Sarkar, S. Synthesis of 10-*α*/*β*-D-Arabinofuranosyl-undecenes as Potential Anti-mycobacterial Agents. WO Patent WO 2013/038430A1, 2013.
(11) (a) Dondoni, A.; Massi, A.; Nuzzi, A. A Serendipitous Discovery of a New C-Furanosyl Glycine Synthesis via Thiazole-Based Aminohomologation of Hexopyranoses. *Synlett* **2007**, *2*, 303–307; (b) Jiang, Y.; Fang, Z.; Zheng, Q.; Jia, H.; Cheng, J.; Zheng, B. Stereocontrolled Formation of Protected Aminodeoxyalditols from Simple Carbohydrate Precursors by Debenzylating Cycloetherification. *Synthesis* **2009**, *16*, 2756–2760.
(12) (a) Martin, O. R.; Yang, F.; Xie, F. Spontaneous cyclization of triflates derived from δ-benzyloxy alcohols: Efficient and general synthesis of C-vinyl furanosides. *Tetrahedron Letters* **1995**, *36*, 47–50; (b) Yang, B.-H.; Jiang, J.-Q.; Ma, K.; Wu, H.-M. Stereospecific cyclization to form C-furanosides. *Tetrahedron Letters* **1995**, *36*, 2831–2834; (c) Persky, R.; Albeck, A. An Unexpected Rearrangement during Mitsunobu Epimerization Reaction of Sugar Derivatives. *J. Org. Chem.* **2000**, *65,* 3775–3780; (d) Persky, R.; Albeck, A. Synthesis of Selectively Labeled D-Fructose and D-Fructose Phosphate Analogues Locked in the Cyclic Furanose Form. *J. Org. Chem.* **2000**, *65*, 5632–5638. (e) Sisu, E.; Sollogoub, M.; Mallet, J.-

M.; Sinaÿ, P. Cycloheptanic Sugar Mimetics, Bridging the Gap in the Homologous Series of Carbocyclic Analogues. *Tetrahedron* **2002**, *58*, 10189–10196.
(13) Buchanan, J. G.; Quijano, M. L.; Wightman, R. H.; New and More Direct Synthesis of 3-(*β*-D-Xylofuranosyl)pyrazol. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1573–1576.
(14) Tikad, A.; Delbrouck, J. A.; Vincent, S. P. Debenzylative Cycloetherification: An Overlooked Key Strategy for Complex Tetrahydrofuran Synthesis. *Chem. Eur. J.* **2016**, *22*, 9456–9476.
(15) Delbrouck, J. A.; Bochatay, V. N.; Tikad, A.; Vincent, S. P. Regioselective Synthesis of Difluorinated C-Furanosides Involving a Debenzylative Cycloetherification. *Org. Lett.* **2019**, *21*, 5562−5566.
(16) (a) Jarosz, S.; Gajewska, A.; Luboradzki, R. Synthesis of Higher Carbon Sugars. Unexpected Rearrangement of Higher Sugar Allylic Alcohols. *Tetrahedron: Asymmetry* **2008**, *19*, 1385–1391; (b) Potopnyk, M. A.; Cmoch, P.; Cieplak, M.; Gajewska, A.; Jarosz, S. The Synthesis of Higher Carbon Sugars: a Study on the Rearrangement of Higher Sugar Allylic Alcohols. *Tetrahedron: Asymmetry* **2011**, *22*, 780–786.
(17) Foucart, Q.; Marrot, J.; Désiré, J.; Blériot, Y. Site-Selective Debenzylation of C-Allyl Iminosugars Enables Their Stereocontroled Structure Diversification at the C-2 Position. *Org. Lett.* **2019**, *21*, 4821−4825.
(18) Zhang, J.; Fu, J.; Si, W.; Wang, X.; Wang, Z.; Tang, J. A Highly Efficient Deprotection of the 2,2,2-Trichloroethyl Group at the Anomeric Oxygen of Carbohydrates. *Carbohydrate Research* **2011**, *346*, 2290–2293.
(19) Hollingsworth, R. I.; Song, X. A Facile and General Synthesis of Rare L-Sugar Lactones. *Synlett* **2007**, *8*, 1247–1250.
(20) (a) Dondoni, A; Massi, A.; Sabbatini, S.; Bertolasi, V. Synthesis of *C*-Glycosyl *β*-Amino Acids by Asymmetric Mannich-Type Three-Component Reactions. *Tetrahedron Letters* **2004**, *45*, 2381–2384; (b) Dondoni, A., Massi, A.; Sabbatini, S.; Bertolasi, V. Three-Component Staudinger-Type Stereoselective Synthesis of *C*-Glycosyl-*β*-lactams and their Use as Precursors for C-Glycosyl Isoserines and Dipeptides. A Polymer-Assisted Solution-Phase Approach. *Adv. Synth. Catal.* **2004**, *346*, 1355–1360; (c) Dondoni, A.; Massi, A.; Sabbatini, S. Multiple Component Approaches to *C*-Glycosyl *β*-Amino Acids by Complementary One-Pot Mannich-Type and Reformatsky-Type Reactions. *Chem. Eur. J.* **2005**, *11*, 7110–7125; (d) Guerrini, A.; Varchi, G.; Battaglia, A. Stereoselective One-Pot Synthesis of Constrained *N*,*O*-Orthogonally Protected *C*-Glycosyl Norstatines [C(1')-Aminoglycosyl-1,3-dioxolan-4-ones]. *J. Org. Chem.* **2006**, *71*, 6785–6795.
(21) Spartan'18 Wavefunction, Inc. Irvine, CA
(22) MOPAC2016, James J. P. Stewart, Stewart Computational Chemistry, Colorado Springs, CO, USA, http://OpenMOPAC.net (2016).
(23) Gaussian 16, Revision A.03, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.