## Supporting Information

Authors: Gaetano Speciale, Marco Farren-Dai, Fahimeh S. Shidmoossavee, Spencer J. Williams, ${ }^{*}$ and Andrew J. Bennet ${ }^{*}$

Title: C2-Oxyanion neighboring group participation: Transition state structure for the hydroxidepromoted hydrolysis of 4-nitrophenyl $\alpha$-D-mannopyranoside

Journal: Journal of the American Chemical Society

## MATERIALS AND METHODS

## Chemical Synthesis

${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra were recorded using a Varian Inova-400 $\left(399.7 \mathrm{MHz}\right.$ for ${ }^{1} \mathrm{H}$ and 100.5 MHz for $\left.{ }^{13} \mathrm{C}\right)$ at $25.0{ }^{\circ} \mathrm{C}$. All signals were referenced to solvent peaks $\left(\mathrm{CDCl}_{3} \delta 7.27 \mathrm{ppm}\right.$ for ${ }^{1} \mathrm{H}$ and 77.16 ppm for ${ }^{13} \mathrm{C} ; \mathrm{d}_{4}-\mathrm{MeOH}: \delta 3.49 \mathrm{ppm}$ for ${ }^{1} \mathrm{H}$ and 49.00 ppm for ${ }^{13} \mathrm{C}$ ). TLC analysis used aluminiumbacked Merck Silica Gel $60 \mathrm{~F}_{254}$ sheets, detection was achieved using UV light, or $10 \% \mathrm{H}_{2} \mathrm{SO}_{4}$ in MeOH with charring. Flash chromatography was performed using Geduran silica gel according to the method of Still et al. ${ }^{1}$ Dry $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ was obtained from a dry solvent apparatus (Glass Contour of SG Water, Nashua, USA). ${ }^{2}$ Optical rotations were obtained using a JASCO DIP-1000 polarimeter (Melbourne, Australia). $[\alpha]_{\mathrm{D}}$ values are given in deg. $\mathrm{dm}^{-1} \mathrm{~cm}^{3} \mathrm{~g}^{-1}$. Melting points were obtained using a Reichert-Jung hot stage melting point apparatus. High resolution mass spectra (HRMS) were acquired at the Bio21 Institute, University of Melbourne on an Agilent ESI-TOF. Potassium tert-butoxide was purified by sublimation at $220^{\circ} \mathrm{C}$ under vacuum $(0.1 \mathrm{mmHg})$ in a Schlenk tube fitted with a cold finger. $\left(1-{ }^{13} \mathrm{C}\right)-,\left(1-{ }^{13} \mathrm{C}, 1-{ }^{2} \mathrm{H}\right)-,\left(2-{ }^{13} \mathrm{C}\right)-,\left(1-{ }^{13} \mathrm{C}, 2-{ }^{13} \mathrm{C}\right)-,\left(2-{ }^{1} \mathrm{H}, 2-{ }^{13} \mathrm{C}\right)$-, and $\left(2-{ }^{13} \mathrm{C}, 2-{ }^{18} \mathrm{O}\right)$-D-mannose were purchased from Omicron Biochemicals (USA).

## $\left({ }^{18} \mathrm{O}\right)$-4-Nitrophenol ( $\mathrm{pNP}^{18} \mathrm{OH}$ )

Freshly sublimed potassium tert-butoxide ( $67.3 \mathrm{mg}, 0.60 \mathrm{mmol}$ ) was added to a stirred slurry of 1-fluoro-4-nitrobenzene ( $113 \mu \mathrm{~L}, 0.60 \mathrm{mmol}$ ) in dry tert-butanol $(0.75 \mathrm{~mL}) . \mathrm{H}_{2}{ }^{18} \mathrm{O}(4 \mu \mathrm{~L}, 0.2 \mathrm{mmol}, 95 \%$ atom ${ }^{18} \mathrm{O}$ ) was added dropwise over 2 min . After 30 min the mixture was heated up to $95{ }^{\circ} \mathrm{C}$ for 24 h . The reaction was allowed to cool to room temperature, then water was added to dissolve the solid. The mixture was extracted with diethyl ether $(4 \times 10 \mathrm{~mL})$, and the organic phase extracted with 1 M NaOH $(2 \times 10 \mathrm{~mL})$. The combined aqueous phases were acidified to $\mathrm{pH}=1$ with conc. HCl , then extracted with diethyl ether $(4 \times 10 \mathrm{~mL})$. The combined organic fractions from the second extraction were dried $\left(\mathrm{MgSO}_{4}\right)$ and concentrated to give a brown solid residue, which was purified by flash chromatography
(AcOEt:hexane, 25:75) to give white crystals ( $81 \mathrm{mg}, 98 \%$ ), m.p. $112-114{ }^{\circ} \mathrm{C} .{ }^{3}$ Label incorporation was determined to be $67 \%$ by ESI-MS analysis.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 5.75(1 \mathrm{H}, \mathrm{s}, \mathrm{OH}), 6.91(2 \mathrm{H}, \mathrm{m}, \mathrm{H} 2,6), 8.17(2 \mathrm{H}, \mathrm{m}, \mathrm{H} 3,5) ;{ }^{13} \mathrm{C}$ NMR (125 MHz, $\mathrm{d}_{6}$-DMSO) $\delta 115.8$ (2 C, C2,6), 126.2 (2 C, C3,5), 139.6 (1 C, C4), 163.9 ( $1 \mathrm{C}, \mathrm{C} 1$ ); HRMS $(\mathrm{ESI})^{-} \mathrm{m} / \mathrm{z} 140.0240\left[\mathrm{O}_{2} \mathrm{NC}_{6} \mathrm{H}_{4}{ }^{18} \mathrm{OH}(\mathrm{M}-\mathrm{H})^{-}\right.$requires 140.0239].

## 4-Nitrophenyl $\alpha$-D-mannopyranoside (1a)

Penta-O-acetyl-D-mannopyranose: Concentrated sulfuric acid (2 drops) was added to a mixture of acetic anhydride $(11 \mathrm{ml})$ and D-mannose $(2.00 \mathrm{~g}, 11.1 \mathrm{mmol})$ at $0^{\circ} \mathrm{C}$. The mixture was stirred for 10 $\min$ at $0^{\circ} \mathrm{C}$ and then allowed to warm to rt . After a further 2 h the mixture was poured onto ice/water $(30 \mathrm{ml})$ and the organic phase was extracted with EtOAc $(60 \mathrm{ml})$. The organic extract was washed with water $(1 \times 30 \mathrm{ml})$, sat aq. $\mathrm{NaHCO}_{3}(4 \times 30 \mathrm{ml})$, brine $(30 \mathrm{ml})$, dried $\left(\mathrm{MgSO}_{4}\right)$ and concentrated under reduced pressure. The crude product was subjected to flash chromatography (EtOAc:pet spirits, 6:4 $\mathrm{v} / \mathrm{v})$ to afford the acetylated sugar as a mixture of anomers $(6.5: 1 \alpha / \beta)$ as a colorless oil $(4.10 \mathrm{~g}, 95 \%)$.

4-Nitrophenyl 2,3,4,6-tetra-O-acetyl- $\alpha$-D-mannopyranoside: Boron trifluoride diethyl etherate (3.4 $\mathrm{mL}, 27.6 \mathrm{mmol}$ ) was added dropwise to a solution of the mannose penta- $O$-acetate ( $2.0 \mathrm{~g}, 5.0 \mathrm{mmol}$ ) and 4-nitrophenol $(2.0 \mathrm{~g}, 15 \mathrm{mmol})$ in dry $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ at $0{ }^{\circ} \mathrm{C}$. The resulting solution was stirred under nitrogen at rt for 24 h . The solution was diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and washed twice with 1 N NaOH and water, dried $\left(\mathrm{MgSO}_{4}\right)$, and then the solvent was evaporated. The residue was recrystallized from AcOEt-MeOH to afford the tetra-O-acetate $(5.28 \mathrm{~g}, 75 \%)$ as a white solid.

4-Nitrophenyl $\alpha$-D-mannopyranoside (PNPMan): The tetra-O-acetate was dissolved in MeOH (50 $\mathrm{mL})$ and a solution of sodium methoxide in $\mathrm{MeOH}(0.2 \mathrm{ml}, 1.0 \mathrm{M})$ was added and the progress of the reaction monitored by TLC. Amberlite ${ }^{\circledR}$ IR-120 resin ( $\mathrm{H}^{+}$form) was added to neutralize the solution and, following filtration, the solvent was evaporated under reduced pressure to give a white solid. The
residue was recrystallized from EtOH to afford the tetraol $\mathbf{1}$ as white crystals ( $3.34 \mathrm{~g}, 74 \%$ over two steps), mp $176-178{ }^{\circ} \mathrm{C}\left(\right.$ lit. $\left.^{4} 182{ }^{\circ} \mathrm{C}\right),[\alpha]_{\mathrm{D}}{ }^{24}+144^{\circ}\left(\mathrm{c} 1.0, \mathrm{CH}_{3} \mathrm{OH}\right)$.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \delta 3.52\left(1 \mathrm{H}, \mathrm{ddd}, J_{4,5}=9.8, J_{5,6}=5.6, J_{5,6 \mathrm{a}}=2.5 \mathrm{~Hz}, \mathrm{H} 5\right), 3.71(1 \mathrm{H}, \mathrm{dd}$, $\left.J_{6,6 \mathrm{a}}=12.0, J_{5,6}=5.6 \mathrm{~Hz}, \mathrm{H} 6\right), 3.75\left(1 \mathrm{H}\right.$, app. t, $\left.J_{4,5}=J_{3,4}=9.6 \mathrm{~Hz}, \mathrm{H} 4\right), 3.79\left(1 \mathrm{H}, \mathrm{dd}, J_{6,6 \mathrm{a}}=12.0, J_{5,6 \mathrm{a}}\right.$ $=2.5 \mathrm{~Hz}, \mathrm{H} 6 \mathrm{a}), 3.91\left(1 \mathrm{H}, \mathrm{dd}, J_{3,4}=9.5, J_{2,3}=3.4 \mathrm{~Hz}, \mathrm{H} 3\right), 4.05\left(1 \mathrm{H}, \mathrm{dd}, J_{2,3}=3.4, J_{1,2}=1.9, \mathrm{H} 2\right), 5.67$ $\left(1 \mathrm{H}, \mathrm{d}, J_{1,2}=1.8, \mathrm{H} 1\right), 7.31(2 \mathrm{H}, \mathrm{m}, J=9.3 \mathrm{~Hz}, \mathrm{Ar}), 8.24(2 \mathrm{H}, \mathrm{m}, J=9.3 \mathrm{~Hz}, \mathrm{Ar}) ;{ }^{13} \mathrm{C}$ NMR $(101$ $\left.\mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \delta 62.6(1 \mathrm{C}, \mathrm{C} 6), 68.2(1 \mathrm{C}, \mathrm{C} 4), 71.6(1 \mathrm{C}, \mathrm{C} 2), 72.2(1 \mathrm{C}, \mathrm{C} 3), 76.1(1 \mathrm{C}, \mathrm{C} 5), 100.1$ $(1 \mathrm{C}, \mathrm{C} 1), 117.8,126.7,143.8,162.8(4 \mathrm{C}, \mathrm{Ar}) ; \mathrm{HRMS}(\mathrm{ESI})^{+} \mathrm{m} / \mathrm{z} 302.0872\left[\mathrm{C}_{12} \mathrm{H}_{16} \mathrm{NO}_{8}(\mathrm{M}+\mathrm{H})^{+}\right.$ requires 302.0876$]$.

## Investigation of $\mathbf{S}_{\mathbf{N}} \mathbf{A r}$ mechanism for alkaline hydrolysis of PNPMan

PNPMan $1(0.5 \mathrm{mg}, 2 \mu \mathrm{~mol})$ was treated with $100 \mu \mathrm{~L}$ of a 0.024 M solution of NaOH in $\mathrm{H}_{2} \mathrm{O}$, or $\mathrm{Na}^{18} \mathrm{OH}$ in $\mathrm{H}_{2}{ }^{18} \mathrm{O}$, and heated to $50{ }^{\circ} \mathrm{C}$. After TLC analysis shown complete consumption of starting material, the reactions were cooled to room temperature and the solution quenched by addition of Amberlite ${ }^{\circledR}$ IR-120 resin $\left(\mathrm{H}^{+}\right.$form) to avoid oxygen exchange, ${ }^{5}$ filtered and the crude solutions immediately analyzed by ESI-TOF MS in negative mode. No significant changes were noted in the peak intensities for the $\mathrm{M}^{-},[\mathrm{M}+1]^{-}$and $[\mathrm{M}+2]^{-}$.

## Kinetic Assays

The hydrolysis of PNPMan was monitored using a Cary 3E UV-Vis spectrophotometer equipped with a Peltier temperature controller. Reactions were initiated by the addition of a stock solution of PNPMan into a thermostatted $\left(25^{\circ} \mathrm{C}\right)$ sodium hydroxide solution $(1 \mathrm{M}, 0.5 \mathrm{M}$, or 0.1 M$)$ and the change in absorbance at a wavelength of 400 nm was monitored. Rate constants were calculated by fitting the absorbance versus time data to a standard first-order exponential equation.

## Kinetic Isotope Effect Measurements

NMR spectra were acquired on a Bruker AVANCE II spectrometer equipped with a QNP cryoprobe operating at 600 MHz for ${ }^{1} \mathrm{H}, 150 \mathrm{MHz}$ for ${ }^{13} \mathrm{C}$, and 92 MHz for ${ }^{2} \mathrm{H}$. The reaction solvent was $\mathrm{H}_{2} \mathrm{O}$ containing $5 \% \mathrm{D}_{2} \mathrm{O}$ for spectral locking. Carbon-13 $\mathrm{T}_{1}$ values for two labelled PNPMan isotopologues were measured using a standard inversion recovery pulse sequence and the values for C-1 and C-2 of 1a and $\mathbf{1 e}$ were determined to be 0.834 and 0.832 seconds, respectively.

In a typical experiment, a range (two to six) of labelled PNPMan isotopologues ( $\sim 0.6 \mathrm{mg}$ of each) were dissolved in $\mathrm{H}_{2} \mathrm{O}(\sim 300 \mu \mathrm{~L})$ containing $5 \% \mathrm{D}_{2} \mathrm{O}$. Methyl $\alpha-\mathrm{D}-\left(1-{ }^{13} \mathrm{C}\right)$ glucopyranoside $(\sim 0.3 \mathrm{mg})$ was added to the solution as an inert internal standard. NaCl solution (final concentration of 0.3 M ) was added to keep the ionic strength constant. Lastly, sodium hydroxide (final concentration of 0.1 M ) was added to the reaction mixture, and the resulting solution was immediately transferred into a Teflon liner that was placed inside a standard glass NMR tube. The magnetic field was shimmed manually to obtain symmetrical (as close to a Lorentzian shape as possible) peaks. A ${ }^{1} \mathrm{H}$ NMR spectrum and a ${ }^{13} \mathrm{C}$ NMR spectrum were then acquired before sequentially acquiring, with simultaneous proton- and deuteriumdecoupling, more than fifty quantitative ${ }^{13} \mathrm{C} \operatorname{NMR}\left({ }^{13} \mathrm{C}\left[{ }^{1} \mathrm{H},{ }^{2} \mathrm{H}\right]\right)$ spectra.

The resultant quantitative ${ }^{13} \mathrm{C}\left[{ }^{1} \mathrm{H},{ }^{2} \mathrm{H}\right]$ spectra were deconvolved by performing the following operations: i) all spectra were phased and baseline corrected using Bruker's Topspin software; ii) each spectral chemical shift scale was calibrated by setting the chemical shift of the anomeric carbon signal of the internal standard methyl $\alpha-\mathrm{D}-\left(1-{ }^{13} \mathrm{C}\right)$ glucopyranoside to be 99.43 ppm ; iii) each spectrum was fit to a series of mixed Gaussian-Lorentzian peaks as detailed by Fyfe et al., ${ }^{6}$ using the 'NonlinearRegress' function in a Mathematica notebook and iv) the peak areas were normalized relative to that of the internal standard.

The deconvolved chemical shift ranges were $69.46-70.26,97.84-98.45$, and $99.38-99.46 \mathrm{ppm}$ for the C-2 and C-1 peaks of PNPMan isotopologues, and the internal standard, respectively. To optimize the calculated Mathematica fit, peak positions, peak widths at half-height, and optimal combination of

Lorentzian and Gaussian (L/G) shapes for each individual peak were allowed to vary. Then, for each spectrum the fraction of reaction $\left(F_{L}\right)$ for the lighter isotopologue and the associated $R / R_{0}$ values were calculated from the respective integrals. These data were then fit, using standard non-linear least squares regression, to equation 1 .

$$
\begin{equation*}
R / R_{0}=\left(1-F_{L}\right)^{(1 / K I E)-1} \tag{1}
\end{equation*}
$$

## Computational Ground state and Transition State Optimization:

The local ground state reactant and oxirane product conformations of PNPMan was optimized with Gaussian 09 (Revision D.02), ${ }^{7}$ using the B3LYP method in conjunction with a $6-311 \mathrm{G}++\mathrm{G}(\mathrm{d}, \mathrm{p})$ basis set. Solvation was modeled by the Self Consistent Reaction Field (SCRF) method and Integral Equation Formalism Polarizable Continuum Model (IEF-PCM) in the dielectric environment of water with the dielectric constant set to $\varepsilon=78$. Two local ground state and oxirane structures were used in the calculation, which were two conformers of the $\mathrm{C} 6-\mathrm{CH}_{2} \mathrm{OH}$ group (gauche-gauche and trans-gauche). Two transition state structures (gauche-gauche and trans-gauche) were located using QST3 calculations that require reactant, product and initial structure for the transition state and utilizes the Synchronous Transit-Guided Quasi-Newton (STQN) method to locate the transition state. An overall formal negative charge was placed onto the reactants and the first-formed intermediate pair, which consists of an oxirane and a 4-nitrophenoxide ion. For these calculations the formal charge for the reactants was an explicit hydroxide ion that became $p$-nitrophenoxide at the intermediate oxirane. An Internal Reaction Coordinate (IRC) calculation was performed to ensure that this TS structure connected the products to the starting materials. Calculations for the transition state were performed with the same parameters used above for the calculation of the ground state structure. In addition, an explicit solvent water was incorporated (solvating the nucleophilic O 2 atom) to prevent formation of a $\mathrm{C} 3-\mathrm{OH}$ to $\mathrm{C} 2-\mathrm{O}^{-}$hydrogen bond that would result in a conformational restriction to approach of the TS structure. From the reactant and product geometries optimized as described above, TSs were located
using B3LYP 6-31+G(d,p) with the same solvation via SCRF method and IEF-PCM but also implementing a Bondi atomic radii which improved the resulting associated KIEs. Additional TSs were modelled by altering and freezing the two heavy-atom distances along the reaction coordinate, that is the $[\mathrm{C} 2] \mathrm{O}-\mathrm{C} 1(d 1)$ and $\mathrm{C} 1-[\mathrm{C} 1] \mathrm{O}(d 2)$ distances, and then allowing all other atomic coordinates to vary during energy minimization of the TS. The KIEs associated with each putative TS structure, for the base-promoted hydrolysis of PNPMan, were calculated from the vibrational frequencies of the transition state global ground state (optimized at the same level of theory as the TS but omitting the explicit water molecule) and using the ISOEFF98 program, ${ }^{8}$ with a scale factor of $0.9614 .{ }^{9}$ These calculations were performed to try to match the experimental KIEs at the various heavy-atom positions in the following order: (i) C-2 ${ }^{18} \mathrm{O}$; (ii) leaving group ${ }^{18} \mathrm{O}$; and (iii) anomeric ${ }^{13} \mathrm{C}$.


Figure S1: Unconstrained local ground state structure for the gauche-gauche $\mathrm{C} 6-\mathrm{CH}_{2} \mathrm{OH}$ conformer calculated at B3LYP6311++G (d, p) level of theory with SCRF method and IEF-PCM water dielectric environment.


Figure S2: Unconstrained local ground state structure for the trans-gauche $\mathrm{C} 6-\mathrm{CH}_{2} \mathrm{OH}$ conformer calculated at B3LYP6311++G (d, p) level of theory with SCRF method and IEF-PCM water dielectric environment.


Figure S3. Calculated transition state structures for the formation of the oxirane intermediate, from the trans-gauche $\mathrm{C} 6-\mathrm{CH}_{2} \mathrm{OH}$ conformer, during the base-promoted hydrolysis of 4-nitrophenyl $\alpha$-Dmannopyranoside. Unconstrained TS is shown in teal (left hand structure), the constrained TS, which was obtained by systematic variation of the two reaction coordinate $\mathrm{C}-\mathrm{O}$ bonds, is shown in green (right hand structure) and an overlay of the two calculated transition states. Unconstrained TS structure calculated at B3LYP6311++G (d, p) level of theory with SCRF method and IEF-PCM water dielectric environment and the constrained TS structure was calculated at a B3LYP631+G (d, p) level of theory with SCRF method and IEF-PCM water dielectric environment and Bondi Atomic Radii.


Figure S4. Calculated fractional errors between the measured kinetic isotope effects on the basepromoted hydrolysis of 4-nitrophenyl $\alpha$-D-mannopyranoside $\left(\mathrm{T}=25^{\circ} \mathrm{C}\right)$ and those calculated for the trans-gauche conformer at the B3LYP/6-31G* level of theory, a negative value indicates that the calculated KIE is smaller that the experimental value. Panel A, interatomic distance between the anomeric carbon and the leaving group oxygen (C1-O1) was fixed at $2.2893 \AA$. Panel B, interatomic distance between the anomeric carbon and the nucleophilic oxygen (C1-O2) was fixed at $1.8824 \AA$. Secondary deuterium KIEs are in blue $\alpha$-SDKIE (filled circle, solid line), $\beta$-SDKIE (hollow circle, dashed line), ${ }^{18} \mathrm{O}$-KIE are in red, leaving group- ${ }^{18} \mathrm{O}$ (filled triangle, solid line), and nucleophilic${ }^{18} \mathrm{O}$ (hollow triangle, dashed line), and anomeric- ${ }^{13} \mathrm{C}$ KIEs are in black (diamond).

Table S1: Characteristic ${ }^{1} \mathrm{H}$ NMR Spectroscopic data for the labeled mannosides $\mathbf{1 b} \mathbf{- g}$ that were synthesized according to the described procedure for $\mathbf{1 a}$, with the exception of $\mathbf{1 h}$, for which $\mathbf{p N P}{ }^{\mathbf{1 8}} \mathbf{O H}$ was used.

| Compound | Label \% | Characteristic NMR shifts |
| :---: | :---: | :---: |
| 1b | $1-{ }^{13} \mathrm{C}: 99$ | ${ }^{1}$ H NMR $4.05\left(1 \mathrm{H}, \mathrm{dt}, J_{2,3}=3.3, J_{1,2}=1.8 \mathrm{~Hz}, \mathrm{H} 2\right)$, $5.64(1$ $\left.H, ~ d d, J_{\mathrm{C}, \mathrm{H}}=172.1, J_{1,2}=1.8 \mathrm{~Hz}, \mathrm{H} 1\right)$. <br> ${ }^{13} \mathrm{C}$ NMR 100.1 ( $1 \mathrm{C}, \mathrm{C} 1$ ). |
| 1c | $\begin{aligned} & 1-{ }^{13} \mathrm{C}: 99 \\ & 1-{ }^{2} \mathrm{H}: 99 \end{aligned}$ | ${ }^{1} \mathrm{H}$ NMR H 1 is ${ }^{2} \mathrm{H}$, no signal. ${ }^{13} \mathrm{C}$ NMR 100.1 ( $1 \mathrm{C}, \mathrm{C} 1$ ) |
| 1d | $2-{ }^{13} \mathrm{C}: 99$ | ${ }^{1} \mathrm{H}$ NMR $4.05\left(1 \mathrm{H}\right.$, ddd, $J_{\mathrm{C}, \mathrm{H}}=148.3, J_{2,3}=3.3, J_{1,2}=1.8 \mathrm{~Hz}$, <br> H2). <br> ${ }^{13} \mathrm{C}$ NMR 71.6 (1 C, C2). |
| 1e | $\begin{aligned} & 1-{ }^{13} \mathrm{C}: 99 \\ & 2-{ }^{13} \mathrm{C}: 99 \end{aligned}$ | $\begin{gathered} { }^{1} \mathrm{H} \text { NMR } 4.05\left(1 \mathrm{H}, \mathrm{ddt}, J_{\mathrm{C}, \mathrm{H}}=148.3, J_{2,3}=3.3, J_{1,2}=1.8 \mathrm{~Hz},\right. \\ \text { H2 }), 5.66\left(1 \mathrm{H}, \mathrm{dt}, J_{\mathrm{C}, \mathrm{H}}=172.1, J_{1,2}=1.8 \mathrm{~Hz}, \mathrm{H} 1\right) . \\ { }^{13} \mathrm{C} \text { NMR } 71.6\left(1 \mathrm{C}, \mathrm{~d}, J_{1,2}=47.8 \mathrm{~Hz}, \mathrm{C} 2\right), 100.1\left(1 \mathrm{C}, \mathrm{~d}, J_{1,2}\right. \\ =47.8 \mathrm{~Hz}, \mathrm{C} 1) . \end{gathered}$ |
| 1f | $\begin{aligned} & 2-{ }^{13} \mathrm{C}: 99 \\ & 2-{ }^{2} \mathrm{H}: 98 \end{aligned}$ | ${ }^{1} \mathrm{H}$ NMR H2 is ${ }^{2} \mathrm{H}$, no signal. ${ }^{13} \mathrm{C}$ NMR 71.6 (1 C, C2). |
| 1 g | $\begin{aligned} & 2-{ }^{13} \mathrm{C}: 99 \\ & 2-{ }^{18} \mathrm{O}: 90 \end{aligned}$ | ${ }^{1} \mathrm{H}$ NMR $4.05\left(1 \mathrm{H}\right.$, ddd, $J_{\mathrm{C}, \mathrm{H}}=148.5, J_{2,3}=3.3, J_{1,2}=1.8$ $\mathrm{Hz}, \mathrm{H} 2), 5.66\left(1 \mathrm{H}, \mathrm{t}, \mathrm{J}_{1,2}=1.8 \mathrm{~Hz}, \mathrm{H} 1\right)$. <br> ${ }^{13} \mathrm{C}$ NMR $71.6(1 \mathrm{C}, \mathrm{C} 2)$. |
| 1h | $\begin{aligned} & 1-{ }^{13} \mathrm{C}: 99 \\ & 1-{ }^{18} \mathrm{O}: 67 \end{aligned}$ | ${ }^{1} \mathrm{H}$ NMR $5.64\left(1 \mathrm{H}, \mathrm{dd}, J_{\mathrm{C}, \mathrm{H}}=172.1, J_{1,2}=1.8 \mathrm{~Hz}, \mathrm{H} 1\right), 4.05$ <br> $\left(1 \mathrm{H}, \mathrm{dt}, J_{2,3}=3.3, J_{1,2}=1.8 \mathrm{~Hz}, \mathrm{H} 2\right)$. <br> ${ }^{13} \mathrm{C}$ NMR 100.1 ( $1 \mathrm{C}, \mathrm{C} 1$ ). |

Table S2: Measured kinetic isotope effects on the base-promoted hydrolysis of 4-nitrophenyl $\alpha$-Dmannopyranoside in $100 \mathrm{mM} \mathrm{NaOH}(I=0.4, \mathrm{NaCl})$ at $\mathrm{T}=25^{\circ} \mathrm{C}$.

| Effect | Run-1 | Run-2 | Run-3 | Mean $\pm$ SD |
| :---: | :---: | :---: | :---: | :---: |
| $1-{ }^{2} \mathrm{HKIE}$ | $1.114 \pm 0.007$ | $1.107 \pm 0.003$ | $1.114 \pm 0.005$ | $1.112 \pm 0.004$ |
| $2-{ }^{2} \mathrm{HKIE}$ | $1.042 \pm 0.002$ | $1.051 \pm 0.006$ | $1.044 \pm 0.002$ | $1.045 \pm 0.005$ |
| $1-{ }^{13} \mathrm{CKIE}$ | $1.023 \pm 0.003$ | $1.033 \pm 0.004$ | $1.022 \pm 0.002$ | $1.026 \pm 0.006$ |
| $2-{ }^{13} \mathrm{CKIE}$ | $1.004 \pm 0.004$ | $0.994 \pm 0.002$ | $0.999 \pm 0.002$ | $0.999 \pm 0.005$ |
| $1-{ }^{18} \mathrm{OKIE}$ | $1.027 \pm 0.002$ | $1.049 \pm 0.003$ | $1.044 \pm 0.003$ | $1.040 \pm 0.012$ |
| $2-{ }^{18} \mathrm{OKIE}$ | $1.051 \pm 0.004$ | $1.039 \pm 0.003$ | $1.043 \pm 0.002$ | $1.044 \pm 0.006$ |

Table S3. Kinetic isotope effects on the base-promoted hydrolysis of 4-nitrophenyl $\alpha$-Dmannopyranoside in $100 \mathrm{mM} \mathrm{NaOH}(I=0.4, \mathrm{NaCl})$ at $\mathrm{T}=25^{\circ} \mathrm{C}$, and the calculated KIEs for the trans-gauche $\mathrm{C} 6-\mathrm{CH}_{2} \mathrm{OH}$ conformer at the B3LYP/6-31G* level of theory.

|  | Experimental <br> KIEs | Calculated KIEs |  |  |
| :---: | :---: | :---: | :---: | :---: |
| Position of KIE | Mean $\pm \mathbf{~ S D}$ | Initial TS | Unconstrained TS | Constrained TS |
| $\mathbf{1 - { } ^ { \mathbf { 2 } } \mathbf { H }}$ | $1.112 \pm 0.004$ | 1.1504 | 1.1544 | 1.1101 |
| $\mathbf{2 - { } ^ { \mathbf { 2 } } \mathbf { H }}$ | $1.045 \pm 0.005$ | 1.1119 | 1.0719 | 1.0690 |
| $\mathbf{1 -}{ }^{\mathbf{1 3}} \mathbf{C}$ | $1.026 \pm 0.006$ | 1.0491 | 1.0380 | 1.0447 |
| $\mathbf{2 -}{ }^{\mathbf{1 3}} \mathbf{C}$ | $0.999 \pm 0.005$ | 1.0062 | 1.0060 | 1.0074 |
| $\mathbf{1 - 1 8} \mathbf{O}$ | $1.040 \pm 0.012$ | 1.0362 | 1.0435 | 1.0332 |
| $\mathbf{2 - 1 8} \mathbf{O}$ | $1.044 \pm 0.006$ | 1.0335 | 1.0349 | 1.0481 |

Table S4. Calculated KIEs optimized with B3LYP/6-31+G(d,p), SCRF method, IEF-PCM water dielectric and Bondi radii for the base-promoted hydrolysis of the gauche-gauche $\mathrm{C} 6-\mathrm{CH}_{2} \mathrm{OH}$ conformer of 4-nitrophenyl $\alpha$-D-mannopyranoside with the C1-O2 interatomic distance fixed to be 1.8824 Å.

| $\mathrm{C} 1-\mathrm{O} 1(\AA)$ | anomeric ${ }^{13} \mathrm{C}-\mathrm{KIE}$ | leaving group ${ }^{18} \mathrm{O}-\mathrm{KIE}$ | nucleophile ${ }^{18} \mathrm{O}-\mathrm{KIE}$ |
| :---: | :---: | :---: | :---: |
| 2.0893 | 1.05195 | 1.03370 | 1.03947 |
| 2.1893 | 1.04854 | 1.03298 | 1.04333 |
| 2.2893 | 1.04422 | 1.03314 | 1.04784 |
| 2.3893 | 1.03987 | 1.03378 | 1.05174 |
| 2.4893 | 1.03668 | 1.03345 | 1.05516 |
| 2.5893 | 1.03427 | 1.03383 | 1.05743 |

Table S5. Calculated KIEs optimized with B3LYP/6-31+G(d,p), SCRF method, IEF-PCM water dielectric and Bondi radii for the base-promoted hydrolysis of the trans-gauche $\mathrm{C} 6-\mathrm{CH}_{2} \mathrm{OH}$ conformer of 4-nitrophenyl $\alpha$-D-mannopyranoside with the C1-O2 interatomic distance fixed to be $1.8824 \AA$.

| $\mathrm{C} 1-\mathrm{O} 1(\AA)$ | anomeric ${ }^{13} \mathrm{C}-\mathrm{KIE}$ | leaving group ${ }^{18} \mathrm{O}-\mathrm{KIE}$ | nucleophile ${ }^{18} \mathrm{O}-\mathrm{KIE}$ |
| :---: | :---: | :---: | :---: |
| 2.0893 | 1.05278 | 1.03380 | 1.03865 |
| 2.1893 | 1.04868 | 1.03312 | 1.04351 |
| 2.2893 | 1.04469 | 1.03325 | 1.04806 |
| 2.3893 | 1.04112 | 1.03356 | 1.05157 |
| 2.4893 | 1.03841 | 1.03415 | 1.05420 |
| 2.5893 | 1.03594 | 1.03311 | 1.05723 |

Table S6. Calculated KIEs optimized with B3LYP/6-31+G(d,p), SCRF method, IEF-PCM water dielectric and Bondi radii for the base-promoted hydrolysis of the gauche-gauche $\mathrm{C} 6-\mathrm{CH}_{2} \mathrm{OH}$ conformer of 4-nitrophenyl $\alpha$-D-mannopyranoside with the C1-O1 interatomic distance fixed to be 2.2893 Å.

| C1-O2 ( $\AA$ ) | anomeric ${ }^{13} \mathrm{C}-\mathrm{KIE}$ | leaving group ${ }^{18} \mathrm{O}-\mathrm{KIE}$ | nucleophile ${ }^{18} \mathrm{O}$-KIE |
| :---: | :---: | :---: | :---: |
| 1.7824 | 1.04385 | 1.03102 | 1.05022 |
| 1.8824 | 1.04422 | 1.03314 | 1.04784 |
| 1.9824 | 1.04254 | 1.03613 | 1.04233 |

Table S7. Calculated KIEs optimized with B3LYP/6-31+G(d,p), SCRF method, IEF-PCM water dielectric and Bondi radii for the base-promoted hydrolysis of the trans-gauche $\mathrm{C} 6-\mathrm{CH}_{2} \mathrm{OH}$ conformer of 4-nitrophenyl $\alpha$-D-mannopyranoside with the C1-O1 interatomic distance fixed to be $2.2893 \AA$.

| $\mathrm{C} 1-\mathrm{O} 2(\AA)$ | anomeric ${ }^{13} \mathrm{C}$-KIE | leaving group ${ }^{18} \mathrm{O}-\mathrm{KIE}$ | nucleophile ${ }^{18} \mathrm{O}$-KIE |
| :---: | :---: | :---: | :---: |
| 1.7824 | 1.04479 | 1.03078 | 1.05014 |
| 1.8824 | 1.04469 | 1.03325 | 1.04806 |
| 1.9824 | 1.04295 | 1.03708 | 1.04266 |

Table S8. Calculated bond lengths for the local ground state and transition state structures for the base-promoted hydrolysis of 4-nitrophenyl $\alpha$-D-mannopyranoside in the gauche-gauche conformer.

| Model | $\mathrm{C} 1-\mathrm{O} 1(\AA)$ | $\mathrm{C} 1-\mathrm{O} 2$ | $\mathrm{C} 2-\mathrm{O} 2(\AA)$ | $\mathrm{C} 1-\mathrm{O} 5(\AA)$ | $\mathrm{C} 1-\mathrm{H} 1(\AA)$ | $\mathrm{C} 2-\mathrm{H} 2(\AA)$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Local GS | 1.45513 | 2.38718 | 1.36845 | 1.40160 | 1.09049 | 1.11105 |
| Unconstrained | 2.26364 | 2.03162 | 1.38868 | 1.29898 | 1.07993 | 1.09899 |
| Constrained | 2.28933 | 1.88240 | 1.41008 | 1.31444 | 1.07927 | 1.09631 |
| Oxirane | $\mathrm{NA}^{a}$ | 1.43753 | 1.45529 | 1.37520 | 1.08452 | 1.08638 |

${ }^{a} \mathrm{NA}=$ not applicable.

Table S9. Calculated bond lengths for the local ground state and transition state structures for the base-promoted hydrolysis of 4-nitrophenyl $\alpha$-D-mannopyranoside in the trans-gauche conformer.

| Model | C1-O1 $(\AA)$ | C1-O2 | C2-O2 $(\AA)$ | C1-O5 $(\AA)$ | C1-H1 $(\AA)$ | C2-H2 $(\AA)$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Local GS | 1.45123 | 2.38705 | 1.36843 | 1.40459 | 1.09030 | 1.11118 |
| Unconstrained | 2.30550 | 2.05632 | 1.39756 | 1.29999 | 1.08146 | 1.09938 |
| Constrained | 2.28933 | 1.88240 | 1.41090 | 1.31593 | 1.07899 | 1.09617 |
| Oxirane | $\mathrm{NA}^{a}$ | 1.43579 | 1.45686 | 1.37654 | 1.08430 | 1.08629 |

${ }^{a} \mathrm{NA}=$ not applicable.

Table S10. Calculated bond and torsional angles for the local ground state and transition state structures for the base-promoted hydrolysis of 4-nitrophenyl $\alpha$-D-mannopyranoside in the gauchegauche conformer.

| Model | O2-C2-C1-O1 $\left({ }^{\circ}\right)$ | O2-C2-H2 $\left({ }^{\circ}\right)$ | $\mathrm{O} 2-\mathrm{C} 2-\mathrm{C} 1\left({ }^{\circ}\right)$ | $\mathrm{C} 2-\mathrm{C} 1-\mathrm{O} 1\left({ }^{\circ}\right)$ | $\mathrm{O} 1-\mathrm{C} 1-\mathrm{H} 1\left({ }^{\circ}\right)$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Local GS | 165.662 | 113.222 | 109.737 | 108.124 | 108.867 |
| Unconstrained | 164.475 | 115.023 | 90.187 | 96.836 | 90.557 |
| Constrained | 163.859 | 114.735 | 81.774 | 96.983 | 85.747 |
| Oxirane | $\mathrm{NA}^{\underline{a}}$ | 114.187 | 58.922 | NA | NA |

${ }^{a} \mathrm{NA}=$ not applicable.

Table S11. Calculated bond and torsional angles for the local ground state and transition state structures for the base-promoted hydrolysis of 4-nitrophenyl $\alpha$-D-mannopyranoside in the trans-gauche conformer.

| Model | $\mathrm{O} 2-\mathrm{C} 2-\mathrm{C} 1-\mathrm{O} 1\left({ }^{\circ}\right)$ | $\mathrm{O} 2-\mathrm{C} 2-\mathrm{H} 2\left({ }^{\circ}\right)$ | $\mathrm{O} 2-\mathrm{C} 2-\mathrm{C} 1\left({ }^{\circ}\right)$ | $\mathrm{C} 2-\mathrm{C} 1-\mathrm{O} 1\left({ }^{\circ}\right)$ | $\mathrm{O} 1-\mathrm{C} 1-\mathrm{H} 1\left({ }^{\circ}\right)$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Local GS | 165.804 | 113.184 | 109.727 | 108.409 | 109.020 |
| Unconstrained | 162.211 | 114.317 | 91.118 | 97.640 | 88.747 |
| Constrained | 163.779 | 114.735 | 81.754 | 97.457 | 85.465 |
| Oxirane | $\mathrm{NA}^{a}$ | 114.199 | 58.857 | $\mathrm{NA}^{a}$ | $\mathrm{NA}^{a}$ |

${ }^{a} \mathrm{NA}=$ not applicable.

Table S12. Calculated equilibrium isotope effects at the B3LYP/6-311++G(d,p) level of theory with SCRF method and IEF-PCM dielectric, using the local gauche-gauche ground state and oxirane structures.

| Effect | Experimental KIE | Calculated EIE |
| :---: | :---: | :---: |
| $1-{ }^{2} \mathrm{HKIE}$ | $1.112 \pm 0.004$ | 1.1057 |
| $2-{ }^{2} \mathrm{HKIE}$ | $1.045 \pm 0.005$ | 1.0819 |
| $1-{ }^{13} \mathrm{CKIE}$ | $1.026 \pm 0.006$ | 1.0083 |
| $2-{ }^{13} \mathrm{CKIE}$ | $0.999 \pm 0.005$ | 1.0130 |
| $1-{ }^{18} \mathrm{OKIE}$ | $1.040 \pm 0.012$ | 1.0314 |
| $2-{ }^{18} \mathrm{OKIE}$ | $1.044 \pm 0.006$ | 1.0097 |

Table S13. Calculated equilibrium isotope effects at the B3LYP/6-311++G(d,p) level of theory with SCRF method and IEF-PCM dielectric, using the local trans-gauche ground state and oxirane structures.

| Effect | Experimental KIE | Calculated EIE |
| :---: | :---: | :---: |
| $1-{ }^{2} \mathrm{HKIE}$ | $1.112 \pm 0.004$ | 1.0995 |
| $2-{ }^{2} \mathrm{HKIE}$ | $1.045 \pm 0.005$ | 1.0809 |
| $1-{ }^{13} \mathrm{CKIE}$ | $1.026 \pm 0.006$ | 1.0080 |
| $2-{ }^{13} \mathrm{CKIE}$ | $0.999 \pm 0.005$ | 1.0126 |
| $1-{ }^{18} \mathrm{OKIE}$ | $1.040 \pm 0.012$ | 1.0312 |
| $2-{ }^{18} \mathrm{OKIE}$ | $1.044 \pm 0.006$ | 1.0010 |

Table S14 Unconstrained local ground state structure for the gauche-gauche conformed calculated at B3LYP6311++G ( $\mathrm{d}, \mathrm{p}$ ) level of theory with SCRF method and IEF-PCM water dielectric environment.

| Atom |  |  |  |
| :--- | ---: | ---: | ---: |
| C | 0.8075 | -0.5409 | -0.6880 |
| C | 1.5828 | 1.4996 | 0.3332 |
| C | 2.9387 | 0.8468 | 0.6527 |
| C | 2.7418 | -0.6459 | 0.8725 |
| C | 2.1264 | -1.2952 | -0.3932 |
| H | 0.4140 | -0.8736 | -1.6491 |
| H | 3.6313 | 1.0032 | -0.1749 |
| H | 2.0486 | -0.7792 | 1.7155 |
| H | 1.8237 | -2.3235 | -0.1007 |
| H | 0.9354 | 1.3946 | 1.2133 |
| O | 3.4855 | 1.3958 | 1.8658 |
| O | 3.9800 | -1.2910 | 1.1906 |
| H | 4.3862 | -0.7687 | 1.8940 |
| C | 1.6636 | 2.9811 | 0.0149 |
| H | 1.9474 | 3.5178 | 0.9268 |
| H | 0.6702 | 3.3264 | -0.2913 |
| O | 2.6222 | 3.2078 | -1.0234 |
| H | 2.6350 | 4.1501 | -1.2211 |
| O | 0.9586 | 0.8486 | -0.7924 |
| O | 2.9336 | -1.2639 | -1.4977 |
| H | 4.0988 | -2.2482 | -1.3886 |
| H | 4.0548 | 2.1403 | 1.6450 |
| O | -0.1498 | -0.8783 | 0.3546 |
| C | -1.4647 | -0.6220 | 0.1874 |
| C | -2.0088 | 0.0813 | -0.9008 |
| C | -2.3121 | -1.1132 | 1.1980 |
| C | -3.3800 | 0.2720 | -0.9786 |
| H | -1.3703 | 0.4937 | -1.6675 |
| C | -3.6770 | -0.9186 | 1.1227 |
| H | -1.8746 | -1.6503 | 2.0301 |
| C | -4.2065 | -0.2262 | 0.0285 |
| H | -3.8102 | 0.8112 | -1.8108 |
| H | -4.3337 | -1.2964 | 1.8936 |
| N | -5.6416 | -0.0173 | -0.0575 |
| O | -6.3545 | -0.4541 | 0.8488 |
| O | -6.0920 | 0.5876 | -1.0329 |
| -2.8966 | -1.2813 |  |  |
|  | -2.7374 | -0.3657 |  |

Sum of Electronic and Zero-Point Energies: - 1198.782485 hartree

Table S15 Unconstrained local ground state structure for the trans-gauche conformer calculated at
B3LYP6311++G ( $\mathrm{d}, \mathrm{p}$ ) level of theory with SCRF method and IEF-PCM water dielectric environment.

| Atom |  |  |  |
| :--- | ---: | ---: | ---: |
| C | 0.79144 | -0.704031 | -0.657746 |
| C | 1.633253 | 1.488319 | -0.106824 |
| C | 2.977503 | 0.88559 | 0.336983 |
| C | 2.765352 | -0.533369 | 0.842261 |
| C | 2.109451 | -1.4079 | -0.253968 |
| H | 0.366823 | -1.213805 | -1.522958 |
| H | 3.66592 | 0.86542 | -0.515488 |
| H | 2.091352 | -0.485686 | 1.708722 |
| H | 1.800332 | -2.351675 | 0.244478 |
| H | 1.004777 | 1.627817 | 0.78165 |
| O | 3.549701 | 1.64025 | 1.414986 |
| O | 4.003926 | -1.125388 | 1.256401 |
| H | 4.421857 | -0.500702 | 1.861908 |
| C | 1.780392 | 2.819436 | -0.839032 |
| H | 0.791885 | 3.18373 | -1.134943 |
| H | 2.387005 | 2.671392 | -1.738465 |
| O | 2.416461 | 3.750698 | 0.050464 |
| H | 2.637547 | 4.550011 | -0.439481 |
| O | 0.960545 | 0.63449 | -1.048431 |
| O | 2.882391 | -1.613216 | -1.364372 |
| H | 4.058859 | -2.559644 | -1.07937 |
| H | 3.532147 | 2.573282 | 1.150619 |
| O | -0.138653 | -0.801255 | 0.452004 |
| C | -1.457608 | -0.578941 | 0.261291 |
| C | -2.020946 | -0.102195 | -0.934447 |
| C | -2.28584 | -0.860466 | 1.36328 |
| C | -3.393761 | 0.07091 | -1.024938 |
| H | -1.39644 | 0.150492 | -1.778418 |
| C | -3.652426 | -0.684104 | 1.273957 |
| H | -1.832979 | -1.224336 | 2.276852 |
| C | -4.201733 | -0.220252 | 0.074003 |
| H | -3.839244 | 0.437358 | -1.939155 |
| H | -4.295358 | -0.903267 | 2.114677 |
| N | -5.639191 | -0.032555 | -0.027059 |
| O | -6.335928 | -0.291268 | 0.956615 |
| O | -6.106959 | 0.377283 | -1.091545 |
| O | 4.854914 | -3.171863 | -0.853357 |
| H | 5.118205 | -2.828326 | 0.00775 |
|  |  |  |  |

Sum of Electronic and Zero-Point Energies: - 1198.783557 hartree

Table S16 Unconstrained oxirane structure for the gauche-gauche conformer calculated at B3LYP6311++G ( $\mathrm{d}, \mathrm{p}$ ) level of theory with SCRF method and IEF-PCM water dielectric environment.

| Atom |  |  |  |
| :--- | ---: | ---: | ---: |
| C | -2.8045 | -0.0054 | 1.9480 |
| C | -2.1468 | 1.3228 | 0.0491 |
| C | -2.8461 | 0.2823 | -0.8412 |
| C | -2.4951 | -1.1148 | -0.3384 |
| C | -2.7225 | -1.2313 | 1.1456 |
| H | -2.5503 | -0.0047 | 3.0023 |
| H | -3.9273 | 0.4298 | -0.7955 |
| H | -1.4268 | -1.2855 | -0.5182 |
| H | -2.3889 | -2.1565 | 1.6070 |
| H | -1.0762 | 1.0900 | 0.0908 |
| O | -2.3956 | 0.3558 | -2.1955 |
| O | -3.2665 | -2.1276 | -1.0040 |
| H | -3.0922 | -2.0452 | -1.9507 |
| C | -2.3076 | 2.7498 | -0.4326 |
| H | -1.6710 | 2.8921 | -1.3120 |
| H | -1.9601 | 3.4264 | 0.3551 |
| O | -3.6790 | 3.0010 | -0.7573 |
| H | -3.7625 | 3.9200 | -1.0330 |
| O | -2.6807 | 1.2492 | 1.3987 |
| O | -3.9999 | -0.7434 | 1.6435 |
| H | -5.8194 | -1.5600 | 0.6515 |
| H | -2.9110 | 1.0297 | -2.6531 |
| O | 0.8298 | -0.3852 | 0.0811 |
| C | 2.0912 | -0.3084 | 0.0610 |
| C | 2.7999 | 0.8811 | 0.4894 |
| C | 2.9261 | -1.4029 | -0.3923 |
| C | 4.1673 | 0.9621 | 0.4684 |
| H | 2.2073 | 1.7214 | 0.8348 |
| C | 4.2933 | -1.3172 | -0.4107 |
| H | 2.4302 | -2.3096 | -0.7219 |
| C | 4.9401 | -0.1345 | 0.0190 |
| H | 4.6735 | 1.8613 | 0.9944 |
| H | 4.8955 | -2.1487 | -0.7526 |
| N | 6.3456 | -0.0497 | -0.0001 |
| O | 7.0175 | -1.0283 | -0.3991 |
| O | 6.9054 | 1.0031 | 0.3826 |
| O | -6.0146 | -2.1250 | -0.1072 |
| H | -5.1431 | -2.2108 | -0.5322 |
|  |  |  |  |

Sum of Electronic and Zero-Point Energies: -1198.78017 hartree

Table S17 Unconstrained oxirane structure for the trans-gauche conformer calculated at B3LYP6311++G ( $\mathrm{d}, \mathrm{p}$ ) level of theory with SCRF method and IEF-PCM water dielectric environment.

| Atom |  |  |  |
| :--- | ---: | ---: | ---: |
| C | -2.619609 | 0.169928 | 1.892477 |
| C | -2.228134 | 1.355194 | -0.183868 |
| C | -2.913526 | 0.182207 | -0.903256 |
| C | -2.426320 | -1.132283 | -0.298761 |
| C | -2.534208 | -1.119678 | 1.201982 |
| H | -2.282815 | 0.287088 | 2.916468 |
| H | -3.997797 | 0.259448 | -0.793609 |
| H | -1.364230 | -1.248262 | -0.545956 |
| H | -2.117993 | -1.980612 | 1.717338 |
| H | -1.142065 | 1.223685 | -0.254029 |
| O | -2.558333 | 0.146628 | -2.288551 |
| O | -3.169027 | -2.252978 | -0.804456 |
| H | -3.068944 | -2.253684 | -1.765379 |
| C | -2.606060 | 2.727187 | -0.718601 |
| H | -2.298977 | 2.810342 | -1.761740 |
| H | -2.065074 | 3.487890 | -0.144759 |
| O | -4.012013 | 2.970683 | -0.680928 |
| H | -4.295584 | 2.895099 | 0.238424 |
| O | -2.602764 | 1.371598 | 1.221234 |
| O | -3.794678 | -0.643783 | 1.756219 |
| H | -4.975691 | -2.432065 | -0.149188 |
| H | -3.202800 | 0.654978 | -2.792324 |
| O | 0.829854 | -0.233184 | -0.166467 |
| C | 2.091689 | -0.192678 | -0.106307 |
| C | 2.926327 | -1.242641 | -0.655046 |
| C | 2.800908 | 0.907302 | 0.516145 |
| C | 4.293874 | -1.196846 | -0.587041 |
| H | 2.429900 | -2.082338 | -1.129587 |
| C | 4.168771 | 0.948909 | 0.580702 |
| H | 2.208389 | 1.712476 | 0.937320 |
| C | 4.941291 | -0.101677 | 0.031884 |
| H | 4.895769 | -1.993737 | -1.003974 |
| H | 4.675572 | 1.781837 | 1.050296 |
| N | 6.347054 | -0.057377 | 0.101182 |
| O | 6.907219 | 0.918116 | 0.651505 |
| O | 7.018903 | -0.994061 | -0.388190 |
| O | -5.815958 | -2.385122 | 0.340221 |
| H | -5.622683 | -1.733233 | 1.025873 |
|  |  |  |  |
|  |  |  |  |

Sum of Electronic and Zero-Point Energies: - 1198.78142 hartree

Table S18 Initial unconstrained TS structure for the gauche-gauche conformer calculated at B3LYP6311++G ( $\mathrm{d}, \mathrm{p}$ ) level of theory with SCRF method and IEF-PCM water dielectric environment.

| Atom |  |  |  |
| :---: | :---: | :---: | :---: |
| C | 1.2588 | -0.4420 | -1.0809 |
| C | 1.6550 | 1.4138 | 0.3649 |
| C | 2.9812 | 0.7636 | 0.7913 |
| C | 2.8039 | -0.7470 | 0.8638 |
| C | 2.3231 | -1.2804 | -0.4893 |
| H | 0.7477 | -0.7999 | -1.9623 |
| H | 3.7642 | 1.0030 | 0.0710 |
| H | 2.0383 | -0.9743 | 1.6174 |
| H | 2.0167 | -2.3304 | -0.3824 |
| H | 0.8847 | 1.1816 | 1.1053 |
| O | 3.3409 | 1.2239 | 2.0977 |
| O | 4.0261 | -1.3996 | 1.2112 |
| H | 4.3449 | -0.9893 | 2.0251 |
| C | 1.7091 | 2.9140 | 0.1751 |
| H | 1.8396 | 3.3754 | 1.1599 |
| H | 0.7521 | 3.2511 | -0.2367 |
| O | 2.7898 | 3.2444 | -0.6962 |
| H | 2.7805 | 4.1958 | -0.8458 |
| O | 1.1776 | 0.8423 | -0.9040 |
| O | 3.1432 | -1.0158 | -1.5783 |
| H | 4.6040 | -1.8909 | -1.5059 |
| H | 3.9312 | 1.9807 | 2.0155 |
| O | -0.4306 | -1.1877 | 0.2284 |
| C | -1.6644 | -0.8687 | 0.1457 |
| C | -2.1634 | 0.1122 | -0.7841 |
| C | -2.6446 | -1.4906 | 1.0003 |
| C | -3.4983 | 0.4287 | -0.8517 |
| H | -1.4590 | 0.6099 | -1.4387 |
| C | -3.9767 | -1.1704 | 0.9298 |
| H | -2.2960 | -2.2323 | 1.7103 |
| C | -4.4239 | -0.2058 | 0.0018 |
| H | -3.8537 | 1.1677 | -1.5575 |
| H | -4.6959 | -1.6509 | 1.5799 |
| N | -5.7998 | 0.1250 | -0.0705 |
| O | -6.6051 | -0.4433 | 0.6945 |
| O | -6.1813 | 0.9781 | -0.8974 |
| O | 5.4388 | -2.3748 | -1.2744 |
| H | 5.4452 | -2.2758 | -0.3137 |

Imaginary Frequency: - 195.46
Sum of Electronic and Zero-Point Energies $=-1198.759059$ hartree

Table S19 Initial unconstrained TS structure for the trans-gauche conformer calculated at B3LYP6311++G ( $\mathrm{d}, \mathrm{p}$ ) level of theory with SCRF method and IEF-PCM water dielectric environment.

| Atom |  |  |  |
| :--- | ---: | ---: | ---: |
| C | 1.167091 | -0.621485 | -1.001308 |
| C | 1.855320 | 1.454306 | -0.041068 |
| C | 3.134128 | 0.771697 | 0.471201 |
| C | 2.839592 | -0.672602 | 0.851360 |
| C | 2.216302 | -1.414006 | -0.331677 |
| H | 0.546704 | -1.097127 | -1.746006 |
| H | 3.899305 | 0.788183 | -0.312813 |
| H | 2.115806 | -0.673046 | 1.676227 |
| H | 1.852815 | -2.396284 | -0.000149 |
| H | 1.138280 | 1.538949 | 0.779781 |
| O | 3.607573 | 1.428309 | 1.646875 |
| O | 4.027999 | -1.356604 | 1.257632 |
| H | 4.430162 | -0.838677 | 1.965941 |
| C | 2.098789 | 2.814441 | -0.688745 |
| H | 1.147060 | 3.232385 | -1.029858 |
| H | 2.761873 | 2.690488 | -1.551250 |
| O | 2.701337 | 3.655653 | 0.300655 |
| H | 2.971160 | 4.483195 | -0.112281 |
| O | 1.195750 | 0.677036 | -1.090177 |
| O | 2.946317 | -1.425774 | -1.514927 |
| H | 4.387342 | -2.347083 | -0.9622 |
| H | 3.687269 | 2.372678 | 0.6481 |
| O | -0.450362 | -0.931121 | 0.8637 |
| C | -1.691932 | -0.682533 | 0.6129 |
| C | -2.188132 | 0.146326 | -0.7166 |
| C | -2.682339 | -1.228801 | 1.6697 |
| C | -3.530246 | 0.390421 | -0.9616 |
| H | -1.474746 | 0.588053 | -1.5356 |
| C | -4.021932 | -0.980129 | 1.4234 |
| H | -2.335601 | -1.853615 | 2.6807 |
| C | -4.466027 | -0.168302 | 0.1027 |
| H | -3.883468 | 1.015142 | -1.9678 |
| H | -4.749296 | -1.401963 | 2.2329 |
| N | -5.849764 | 0.086885 | -0.1516 |
| O | -6.665426 | -0.412102 | 0.7993 |
| O | -6.227057 | 0.805380 | -1.3269 |
| O | 5.213418 | -2.818223 | -1.1057 |
| H | 5.273615 | -2.545894 | -0.5051 |
|  | 3 |  |  |

Imaginary Frequencies: -221.92
Sum of Electronic and Zero-Point Energies $=-1198.758694$ hartree

Table S20 Optimized unconstrained TS structure for the gauche-gauche conformer calculated at B3LYP631+G (d, p) level of theory with SCRF method and IEF-PCM water dielectric environment and Bondi Atomic Radii.

| Atom |  |  |  |
| :--- | ---: | ---: | ---: |
| C | 1.4928 | -0.8435 | -0.6997 |
| C | 1.3579 | 1.4936 | -0.1431 |
| C | 2.7087 | 1.3667 | 0.5848 |
| C | 2.8055 | 0.0026 | 1.2627 |
| C | 2.6112 | -1.1162 | 0.2363 |
| H | 1.1836 | -1.6195 | -1.3876 |
| H | 3.5343 | 1.4852 | -0.1213 |
| H | 2.0067 | -0.0696 | 2.0143 |
| H | 2.4889 | -2.0789 | 0.7535 |
| H | 0.5487 | 1.4531 | 0.5921 |
| O | 2.7814 | 2.3649 | 1.6078 |
| O | 4.0751 | -0.1838 | 1.8880 |
| H | 4.1951 | 0.5367 | 2.5250 |
| C | 1.1837 | 2.7413 | -0.9848 |
| H | 1.1681 | 3.6061 | -0.3108 |
| H | 0.2177 | 2.6876 | -1.4997 |
| O | 2.2578 | 2.8386 | -1.9240 |
| H | 2.0808 | 3.5854 | -2.5129 |
| O | 1.1318 | 0.3506 | -1.0543 |
| O | 3.5398 | -1.1389 | -0.8060 |
| H | 4.1194 | -2.6199 | -1.1075 |
| H | 3.2126 | 3.1557 | 1.2544 |
| O | -0.2282 | -1.4664 | 0.7109 |
| C | -1.4398 | -1.0962 | 0.4974 |
| C | -1.9932 | -0.9827 | -0.8291 |
| C | -2.3231 | -0.7799 | 1.5934 |
| C | -3.2972 | -0.5930 | -1.0357 |
| H | -1.3596 | -1.2224 | -1.6769 |
| C | -3.6262 | -0.3919 | 1.3854 |
| H | -1.9294 | -0.8585 | 2.6026 |
| C | -4.1308 | -0.2902 | 0.0666 |
| H | -3.6955 | -0.5192 | -2.0407 |
| H | -4.2720 | -0.1595 | 2.2239 |
| N | -5.4644 | 0.1123 | -0.1487 |
| O | -6.2017 | 0.3730 | 0.8349 |
| O | -5.9039 | 0.2073 | -1.3222 |
| O | 4.4780 | -3.5365 | -1.3291 |
| H | 5.2148 | -3.6838 | -0.7211 |
|  |  |  |  |

Imaginary Frequencies: - 166.80
Sum of Electronic and Zero-Point Energies $=-1198.491594$ hartree

Table S21 Optimized unconstrained TS structure for the trans-gauche conformer calculated at B3LYP631+G (d, p) level of theory with SCRF method and IEF-PCM water dielectric environment and Bondi Atomic Radii.

| Atom |  |  |  |
| :--- | ---: | ---: | ---: |
| C | 1.4949 | -0.9775 | -0.6535 |
| C | 1.4568 | 1.4118 | -0.4268 |
| C | 2.8138 | 1.3407 | 0.2954 |
| C | 2.896 | 0.0743 | 1.1427 |
| C | 2.6341 | -1.1589 | 0.2759 |
| H | 1.1396 | -1.8257 | -1.2226 |
| H | 3.623 | 1.3357 | -0.4456 |
| H | 2.1216 | 0.1248 | 1.9203 |
| H | 2.5099 | -2.0447 | 0.9151 |
| H | 0.6571 | 1.5391 | 0.3096 |
| O | 2.9522 | 2.4602 | 1.1731 |
| O | 4.1814 | -0.0743 | 1.7482 |
| H | 4.32 | 0.6788 | 2.3412 |
| C | 1.379 | 2.4955 | -1.5008 |
| H | 0.4002 | 2.4525 | -1.9915 |
| H | 2.1628 | 2.3267 | -2.2481 |
| O | 1.5651 | 3.7587 | -0.8479 |
| H | 1.7268 | 4.4345 | -1.5216 |
| O | 1.1543 | 0.1724 | -1.1552 |
| O | 3.514 | -1.3405 | -0.7946 |
| H | 4.0219 | -2.8739 | -0.9622 |
| H | 2.7818 | 3.2632 | 0.6481 |
| O | -0.2007 | -1.3495 | 0.8637 |
| C | -1.4185 | -1.0252 | 0.6129 |
| C | -1.9752 | -1.0667 | -0.7166 |
| C | -2.3058 | -0.6042 | 1.6697 |
| C | -3.2847 | -0.7207 | -0.9616 |
| H | -1.3401 | -1.3881 | -1.5356 |
| C | -3.6145 | -0.2599 | 1.4234 |
| H | -1.9105 | -0.5665 | 2.6807 |
| C | -4.1218 | -0.3107 | 0.1027 |
| H | -3.6843 | -0.7636 | -1.9678 |
| H | -4.263 | 0.0536 | 2.2329 |
| N | -5.4616 | 0.0453 | -0.1516 |
| O | -6.201 | 0.4032 | 0.7993 |
| O | -5.9047 | 0.0023 | -1.3269 |
| O | 4.3342 | -3.8213 | -1.1057 |
| H | 5.0814 | -3.945 | -0.5051 |
|  |  |  |  |
|  |  |  |  |

Imaginary Frequencies: -185.94
Sum of Electronic and Zero-Point Energies $=-1198.489997$ hartree

Table S22 Constrained TS structure for the gauche-gauche conformer calculated at B3LYP631+G (d, p) level of theory with SCRF method and IEF-PCM water dielectric environment and Bondi Atomic Radii.

| Atom |  |  |  |
| :--- | ---: | ---: | ---: |
| C | -1.1327 | -0.3660 | 0.9471 |
| C | -1.9873 | 1.2676 | -0.5800 |
| C | -3.2390 | 0.3926 | -0.7802 |
| C | -2.8447 | -1.0828 | -0.7549 |
| C | -2.0575 | -1.4146 | 0.5095 |
| H | -0.4122 | -0.5668 | 1.7251 |
| H | -3.9701 | 0.5925 | 0.0069 |
| H | -2.1956 | -1.2814 | -1.6196 |
| H | -1.6303 | -2.4226 | 0.4512 |
| H | -1.2830 | 1.0784 | -1.3976 |
| O | -3.8097 | 0.6588 | -2.0657 |
| O | -3.9913 | -1.9369 | -0.8132 |
| H | -4.4549 | -1.7464 | -1.6429 |
| C | -2.2470 | 2.7593 | -0.5129 |
| H | -2.6061 | 3.0879 | -1.4952 |
| H | -1.3010 | 3.2714 | -0.3022 |
| O | -3.2131 | 3.0376 | 0.5055 |
| H | -3.3201 | 3.9972 | 0.5666 |
| O | -1.2911 | 0.9070 | 0.6605 |
| O | -2.6720 | -1.1044 | 1.7401 |
| H | -4.4029 | -1.2753 | 1.8708 |
| H | -4.4866 | 1.3445 | -1.9783 |
| O | 0.5600 | -0.8608 | -0.5127 |
| C | 1.8045 | -0.6138 | -0.3412 |
| C | 2.2710 | 0.4548 | 0.5128 |
| C | 2.8238 | -1.3976 | -1.0015 |
| C | 3.6116 | 0.7097 | 0.6842 |
| H | 1.5344 | 1.0680 | 1.0216 |
| C | 4.1628 | -1.1392 | -0.8302 |
| H | 2.5006 | -2.2081 | -1.6485 |
| C | 4.5782 | -0.0812 | 0.0162 |
| H | 3.9387 | 1.5181 | 1.3275 |
| H | 4.9088 | -1.7399 | -1.3369 |
| N | 5.9477 | 0.1843 | 0.1907 |
| O | 6.8013 | -0.5196 | -0.4090 |
| O | 6.3108 | 1.1241 | 0.9450 |
| O | -5.3745 | -1.4592 | 1.8253 |
| H | -5.4787 | -1.7122 | 0.8948 |
|  | 3.321 .71 |  |  |

Imaginary Frequencies: -321.71
Sum of Electronic and Zero-Point Energies $=-1198.488896$ hartree

Table S23 Constrained TS structure for the trans-gauche conformer calculated at B3LYP631+G (d, p) level of theory with SCRF method and IEF-PCM water dielectric environment and Bondi Atomic Radii.

| Atom |  |  |  |
| :--- | ---: | ---: | ---: |
| C | 1.049393 | -0.55885 | -0.86282 |
| C | 2.16562 | 1.357333 | 0.035965 |
| C | 3.345114 | 0.456216 | 0.444326 |
| C | 2.834409 | -0.91576 | 0.877495 |
| C | 1.9266 | -1.51939 | -0.1894 |
| H | 0.254851 | -0.90356 | -1.50632 |
| H | 4.028102 | 0.341636 | -0.40669 |
| H | 2.241734 | -0.78974 | 1.793809 |
| H | 1.430505 | -2.42206 | 0.185646 |
| H | 1.532463 | 1.544709 | 0.909957 |
| O | 4.036714 | 1.026318 | 1.558495 |
| O | 3.908856 | -1.83004 | 1.126349 |
| H | 4.406144 | -1.50501 | 1.891489 |
| C | 2.590367 | 2.676687 | -0.60758 |
| H | 1.698903 | 3.233618 | -0.91692 |
| H | 3.209065 | 2.472761 | -1.48905 |
| O | 3.334281 | 3.414919 | 0.373092 |
| H | 3.778913 | 4.154062 | -0.06558 |
| O | 1.323482 | 0.723363 | -0.97442 |
| O | 2.459745 | -1.63607 | -1.49046 |
| H | 4.154487 | -2.04331 | -1.64345 |
| H | 4.21152 | 1.961174 | 1.343808 |
| O | -0.56174 | -0.43991 | 0.759257 |
| C | -1.8149 | -0.31347 | 0.526962 |
| C | -2.31935 | 0.447286 | -0.59315 |
| C | -2.80438 | -0.93027 | 1.380536 |
| C | -3.66788 | 0.572749 | -0.83304 |
| H | -1.6048 | 0.931976 | -1.25088 |
| C | -4.15169 | -0.80119 | 1.140351 |
| H | -2.45239 | -1.50673 | 2.231314 |
| C | -4.60472 | -0.04886 | 0.028234 |
| H | -4.02364 | 1.148954 | -1.67897 |
| H | -4.87543 | -1.27228 | 1.794924 |
| N | -5.98285 | 0.08101 | -0.21978 |
| O | -6.81013 | -0.47487 | 0.548181 |
| O | -6.37895 | 0.751561 | -1.20821 |
| O | 5.105877 | -2.30729 | -1.58205 |
| H | 5.252959 | -2.2721 | -0.62373 |
|  | $38-329.08$ |  |  |

Imaginary Frequencies: -329.08, -5.54
Sum of Electronic and Zero-Point Energies $=-1198.487434$ hartree

## References

(1) Still, W. C.; Kahn, M.; Mitra, A. M. J. Org. Chem. 1978, 43, 2923-2925.
(2) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Organometallics 1996, 15, 1518-1520.
(3) Burns, M.; Lloyd-Jones, G. C.; Moseley, J. D.; Renny, J. S. J. Org. Chem. 2010, 75, 6347-6353.
(4) Westphal, O.; Feier, H. Chem. Ber. 1956, 89, 582-588.
(5) Hengge, A. C. J. Am. Chem. Soc. 1992, 114, 2747-2748.
(6) Fyfe, C. A.; Brouwer, D. H.; Lewis, A. R.; Chézeau, J.-M. J. Am. Chem. Soc. 2001, 123, 68826891.
(7) Frisch, M. J.; Trucks, G. W. S., H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A. J.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Lyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, Revision A.02, Gaussian, Inc., Wallingford CT, 2009.
(8) Anisimov, V.; Paneth, P. J. Math. Chem. 1999, 26, 75-86.
(9) Scott, A. P.; Radom, L. J. Phys. Chem. 1996, 100, 16502-16513.

