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Distal Two-Bond versus Three-Bond Electronegative Oxo-Substituent Effect Controls the Kinetics and Thermodynamics of the Conversion of a *C*-Nitroso Function to the Corresponding Oxime in the Conformationally Locked Pentofuranose (Bicyclo[2.2.1]heptane) System

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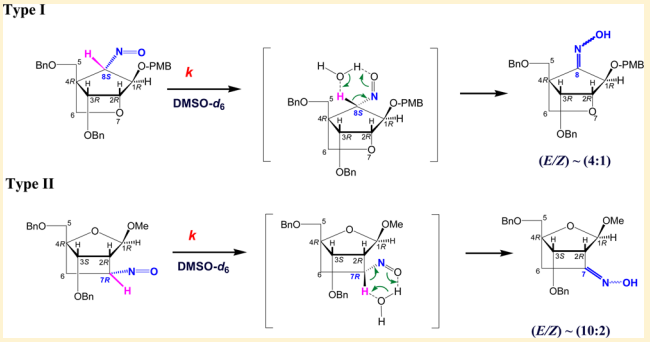
Supporting Information

ABSTRACT: We report the high-yielding and scalable diastereospecific synthesis of isomeric bicyclo[2.2.1]heptane-7- and -8-oximes and their corresponding *C*-nitroso derivatives, which are the key intermediates for the synthesis of carbanucleosides. Neither the (C7-*R*)-nitroso- nor (C8-*S*)-nitroso-bicycloheptane system requires any external base in DMSO-d_6 to afford the corresponding oxime, and no reverse isomerization from the oxime to the *C*-nitroso compound was observed. The conversion of the (C8-*S*)-nitroso compound to the *E*/*Z*-oximes was ∼8 times faster (at 40 °C) than that of the (C7-*R*)-nitroso derivative. The mechanism involves first-order reaction kinetics for the conversion of either the (C7-*R*)- or (C8-*S*)-nitroso derivative to the corresponding *E*/*Z*-oximes. The lower rate of conversion of the (C7-*R*)-nitroso compound to the corresponding oximes compared with that of the (C8-*S*)-nitroso derivative is attributed to the fact that the acidic H8 ionizing center is two bonds away from the OPMB group on C1 in the latter whereas H7 is three bonds away from the C1 OMe group in the former, making the effect of the electron-withdrawing group on C1 stronger in the latter.



INTRODUCTION

We recently completed the synthesis of the conformationally locked bicycloheptane derivatives[1] **21** and **25** (Figure 1) in order to transform them into the corresponding β-D-carbocyclic nucleosides for incorporation into oligo-DNA or -RNA to study their biochemical properties as antisense agents[2a−j] and small interfering RNAs in order to control RNA translation to proteins. The availability of carbocyclic-modified nucleosides without any substitution, such as[3c] **19** obtained using 8-desmethylheptane system **22** (Figure 1), is also important to modify DNA and RNA duplexes at different positions with hydrophobic groups. This hydrophobic modification will enable us to understand if the pentose O4′ actually acts as an important hydration site into the major and minor grooves in DNA/DNA, DNA/RNA, and RNA/RNA duplexes, thereby controlling the *endo*- and *exo*-nucleolytic enzymatic reactions.[2a−j]

In our previous studies,[1] we were able to perform a radical ring closure to form bicyclo[2.2.1]heptane **21** (**20** → **21**; Figure 1), which allowed us to perform a nucleobase coupling without any difficulty to give compound **23**. The main problem of this coupling reaction was that the *S* and *R* diastereomers arising from the methyl group at C8′ were inseparable and therefore could not be used for the synthesis of diastereomerically pure modified oligo-DNA and -RNA for further studies. Another problem was that the coupling worked only with adenine but not with thymine or any other nucleobase despite several changes in the reaction conditions. We therefore turned our interest to the synthesis of the 1-β-*C8*′-desmethyl analogue **19**, which is a known compound,[3c] using Grubbs' catalyst in 19 steps with a low overall yield to construct the carbasugar ring.[3c]

Although 5-*exo* free-radical cyclization to a tethered olefin affords the fused carbacyclic sugars, an exocyclic *C8*-methyl group remains a permanent structural element (as in **20** → **21**, **21**→ **23**, and **24** → **25**). On the other hand, the 5-*exo* free-radical cyclization to a tethered oximino group can provide synthetic access to the corresponding desmethyl sugars (as in **14** → **22** and **22** → **19**), which is necessary for the coupling with the aglycones to give a defined stereochemical outcome.

We were convinced that a free-radical oximino cyclization route[3a] to synthesize 1-β-*C8*′-desmethyl analogue **19** could be a

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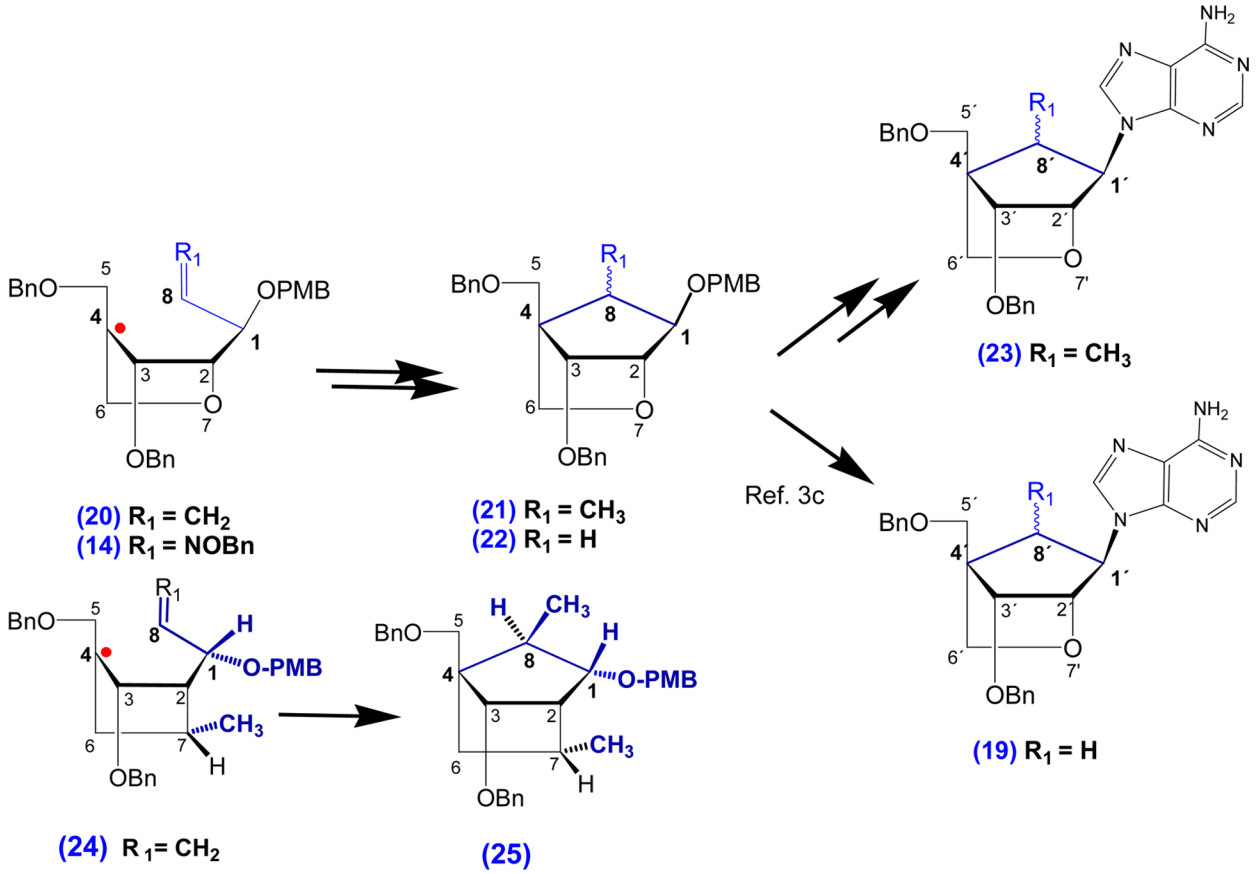

Figure 1. Scheme for *5-exo* free-radical addition to olefins, as in **20** → **21** and **24** → **25**, or to oximino groups, as in **14** → **22**. PMB = *p*-methoxybenzyl.

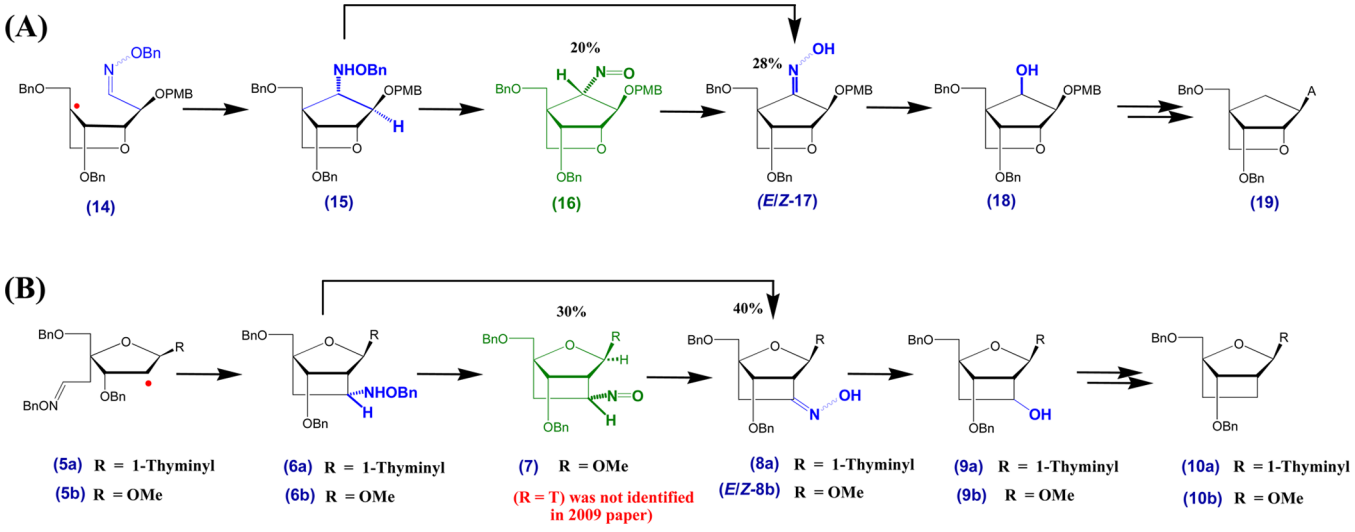

Figure 2. The conversion of *C*-nitroso intermediates **7** and **16** to the corresponding oximes constitutes a key step for the synthesis of the desmethyl fused carbocylic nucleosides **19** and **10a** and carbocylic sugar **10b**.

worthwhile alternative to explore (Figure 2A) via incorporation of an easily removable NHOBn group[3a] at C8 followed by oxidation and deoxygenation steps (**15** → **16** → **17** → **18** → **19**; Figure 2A). We argued[3a] that this would involve fewer synthetic steps than Jacobson's[3c] and Nielsen's[3d] fused carbacycle syntheses via ring closure metathesis (RCM) using Grubbs' catalyst.[3c−f] In the debenzylation reaction of compound **15**, the desired oxime **17** and *C*-nitroso side product **16** (Figure 2A) were isolated and identified.[3a,b] Clearly, the formation of *C*-nitroso compound **16** as a side product adversely affected the yield of the target oxime **17**, although the former could be easily separated from the latter. However, we observed that under neutral NMR conditions at ambient temperature in $CDCl_3$ or DMSO-d_6, *C*-nitroso compound **16** was irreversibly

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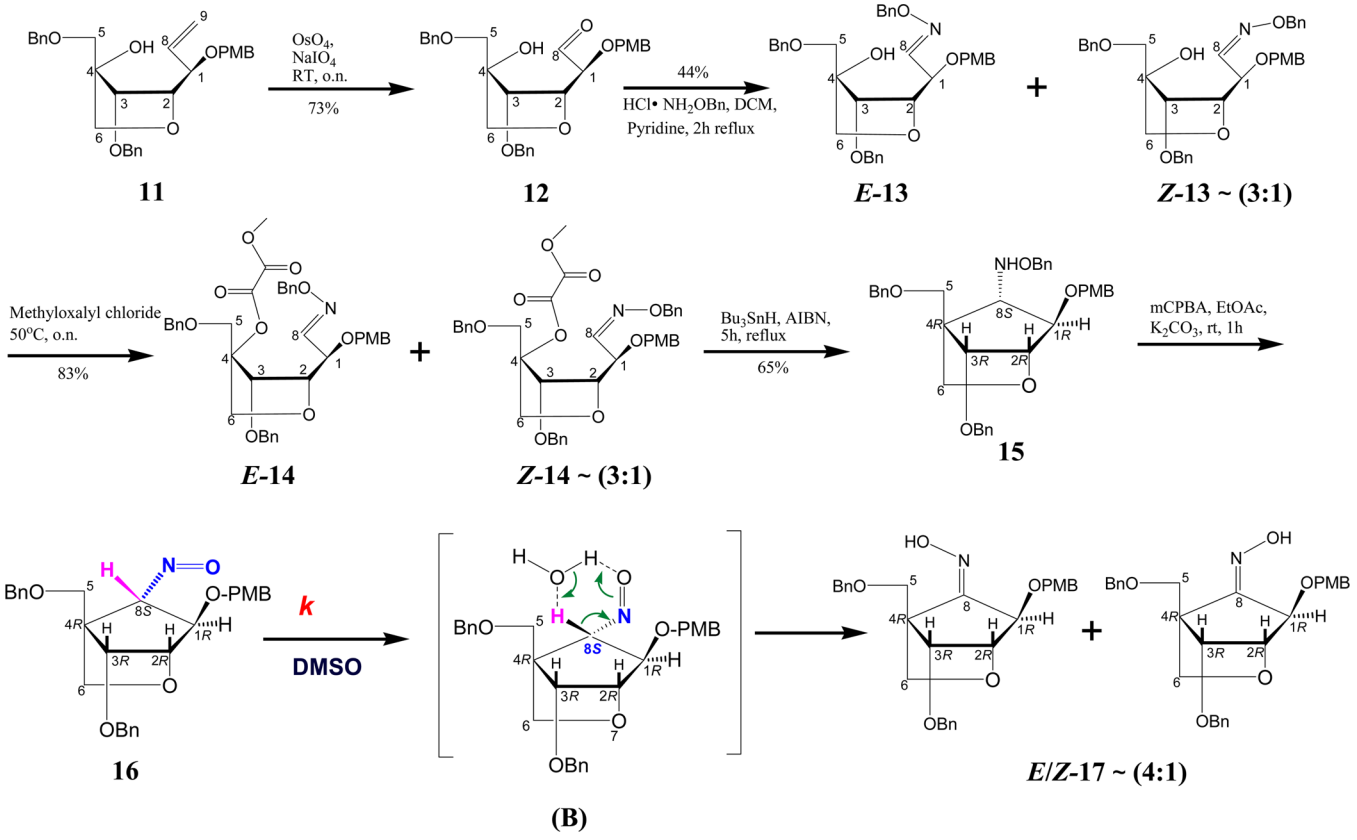
Scheme 1. Synthesis of *C*-Nitroso 16 and the Corresponding Oximes *E*/*Z*-17 and Mechanism of the Conversion from *C*-Nitroso Compound 16 to Oximes *E*/*Z*-17 Showing an Intermolecular H Shuttle Involving a Water Molecule



converted to the isomeric *E*/*Z*-oximes **17**, albeit over a period of 7−10 days. If we could accelerate the rate of conversion of *C*-nitroso derivative **16** to oximes **17**, it would open a new means to use the oximino radical cyclization path to construct the carbocyclic ring.

Hence, we became interested in finding a convenient procedure for the conversion of the former to the latter, which required that we carefully determine the kinetics and thermodynamics of the conversion of the *C*-nitroso derivative **16** to the isomeric *E*/*Z*-oximes **17** in order to make our synthetic scheme effective (Figure 2A). Conversions of various *C*-nitroso compounds to the corresponding oximes requiring various reaction conditions (acidic/basic/neutral)[4a−e] suggested that we needed to characterize the reaction conditions required for the formation of **17** from **16**.

This study also prompted us to reinvestigate the relatively poor yield of the oximes **8a** (Figure 2B) obtained by the removal of the *C*7′-benzyloxyamino group in the 2-oxabicyclo[2.2.1]heptane system **6a** from our previously published work.[3a] Upon re-examination of this oxidative removal (*m*CPBA/K_2CO_3 in EtOAC) of the benzyl protecting group from (C7′-*R*)-NHOBn compound **6a**,[3a] we found that the poor yield reported for the oxime in the above deprotection was due to formation of *C*-nitroso compound **7** as a side product (Figure 2B) in addition to oximes **8b**. Both *C*-nitroso derivative **7** and oximes **8b** were isolated in pure form.

Herein we report the kinetics of the conversion of *C*-nitroso compounds **7** and **16** to the corresponding isomeric *E*/*Z*-oximes **8b** and **17**, respectively, which helped to expedite the synthesis of the target desmethyl fused carbocylic sugar **10b** and carbanucleosides **10a** and **19** (Figure 2).

RESULTS AND DISCUSSION

1. Synthesis of the Bicyclic Nucleoside Precursors *C*-Nitroso 16 and Oximes *E*/*Z*-17. *1.1. Synthesis of Bicyclo[2.2.1]heptane Derivative* ***15***. The synthesis of oxime **17** started from the known tetrahydrofuran derivative **11** (Scheme 1).[1] Compound **11** was treated with OsO_4 in H_2O, *N*-methylmorpholine-*N*-oxide (NMO), and $NaIO_4$ in a one-pot reaction[5] to obtain aldehyde **12** without purification. Aldehyde **12** was then directly used for the oximation[3a] with *O*-benzylhydroxylamine hydrochloride to give benzoximes *E*-**13** and *Z*-**13** as a mixture that was separated (44% overall yield, 3:1 *E*/*Z* by ^{1}H and ^{13}C NMR analysis; see the Experimental Section and the Supporting Information).[6a] Compounds *E*-**13** and *Z*-13 were separately subjected to esterification of the 4-OH with methyloxalyl chloride in dry pyridine at 50 °C. The products obtained from these two individual reactions were the same inseparable mixtures (~3:1 *E*/*Z* by ^{1}H NMR analysis) of the isomers *E*-**14** and *Z*-**14** regardless of the starting isomer employed (*E*-**13** or *Z*-**13**). This result indicates that the thermodynamically more stable product, the *E* isomer, is formed as the major isomer in both cases. The inseparable 3:1 mixture of *E*-**14** and *Z*-**14** was obtained in 68% yield. This mixture was subjected to free-radical cyclization,[1] which was carried out under N_2 in anhydrous toluene with Bu_3SnH under reflux, adding azobis-(isobutyronitrile) (AIBN) as an initiator in a dropwise manner; this resulted in the formation of compound **15** in 65% yield. The hexenyl radical cyclization of compounds *E*-**14** and *Z*-**14** at C4 proceeded in the 5-*exo* cyclization mode[1] to give only one [2.2.1]-fused product, H1,H8-*trans*-fused product **15** with the (8*S*) configuration. Detailed NMR analysis of **15** confirmed that

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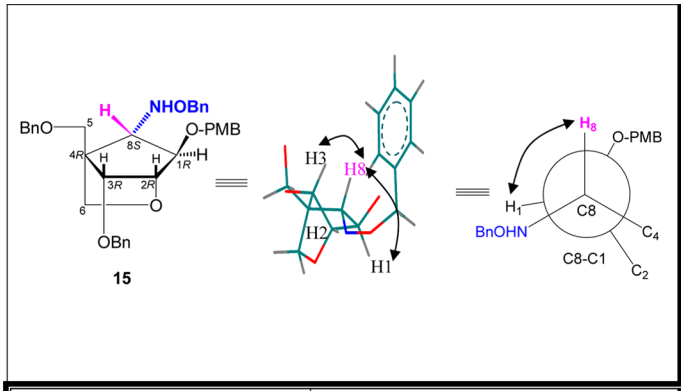
Table 1. NOE Enhancement Data, Computational Simulations (in Hyperchem Pro 6.0),[8] and the Newman Projection(s) across C8/C1, Showing the Configurational Orientation in Compounds 15 and 16; Irradiations at H1 and H8 for Both Compounds, Suggesting the *S* Configuration at C8 and the *R* Configuration at C1, and Vicinal Coupling Constant Data Are Also Shown



H8 Irradiation in 15 /calc. distance/Observed NOE supporting the C8(*S*) Configuration	**H1 Irradiation in 15 /distance/Observed NOE supporting the C1(*R*) Configuration**	**H8 Irradiation in 16 /distance/Observed NOE supporting the C8(*S*) Configuration**	**H1 Irradiation in 16 /distance/Observed NOE supporting the C1(*R*) Configuration**
$d_{H8,H1}$ = 2.5 Å, 1.2%	$d_{H1,H2}$ = 2.8 Å, 2.3%	$d_{H8,H1}$ = 3.0 Å, 1.0%	$d_{H1,H2}$ = 2.7 Å, 1.2%
$d_{H8,H3}$ = 2.4 Å, 3.9%	$d_{H1,H8}$ = 3.0 Å, 1.0%	$d_{H8,H3}$ = 2.5 Å, 2.3%	$d_{H1,H8}$ = 3.0 Å, 1.0%
$d_{H8,H5'}$ = 3.1 Å, 2.9%	$d_{H1,H3}$ = 3.7 Å, 0.88%	$d_{H8,H6'}$ = 3.8 Å, 0.77%	$d_{H1,H3}$ = 3.7 Å, 0.19%
$d_{H8,CH2PMB}$ = 4.3 Å, 1.7%	$d_{H1,CH2PMB}$ = 2.6 Å, 3.0%	$d_{H8,CH2PMB}$ = 3.9 Å, 1.7%	$d_{H1,CH2PMB}$ = 2.2 Å, 2.9%
$d_{H8,NH}$ = 2.6 Å, 2.1%	$d_{H1,NH}$ = 1.2 Å, 1.1%		
vicinal coupling constant in 15	**Torsion angle**	**vicinal coupling constant in 16**	**Torsion angle**
$^3J_{H8,H1}$ = 3.6 ± 0.2 Hz	$\phi_{[H8-C8-C1-H1]}$ = 129 ± 2°	$^3J_{H8,H1}$ = 2 ± 0.2 Hz	$\phi_{[H8-C8-C1-H1]}$ = 116 ± 2°

the diastereotopically pure product **15** exclusively has α-8-NHOBn (C8-*S*) and β-1-OPMB (C1-*R*) configurations. This result was verified by NOE experiments and coupling constant analysis (Table 1; also see the Supporting Information).

1.2. Synthesis of C-Nitroso ***16*** *and the Corresponding Isomeric Oximes E-17 and Z-17.* Oxidation of benzyloxyamine **15** with *m*CPBA in EtOAc in the presence of K_2CO_3 as a base at room temperature for ∼1 h removed the benzyl group to give a mixture of three compounds, *C*-nitroso **16**, oxime *E*-**17**, and oxime *Z*-**17**, all of which have close R_f values by TLC in several solvent systems and very closely overlapping chemical shifts, posing a considerable challenge for purification and structural identification (part II of the Supporting Information). However, we obtained pure *C*-nitroso compound **16** (20%) and the oximes *E*-**17** and *Z*-**17** (28%) as a 4:1 mixture of isomers. The chemical identities were confirmed by detailed 1D and 2D ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry. Indication of the presence of the *C*-nitroso compound in the mixture of the *m*CPBA oxidation reaction was based on the observation of an unexpected H8 resonance[4a−e] at 5.8 ppm that showed a correlation peak to a carbon resonating at 71 ppm. The presence of this extra CH indicated that the new peak most probably originates from the *C*-nitroso[4a−e] compound **16**, since the literature shows that a typical oxime can be formed from a *C*-nitroso intermediate having Hα chemical shifts of 5−6 ppm.[4a−e]

The configurations of *C*-nitroso **16** and oximes *E*-**17** and *Z*-**17** were confirmed by 1D NOEs and coupling constant analysis (Table 1). No NOE enhancements could confirm the configurations in the *E*-**17** and *Z*-**17** isomers (part II of the Supporting Information), but they were confirmed by ^{1}H and/or ^{13}C shifts. The ^{13}C resonances of oximes have been widely studied. For example, for a range of cyclic ketoximes (Figure 3) it was found that when the ═N−OH points toward a specific α_1-carbon atom (i.e., *Z*), this carbon experiences significant upfield shift, whereas the chemical shift of the second α_2-carbon is either unaffected or shows a downfield shift.[6b] On the other hand, in the ^{1}H NMR spectra, protons on the same side of the double bond as the OH (i.e., *E*) show significant downfield shifts.[6b] On this basis, the oxime isomers were assigned as illustrated in Figure 3A. The *E*-**17**:*Z*-**17** isomeric ratio observed when **16** was converted to the oximes in $CDCl_3$ and DMSO-d_6, was ∼4:1.

2. Synthesis of *C*-Nitroso 7 and Oximes *E*-8b and *Z*-8b. We previously synthesized carbacyclic thymidine nucleoside **8a** with *C7′*-NHOBn compound **6a** (Scheme 2).[3a] The same route (**1** → **2a** → **3a** → **4a** → **5a** → **6a**) was not general for the construction of fused carbabicycles lacking C7′ and C8′ substituents by replacing O4′ with an 8′-CH_2. Hence, we became interested in exploring the free-radical cyclization[1] of a vicinal *C4′*-alkyloximino group in a *C1*-methyl glycoside, as in compound **2b** (**1** → **2b** → **3b** → **4b** → **5b** → **6b**; Scheme 2). If successful, this strategy would permit the construction of [2.2.1] carba systems on both the α and β faces of the sugar ring.

The synthesis of oximes *E*-**8b** and *Z*-**8b** started from the known α-D-ribofuranose **1**[3a] (Scheme 2). Compound **1** was treated with *p*-toluenesulfonic acid·H_2O in MeOH to obtain methyl glycoside **2b**[1] as an inseparable mixture of β and α anomers in 81% yield. The ^{1}H NMR assignment showed an anomeric ratio of ∼10:1. Reduction of the nitrile group of **2b** with DIBALH afforded aldehyde **3b**, which was directly used for the oximation[3a] with *O*-benzylhydroxylamine to obtain oxime **4b** as a mixture of *E* and *Z* isomers (1.6:1 by ^{1}H NMR) in 83% yield in two steps. As discussed above,[6a] the findings that *E*-**4b** has a pairwise downfield ^{1}H shift (δ_{H6} = 2.82 ppm) and corresponding upfield ^{13}C shift (δ_{C6} = 30.1 ppm) proved the *E* configuration, whereas the opposite for *Z*-**4b** (δ_H = 2.68 ppm and δ_C = 34.1 ppm) proved the *Z* configuration of the oxime.[6a]

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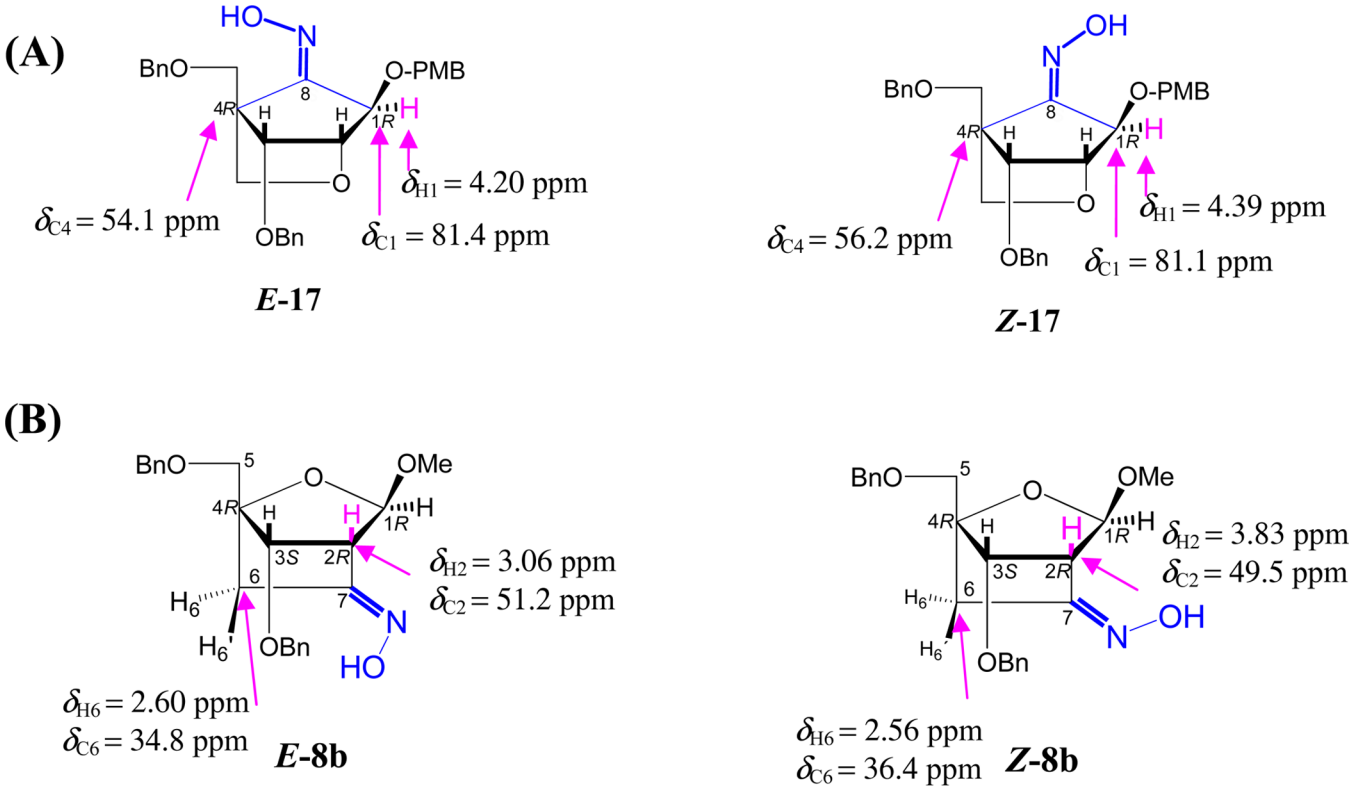

Figure 3. ^{1}H and ^{13}C chemical shifts supporting the assignments of the *E* and *Z* configurations for (A) oxime **17** and (b) oxime **8b**.

Scheme 2. Synthesis of Oxabicyclo[2.2.1]heptan-7-oxime (8b); The Mechanism of the Conversion from *C*-Nitroso 7 to Oxime 8b Involves an Intermolecular Hydrogen Shift

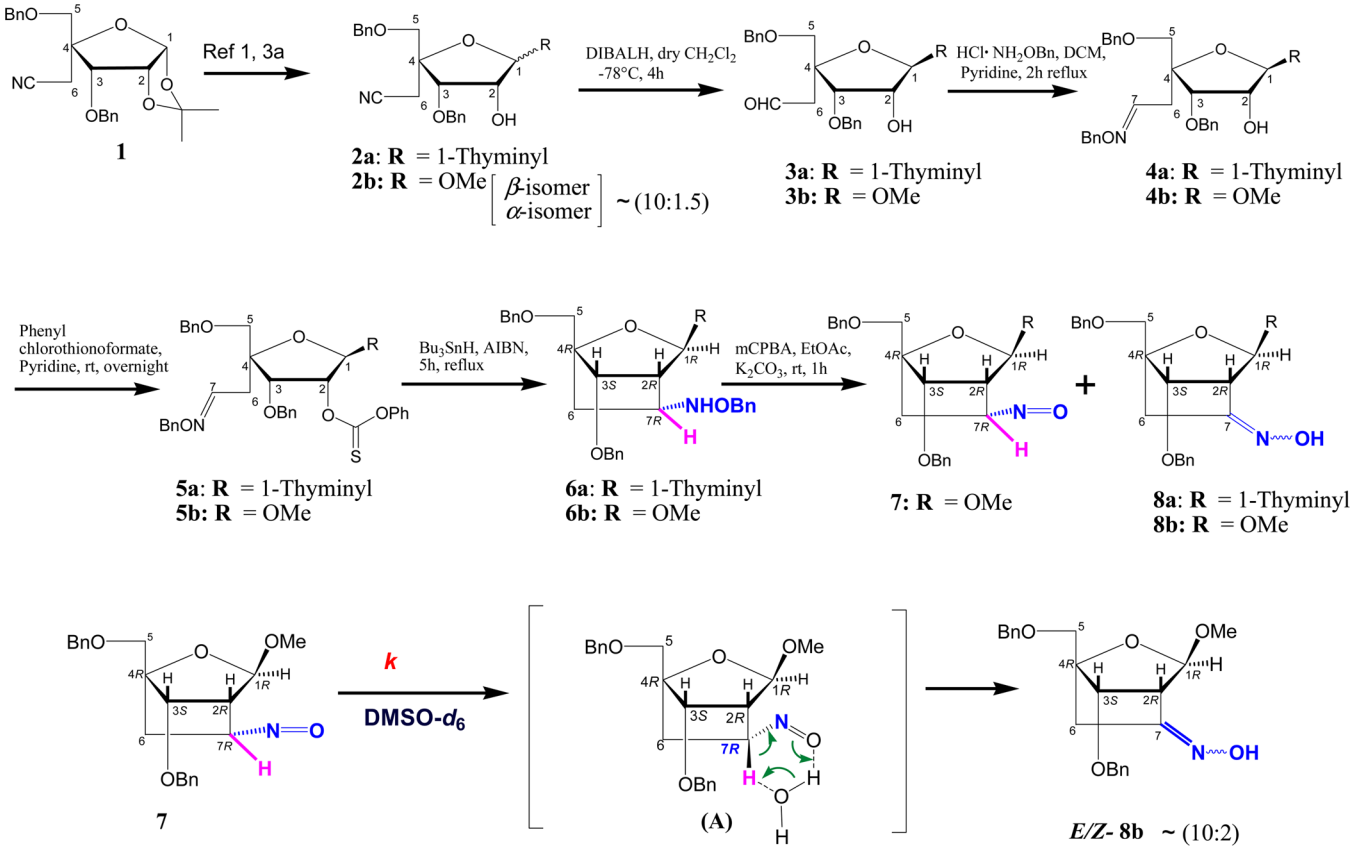

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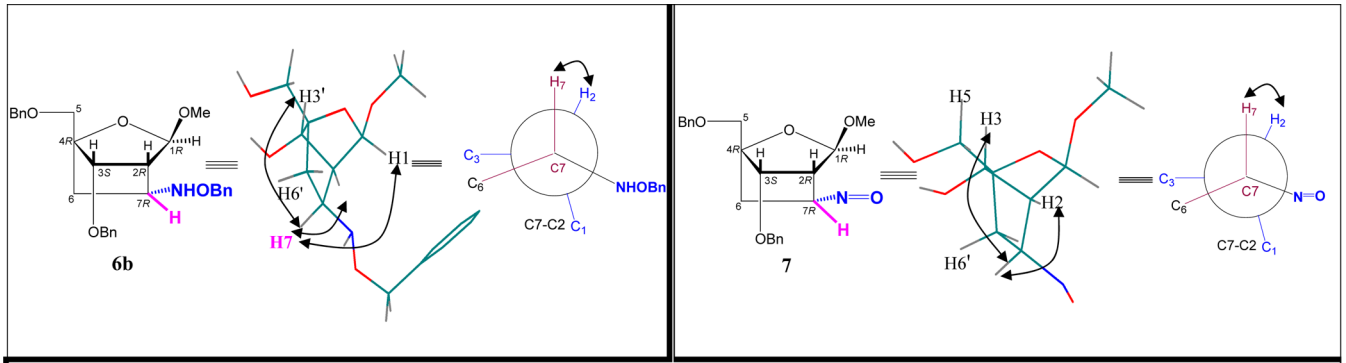
Table 2. NOE Enhancement Data and Modeling (in Hyperchem Pro. 6.0)[8] of Compounds 6b and 7; Irradiations at H1 and H7 for Compound 6b Suggesting the *R* Configuration at C7 and the *R* Configuration at C1, Irradiations at H2 and H7 for Compound 7 Suggesting the *R* Configuration at C7 and the *R* Configuration at C2, and Vicinal Coupling Constant Data Are Also Shown



H1 Irradiation in 6b /calc. distance/Observed NOE supporting the C1(*R*) Configuration	H7 Irradiation in 6b /distance/Observed NOE supporting the C7(*R*) Configuration	H7 Irradiation in 7 /distance/Observed NOE supporting the C7(*R*) Configuration	H2 Irradiation in 7 /distance/Observed NOE supporting the C2(*R*) Configuration
$d_{H1,H2}$ = 2.8 Å, 2.1%	$d_{H7,H2}$ = 2.5 Å, 3.2%	$d_{H7,H2}$ = 2.5 Å, 3.3%	$d_{H2,H7}$ = 2.5 Å, 3.0%
$d_{H1,H7}$ = 3.8 Å, 0.46%	$d_{H7,H6}$ = 2.3 Å, 4.0%	$d_{H7,H6}$ = 2.3 Å, 3.3%	$d_{H2,H3}$ = 2.7 Å, 1.7%
$d_{H1,H3}$ = 3.7 Å, 0.53%	$d_{H7,H6'}$ = 3.1 Å, 0.7%	$d_{H7,H6'}$ = 3.1 Å, 0.6%	$d_{H2,H1}$ = 2.8 Å, 2.7%
$d_{H1,CH2Ph}$ = 3.1 Å, 1.2%	$d_{H7,H1}$ = 3.8 Å, 1.1%	$d_{H7,H3}$ = 3.7 Å, 0.4%	$d_{H2,CH2Ph}$ = 3.7 Å, 0.6%
$d_{H1,H5,5'}$ = 4.6 Å, 0.2%	$d_{H7,H3}$ = 3.8 Å, 1.1%	$d_{H7,CH2Ph}$ = 3.7 Å, 1.1%	
vicinal coupling constant in 6b	**Torsion angle**	**vicinal coupling constant in 7**	**Torsion angle**
$^3J_{H2,H7}$ = 4 ± 0.2 Hz	$\phi_{[H2\text{-}C2\text{-}C7\text{-}H7]}$ = 51 ± 2°	$^3J_{H2,H7}$ = 4.2 ± 0.2 Hz	$\phi_{[H2\text{-}C2\text{-}C7\text{-}H7]}$ = 53 ± 2°

After 2-OH esterification of the isomers *E*-**4b** and *Z*-**4b** with phenyl chlorothionoformate in dry pyridine at room temperature, the key intermediate for the radical cyclization, 2-*O*-phenoxythiocarbonyl **5b**, was obtained in 72% yield. The mixture of *E*- and *Z*-**5b** was subjected to radical ring closure in degassed anhydrous toluene at reflux temperature in the presence of Bu_3SnH, adding AIBN dropwise as a radical initiator.[1,2b] Since the radical transition state[3a] is exactly the same for both *E*-**5b** and *Z*-**5b**, only one C2−C7 *cis*-fused 5-*exo* product **6b**, with the (7*R*) configuration, was obtained in 54% yield. The stereochemistry of the new stereocenters was assigned by 1D NOE enhancement and coupling constant analysis for compound **6b** (Table 2).

Oxidation of benzyloxyamine **6b** with *m*CPBA in EtOAc in the presence of K_2CO_3 as a base at ambient temperature for ∼1 h removed the benzyl group to give *C*-nitroso compound **7** (30%) and oximes *E*- and *Z*-**8b** (40%, 10:2, ^{1}H NMR) as a mixture of isomers. We observed that the conversion of *C*-nitroso compound **7** in DMSO-d_6 or in $CDCl_3$ was very slow at room temperature. However, the reaction at >40 °C for conversion of *C*-nitroso compound **7** in DMSO-d_6 to oximes was faster and quite suitable for our synthetic purposes, even though it was 8 times slower than the conversion of *C*-nitroso derivative **16** (see below). The low boiling point of $CDCl_3$ did not allow the temperature to be raised in order to perform the reaction under neutral conditions, and it was not pursued for our preparative purposes.

The *C*-nitroso derivative **7** and oximes *E*-**8b** and *Z*-**8b** were characterized by detailed 1D and 2D NMR spectroscopy and mass spectrometry. H7 for the *C*-nitroso compound shows a resonance at 5.4 ppm (part I of the Supporting Information), which is connected to a carbon resonating at 66.8 ppm. The presence of H7 indicated that **7** was not an oxime but rather an intermediate (i.e., a *C*-nitroso compound).[6a,b] The configurations of the *C*-nitroso derivative **7** were confirmed by 1D NOE and coupling constant analysis (Table 2). In addition, irradiation of H2 led to a 3% NOE enhancement for H7 ($d_{H2,H7} \approx 2.5$ Å), which confirmed that H2 and H7 are located on the same face in *C*-nitroso **7**. Therefore, these assignments confirmed the *R* configuration at the C7 center and the *R* configuration at the C2 center, which indicates a *cis* orientation of H7 and H2 in **7**. The assignment of these configurations for **7** is also consistent with what was assigned for the precursor 2-oxabicyclo[2.2.1]heptane **6b**. Moreover, we confirmed the configurations in isomers *E*-**8b** and *Z*-**8b** by ^{1}H and/or ^{13}C shifts as shown in Figure 3B.[6b]

3. Mechanism of Conversion of *C*-Nitroso Compounds 16 and 7 to the Corresponding Oximes *E/Z*-17 and *E/Z*-8b: Kinetic and Thermodynamic Studies of Oxime Formation. *3.1. Kinetics and Thermodynamics of the Conversion of C-Nitroso Derivative **16** to Oximes E-17 and Z-17 in the Oxabicyclo[2.2.1]heptane System.* As evidenced above, *C*-nitroso **16** and oximes *E*-**17** and *Z*-**17** were isolated in pure forms and fully characterized by NMR spectroscopy and mass spectrometry, suggesting that these compounds are fairly stable in $CDCl_3$ at room temperature. Therefore, DMSO-d_6 was used for higher-temperature studies. *C*-Nitroso compound **16** was found to be converted almost completely (>99%) to oximes *E*-**17** and *Z*-**17** in DMSO-d_6 in 58 h at 298 K, and no reverse isomerization toward *C*-nitroso compound **16** was observed under our experimental conditions. We subsequently plotted ln([**16**]) as a function of time for the conversion of **16** to *E*-**17** + *Z*-**17** to obtain the first-order rate constant *k* at different temperatures[7a,b] (Table 3). The populations of **16**,

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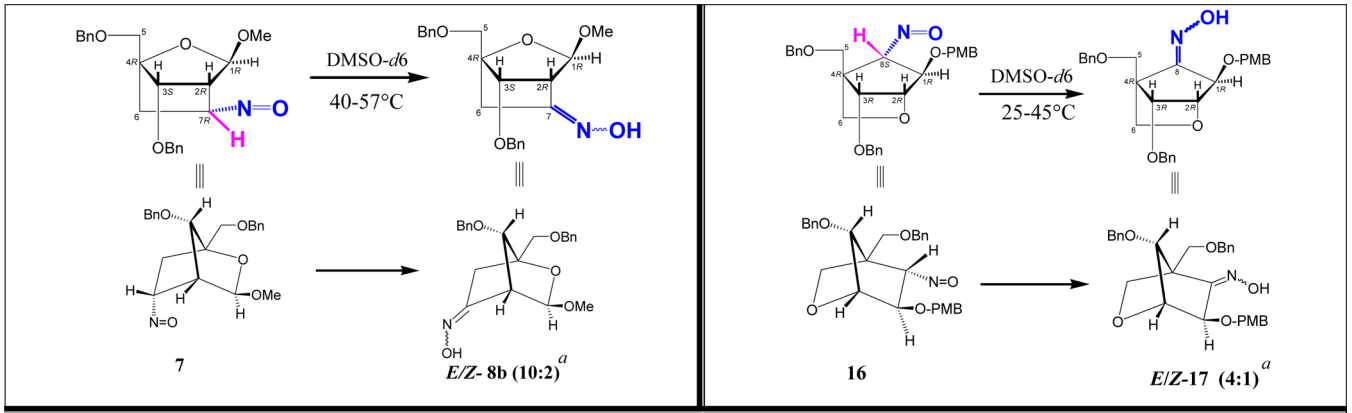
Table 3. Kinetic and Thermodynamic Data (k, $\Delta H^{\ddagger}$, $-T\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$) for the Conversions of Compound 7 to *E*/*Z*-8b and Compound 16 to *E*/*Z*-17



k (10^{-5} s^{-1})	T (K)	E_a [b] (kJ/mol)	$\Delta H^{\ddagger}$ [b] (kJ/mol)	$-T\Delta S^{\ddagger}$ [b] (kJ/mol)	$\Delta G^{\ddagger}$ [b] (kJ/mol)	k (10^{-5} s^{-1})	T (K)	E_a [b] (kJ/mol)	$\Delta H^{\ddagger}$ [b] (kJ/mol)	$-T\Delta S^{\ddagger}$ [b] (kJ/mol)	$\Delta G^{\ddagger}$ [b] (kJ/mol)
k_1 = 1.8 ± 0.2	313	112.6 ± 0.2	110.0 ± 0.1	4.7 ± 0.1	105.2 ± 0.1	k_1 = 2.0 ± 0.2	298	104.1 ± 3	108.9 ± 0.4	9.8 ± 0.4	99.1 ± 0.2
k_2 = 3.5 ± 0.3	318	"	"	4.8 ± 0.1	105.1 ± 0.1	k_2 = 4.7 ± 0.2	303	"	"	9.9 ± 0.4	99.0 ± 0.2
k_3 = 6.6 ± 0.3	323	"	"	4.9 ± 0.1	105.0 ± 0.1	k_3 = 10.5 ± 0.7	308	"	"	10.1 ± 0.4	98.8 ± 0.2
k_4 = 11.0 ± 0.2	326	"	"	5.0 ± 0.1	104.9 ± 0.1	k_4 = 16.2 ± 1.0	313	"	"	10.2 ± 0.4	98.7 ± 0.2
k_5 = 16.3 ± 1.0	330	"	"	5.1 ± 0.1	104.8 ± 0.1	k_5 = 37.5 ± 1.5	318	"	"	10.4 ± 0.4	98.4 ± 0.2

[a]The *E* isomer is the major product for **7** → *E*/*Z*-**8b** (10:2 *E*/*Z* by ^{1}H NMR analysis) and for **16** → *E*/*Z*-**17b** (4:1 *E*/*Z* by ^{1}H NMR analysis). *E*/*Z* isomerization of oximes under various conditions has been reported.[10a−e] The present studies were performed under neutral conditions, and we did not observe any *E*/*Z* isomerization. [b]The activation energy (E_a) was calculated from the Arrhenius equation (see Figures 4A and 5A).[7c] For **7** → *E*-**8b** + *Z*-**8b**, E_a = 112.6 ± 0.2 kJ/mol, and for **16** → *E*-**17b** + *Z*-**17b**, E_a = 104.1 ± 3 kJ/mol. The Eyring equation[7c] gave the activation parameters $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$ (see Figures 4B and 5B).

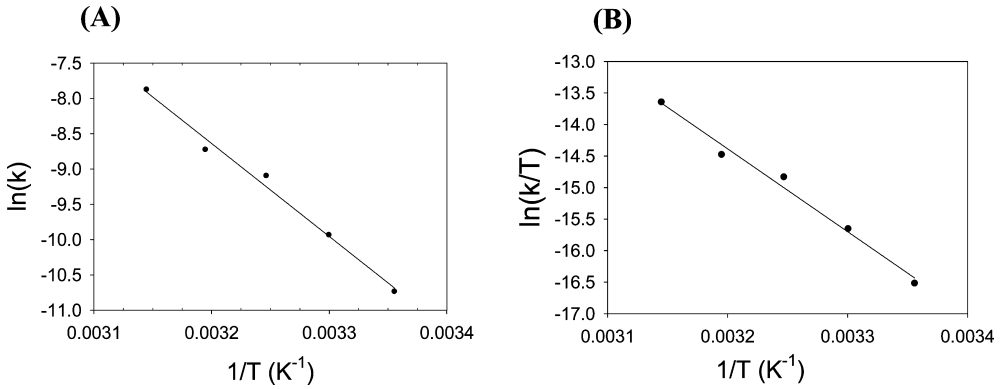


Figure 4. (A) Plot of ln(k) vs 1/T (Arrhenius plot) for the conversion of nitroso compound **16** to *E*/*Z*-**17**. The plot shows a linear correlation (95% confidence level); the slope ($-E_a/R$) gave the activation energy E_a. (B) Plot of ln(k/T) vs 1/T [Eyring plot, based on the equation $\ln(k/T) = -\Delta H^{\ddagger}/RT + \ln(k_B/h) + \Delta S^{\ddagger}/R$] for the conversion of compound **16** to *E*/*Z*-**17**. This plot also shows a linear correlation; the slope ($-\Delta H^{\ddagger}/R$) gave the enthalpy of activation $\Delta H^{\ddagger}$, whereas the intercept gave the entropy of activation $\Delta S^{\ddagger}$.

E-**17**, and *Z*-**17** at different time intervals were obtained from the peak integrals of H8 for the *C*-nitroso compound and H1 for the oximes. The Arrhenius plot[7c] of ln(k) versus 1/T shows a linear correlation (Figure 4A), from which the slope gave E_a. Moreover, a plot of ln(k/T) versus 1/T [based on the Eyring equation,[7c] $\ln(k/T) = -\Delta H^{\ddagger}/RT + \ln(k_B/h) + \Delta S^{\ddagger}/R$, where k_B is the Boltzmann constant and h is the Planck constant] shows a linear correlation (Figure 4B). The slope (which should be equal to $-\Delta H^{\ddagger}/R$) gave the enthalpy of activation $\Delta H^{\ddagger}$, whereas the intercept [which should be equal to $\Delta S^{\ddagger}/R + \ln(k_B/h)$] gave the entropy of activation $\Delta S^{\ddagger}$. The free energy of activation, $\Delta G^{\ddagger}$, was also calculated (Table 3). In $CDCl_3$ and DMSO-d_6 the conversion of *C*-nitroso compound **16** at ambient temperature is very slow (i.e., in a week), but when **16** was converted to oxime **17**, it gave the two isomers *E*-**17** and *Z*-**17** in a 4:1 ratio.

3.2. Kinetics and Thermodynamics of the Conversion of (C7-R)-Nitroso **7** *to Oximes E-***8b** *and Z-***8b** *in the Bicyclo[2.2.1]heptane System.* *C*-Nitroso compound **7** and the isomeric oximes *E*-**8b** and *Z*-**8b** were isolated in pure forms with an isolated yield of 30% for **7** and 40% for *E*-**8b** and *Z*-**8b**. It was found that *C*-nitroso compound **7** is fairly stable in both $CDCl_3$ and DMSO-d_6 under neutral conditions at room temperature. Elevation of the temperature is not feasible in $CDCl_3$ because of its lower boiling point. Hence, an external base was used in our initial study, which was unnecessary when

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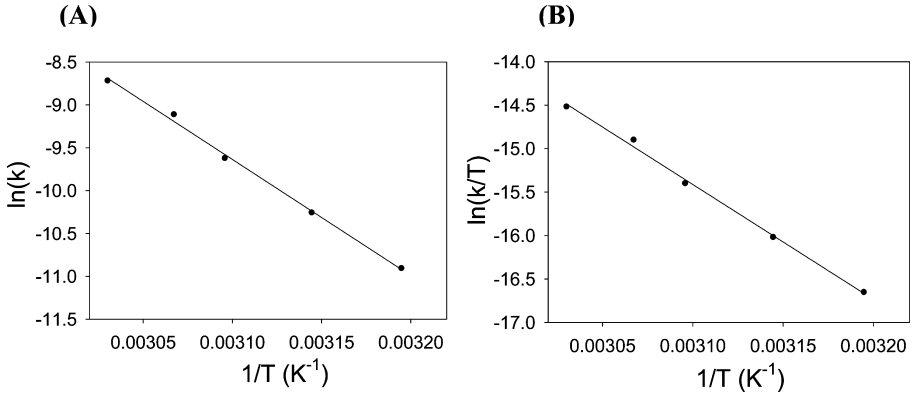

Figure 5. (A): Plot of ln(k) vs $1/T$ (Arrhenius plot) for the conversion of nitroso compound **7** to a mixture of *E*/*Z*-**8b**. The plot shows a linear correlation (95% confidence level); the slope ($-E_a/R$) gave the activation energy E_a. (B) Plot of ln(k/T) versus $1/T$ (Eyring plot) for the conversion of compound **7** to *E*/*Z*-**8b**. This plot also shows a linear correlation; the slope ($-\Delta H^{\ddagger}/R$) gave $\Delta H^{\ddagger}$, whereas the intercept gave $\Delta S^{\ddagger}$.

we employed DMSO as a solvent under neutral conditions, allowing us to study directly the transformation at a higher temperature: The *C*-nitroso compound **7** in DMSO-d_6 was found to be converted almost completely (>99%) to the oxime (*E*-**8b** and *Z*-**8b**) in ∼53 h at 313 K (40 °C) (see the Supporting Information), and no reverse conversion was observed under our experimental conditions. As for the conversion of *C*-nitroso compound **16** to **17**, we monitored the reaction kinetics in neutral DMSO-d_6 at five different temperatures by plotting ln([**7**]) as a function of time for the conversion of *C*-nitroso **7** to the oximes *E*-**8b** + *Z*-**8b**, which gave the first-order rate constant k (Table 3).[7a,b] The populations of **7**, *E*-**8b**, and *Z*-**8b** at different time intervals were obtained from the peak integrals of H7 for the *C*-nitroso compound and H1 for the oximes. The Arrhenius and Eyring plots (Figure 5) show linear correlations, allowing E_a, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$ to be determined (Table 3).

4. What Is the Difference in the Conversions of *C*-Nitroso Compounds 7 and 16? The conversion of *C*-nitroso compound **7** to the mixture of oximes *E*-**8b** and *Z*-**8b** could only be conveniently induced in DMSO-d_6 from 40 to 57 °C. On the other hand, the conversion of *C*-nitroso **16** to the oximes *E*-**17** + *Z*-**17** took place in DMSO-d_6 from 25 to 45 °C. This finding suggests that an intermolecular six-membered TS involving a water molecule and a proton shuttle (Schemes 1 and 2)[4f,g] is most likely in both cases because the conversion of the oxime to the nitroso is ∼3 times faster in DMSO-d_6 (∼30% DOH) at 20 °C compared with that in $CDCl_3$ (0.8% water).

The conversion of **16** to *E*-**17** + *Z*-**17** was ∼8 times faster at 313 K than that of compound **7** to *E*-**8b** + *Z*-**8b** under identical condition at 40 °C in DMSO-d_6. The relative reactivity of the two compounds **7** versus **16** arises from the positions of electron-withdrawing groups. In *C*-nitroso **16**, the acidic H8 (the ionizing center) is situated two bonds away from the OPMB on C1, whereas H7 in *C*-nitroso **7** is situated three bonds away from the C1 OMe group. We have determined and compared the $\Delta G^{\ddagger}$ and E_a values for the two conversions and found that the values for the conversion of **16** to pure oximes *E*-**17** and *Z*-**17** are lower than those for the conversion of **7** to *E*-**8b** and *Z*-**8b** (Table 3). Clearly, the conversion of *C*-nitroso compounds **16** and **7** to the respective pure oximes *E*/*Z*-**17** and *E*/*Z*-**8b** are spontaneous because the product oximes **17** and **8b** are thermodynamically more stable than the *C*-nitroso compounds **16** and **7**. Further work on the mechanisms of these reactions is in progress.

CONCLUSIONS

In this study we synthesized bicyclo[2.2.1]heptane-8-oximes *E*-**17** and *Z*-**17** and bicyclo[2.2.1]heptane-7-oximes *E*-**8b** and *Z*-**8b** and their corresponding *C*-nitroso compounds **16** and **7** via a free-radical ring-closure reaction[3] that gives an NHOBn group at C8/C7 (**15** and **6b**). NMR spectroscopy experiments were employed to characterize the synthesized compounds unambiguously.

The *C*-nitroso derivative **7** is very sluggishly converted to the corresponding oximes *E*-**8b** and *Z*-**8b** both in $CDCl_3$ and DMSO-d_6 at room temperature (almost 10 days to reach completion). *C*-Nitroso compound **7** in DMSO-d_6 under neutral conditions took 24 h at 45 °C to be transformed into the oxime as the sole product. In contrast, *C*-nitroso derivative **16** gave a mixture of oximes *E*-**17** and *Z*-**17** with $t_{99\%}$ = 58 h at 25 °C. In the conversion of **16** to *E*-**17** + *Z*-**17** we observed a rate that is ∼8 times higher (at 40 °C) than that for **7** → *E*-**8b** + *Z*-**8b**.[7a,b] E_a was obtained from the Arrhenius plots, and the Eyring plots gave $\Delta G^{\ddagger}$ = 99.1 ± 0.2 kJ/mol for **16** → *E*-**17** + *Z*-**17** at 313 K in DMSO-d_6 and $\Delta G^{\ddagger}$ = 105.2 ± 0.1 kJ/mol for **7** → *E*-**8b** + *Z*-**8b** at 313 K. Thus, **16** → *E*-**17** + *Z*-**17** needs less energy for conversion compared with **7** → *E*-**8b** + *Z*-**8b**.

The mechanism of the conversions **16** → *E*-**17** + *Z*-**17** and **7** → *E*-**8b** + *Z*-**8b** (Scheme 1) involves a faster intermolecular proton shuttle for the former compared with the latter. This is due to the different acidity of H8 in *C*-nitroso compound **16**. This ionizing center is situated two bonds away from the C1 OPMB group, compared with H7 in *C*-nitroso derivative **7**, which is situated three bonds away from the C1 OMe group. As a consequence, the electron-withdrawing effect of the *p*-methoxybenzyl (PMB) group in the former is felt more strongly.

Work is in progress to exploit this new chemistry and the products for the synthesis of carba-LNA-modified oligonucleotides in order to explore their biological properties.[2a,11] The free-radical cyclization to a C═NOBn moiety at C7/C8 followed by oxidation and deoxygenation steps opens new possibilities for the synthesis of novel chiral carba- or oxabicyclo[2.2.1]-heptane LNAs.[3c] This route involves fewer synthetic steps than the earlier routes described by Jacobson[3c] and Nielsen[3d] for fused carbacycles containing an extra carbon to give carba-ENAs. Our novel synthesis allows the free-radical cyclization to be performed with a tethered oximino function without an extra methyl group in the cyclization to a double bond. It constitutes a high-yielding, scalable route that does not require the use of expensive reagents to the desired carba- or double carbanucleoside analogues.[2a,11]

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EXPERIMENTAL SECTION

General Procedures. All reagents were of the highest commercial quality and were used without further purification. All non-aqueous reactions were carried out under anhydrous conditions in dry, freshly distilled solvents under N_2(g). Reactions were monitored by TLC carried out using UV light and/or cerium ammonium molybdate as the visualizing agent. Flash chromatography was performed using silica gel 60G (230−400 mesh). ^{1}H and ^{13}C NMR spectra were obtained using 500 and 600 MHz instruments for ^{1}H and 125 and 150 MHz instruments for ^{13}C. The same spectrometers were used for the acquisition of ^{1}H−^{1}H homonuclear (COSY and NOE) and ^{1}H−^{13}C heteronuclear (HMQC and HMBC) correlations. Molecular modeling was performed using HyperChem Pro 6.0[8] using molecular mechanics (AMBER) followed by the semiempirical AM1 method (as implemented in HyperChem Pro 6.0) to analyze the structures of all products reported in the schemes. The dihedral angles were obtained using the Karplus equation[9] through the input of coupling constants (NMR data), whereas HyperChem[8] was used where no coupling constants could be obtained. High-resolution mass spectra (HRMS) with correct masses were obtained by MALDI-TOF mass spectroscopy.

4-*C*-Cyanomethyl-3,5-di-*O*-benzyl-1-*O*-methyl-α,β-D-ribofuranoside (2b). Compound **1b** (20 g, 48.84 mmol) was stirred with 6% *p*-toluenesulfonic acid·H_2O in MeOH (400 mL) at rt for 24 h, and the mixture was neutralized with saturated solution of Na_2CO_3, concentrated, diluted with H_2O, and extracted with CH_2Cl_2. After drying over $MgSO_4$, it was purified by silica gel column chromatography (25−30% EtOAc/petroleum ether) to give compound **2b** as a colorless oil (15 g, 80.1%) as an inseparable mixture of α and β anomers.

Major isomer (β): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28−7.40 (13H, m, aromatic), 4.90 (1H, s, H1), 4.69 (1H, d, J_{gem} = 12 Hz, CH_2Ph), 4.58 (1H, d, J_{gem} = 12 Hz, CH_2Ph), 4.57 (1H, bs, H3), 4.12 (2H, q, CH_2Ph), 4.06 (1H, t, H2), 3.68 (1H, d, J_{gem} = 9.5 Hz, H5), 3.46 (1H, d, J_{gem} = 9.5 Hz, H5′), 3.30 (3H, s, OCH_3), 2.92 (2H, s, H6, H6′), 2.62 (1H, bs, OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.7, 138.5 (aromatic), 134.4 (C7), 128.9, 128.4, 128.2, 127.9 (aromatic), 118.3 (C8), 107.6 (C1), 86.8 (C4), 82.1 (C2), 75.2 (C5), 75.1 (C3), 73.3 (CH_2Ph), 72.8 (CH_2Ph), 55.3 (OCH_3), 38.1 (C6). MALDI-TOF *m*/*z* calcd for $C_{22}H_{25}NO_5Na$ [M + Na]$^+$ 406.163; found 406.163.

4-*C*-(Benzyloxyimino)ethyl-3,5-di-*O*-benzyl-1-*O*-methyl-β-D-ribofuranoside (4b). To a solution of **2b** (16 g, 41.72 mmol) in dry dichloromethane (DCM, 300 mL) was added DIBALH (166.9 mL, 1.0 M solution in toluene) dropwise at −78 °C. After 4 h of stirring at the same temperature, the mixture was allowed to warm to 0 °C, and then 1 N HCl solution was added to quench the reaction. The mixture was stirred for 30 min at 0 °C, and the resulting suspension was diluted with DCM. The organic layer was separated and washed with brine, dried over $MgSO_4$, and coevaporated with dry pyridine twice to give crude compound **3b**, which was dissolved in dry DCM (600 mL) and dry pyridine (15 mL). To this solution, *O*-benzylhydroxylamine hydrochloride (16.6 g, 104.3 mmol) was added. The mixture was heated at reflux for 2 h, cooled to rt, and neutralized by the addition of a saturated aqueous solution of $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$, evaporated, and chromatographed over silica gel (15−20% EtOAc/petroleum ether) to give **4b** (17 g, 83%) as a mixture of *Z* and *E* isomers.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (1H, app t, *J* = 6.3 Hz, $H7_E$), 7.22−7.51 (30H, m, aromatic), 7.04 (1H, app t, *J* = 5.3 Hz, $H7_Z$), 5.14 (2H, s, CH_2NOBn_E), 5.10 (2H, s, CH_2NOBn_Z), 4.87 (1H, s, $H1_E$), 4.85 (1H, s, $H1_Z$), 4.68 (2H, d, J_{gem} = 8.2 Hz, CH_2Ph), 4.66 (2H, d, J_{gem} = 8.5 Hz, CH_2Ph), 4.57 (2H, d, J_{gem} = 8.5 Hz, CH_2Ph), 4.55 (2H, d, J_{gem} = 8.2 Hz, CH_2Ph), 4.52 (1H, s, CH_2Ph), 4.47 (1H, s, CH_2Ph), 4.14 (2H, t, 6 Hz, $H3_{E,Z}$), 4.05 (2H, *m*, $H2_{E,Z}$), 3.46 (1H, d, J_{gem} = 8.14 Hz, $H5_E$), 3.43 (1H, d, J_{gem} = 8.14 Hz, $H5_Z$), 3.34 (1H, d, J_{gem} = 8.14 Hz, $H5'_E$), 3.29 (1H, d, J_{gem} = 8.14 Hz, $H5'_Z$), 3.31 (3H, s, OCH_{3E}), 3.28 (3H, s, OCH_{3Z}), 2.93 (1H, dd, J_{gem} = 17 Hz, $J_{6',7}$ = 5.3 Hz, $H6'_Z$), 2.83 (1H, dd, J_{gem} = 16.7 Hz, $J_{6',7}$ = 5.1 Hz, $H6_Z$), (2H, s, H6, $H6'_E$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.3 ($C7_E$), 148.9 ($C7_Z$), 138.0, 137.9, 137.2 (aromatic), 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6 (aromatic), 107.3 ($C1_{E,Z}$), 84.6 ($C4_E$), 84.6 ($C4_Z$), 81.4 ($C3_{E,Z}$), 75.6 ($C5_{E,Z}$), 74.7 ($C2_{E,Z}$), 73.1, 74.7 ($CH_2Ph_{E,Z}$), 54.9 ($OCH_{3E,Z}$), 30.2 ($C6_Z$), 33.8 ($C6_E$). MALDI-TOF *m*/*z* calcd for $C_{29}H_{33}NO_6Na$ [M + Na]$^+$ 514.221; found 514.222.

4-*C*-(Benzyloxyimino)ethyl-3,5-di-*O*-benzyl-1-*O*-methyl-2-*O*-phenoxythiocarbonyl-β-D-ribofuranoside (5b). Compound **4b** (17 g, 34.6 mmol) was dissolved in 400 mL of anhydrous pyridine. The solution was cooled to 0 °C, and then phenyl chlorothionoformate was added dropwise (9.5 mL, 69.2 mmol) while the temperature was maintained at 0 °C. After overnight stirring at room temperature, pyridine was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with a saturated solution of $NaHCO_3$ twice. The organic layer was separated, dried over $MgSO_4$, and concentrated. The concentrate was purified by silica gel column chromatography (0−10% v/v EtOAc in petroleum ether) to give compound **5b** as a yellowish oil (15.6 g, 72%, mixture of *E* and *Z* isomers).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (1H, app t, *J* = 6.5 Hz, $H7_E$), 7.24−7.41 (40H, m, $aromatic_{E,Z}$), 7.02 (1H, app t, *J* = 6.5 Hz, $H7_Z$), 6.98 (4H, d, *J* = 8.5 Hz, $aromatic_{E,Z}$), 5.73 (2H, m, $H2_{E,Z}$), 5.15 (2H, s, CH_2NOBn_E), 5.10 (3H, s, CH_2NOBn_Z, $H1_E$), 5.08 (1H, s, $H1_Z$), 4.59 (4H, d, J_{gem} = 7.5 Hz, CH_2Ph), 4.51 (2H, d, J_{gem} = 8.5 Hz, CH_2Ph), 4.47 (2H, d, J_{gem} = 7.5 Hz, CH_2Ph), 4.44 (1H, d, $J_{2,3}$ = 3 Hz, $H3_E$), 4.42 (1H, d, $J_{2,3}$ = 5 Hz, $H3_Z$), 3.68 (4H, m, H5, $H5'_{E,Z}$), 3.37 (3H, s, OCH_{3E}), 3.35 (3H, s, OCH_{3Z}), 3.01 (1H, dd, J_{gem} = 16.5 Hz, $J_{6',7}$ = 6 Hz, $H6'_E$), 2.79 (1H, dd, J_{gem} = 17 Hz, $J_{6',7}$ = 4.5 Hz, $H6_E$), 2.92 (2H, d, *J* = 6.5 Hz, H6, H6′). ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.4, 194.3 ($C{=}S_{E,Z}$), 149.1 ($C7_E$), 148.6 ($C7_Z$), 138.1, 138.0, 137.6, 137.5, 138.5 ($aromatic_{E,Z}$), 129.6, 129.5, 128.3, 128.1, 127.9, 127.8, 127.6, 127.5, 126.8, 126.6 ($aromatic_{E,Z}$), 121.7, 121.8 ($aromatic_{E,Z}$), 104.7, 104.5 ($C1_{E,Z}$), 84.8, 84.6 ($C2_{E,Z}$), 83.8, 83.7 ($C4_{E,Z}$), 80.15, 79.8 ($C3_{E,Z}$), 75.5, 75.4 ($CH_2Ph_{E,Z}$) 74.8, 74.4 ($C5_{E,Z}$), 73.5, 73.4 ($CH_2Ph_{E,Z}$), 55.1 ($OCH_{3E,Z}$), 33.1 ($C6_Z$), 30.0 ($C6_Z$). MALDI-TOF *m*/*z* calcd for $C_{36}H_{37}NO_7SNa$ [M + Na]$^+$ 650.219; found 650.219.

(1*R*,3*R*,4*R*,5*R*,7*S*)-7-(Benzyloxy)-1-[(benzyloxy)methyl]-3-methoxy-5-benzyloxyamino-2-oxabicyclo[2.2.1]heptane (6b). Compound **5b** (14 g, 22.32 mmol) was dissolved in 500 mL of anhydrous toluene, which was purged with N_2 for half an hour. The mixture was heated to reflux, and Bn_3SnH (12 mL in 60 mL of anhydrous toluene) and AIBN (1.8 g in 60 mL of anhydrous toluene) were added dropwise over 3 h; reflux was continued for 2 h. The solvent was evaporated, and the concentrate was purified by silica gel column chromatography (20−25% v/v EtOAc in petroleum ether) to give compound **6b** as a colorless oil (5.7 g, 54%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15−7.31 (15H, m, aromatic), 4.87 (1H, s, H1), 4.63 (2H, s, CH_2Ph), 4.53 (2H, ABq, J_{gem} = 12 Hz, CH_2Ph), 4.41 (2H, ABq, J_{gem} = 12.5 Hz, CH_2Ph), 4.18 (1H, s, H3), 3.82 (1H, m, H7), 3.54 (2H, ABq, J_{gem} = 11.5 Hz, H5, H5′), 3.26 (3H, s, OCH_3), 2.62 (1H, q, $J_{2,3}$ = 1.5 Hz, $J_{2,7}$ = 4 Hz, H2), 1.97 (2H, m, H6, H6′). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.4, 138.0 (aromatic), 129.6, 128.5, 128.3, 127.3 (aromatic), 101.2 (C1), 86.0 (C4), 82.5 (C3), 73.4 (CH_2Ph), 71.8 (CH_2Ph), 68.8 (C5), 56.7 (C7), 54.9 (OCH_3), 46.2 (C2), 32.2 (C6). MALDI-TOF *m*/*z* calcd for $C_{29}H_{33}NO_5Na$ [M + Na]$^+$ 498.226; found 498.226.

(1*R*,3*R*,4*R*,5*R*,7*S*)-7-(Benzyloxy)-1-[(benzyloxy)methyl]-3-methoxy-5-nitroso-2-oxabicyclo[2.2.1]heptane (7) and *N*-[(1*R*,3*R*,4*R*,5*Z*/*E*,7*S*)-7-(Benzyloxy)-1-[(benzyloxy)methyl]-3-methoxy-2-oxabicyclo[2.2.1]heptan-5-ylidene]hydroxylamine (8b). To compound **6b** (950 mg, 1.99 mmol) were added *m*CPBA (837 mg, 3.4 mmol) and K_2CO_3 (550 mg, 3.98 mmol). The reaction mixture was stirred at rt for 1 h, after which it was diluted with EtOAc and extracted with saturated aqueous $NaHCO_3$. The organic phase was dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (25−35% EtOAc in petroleum ether) to give **7** (230 mg, 30%) and a 10:2 mixture of *E*- and *Z*-**8b** (300 mg, 40%).

Nitroso **7**: ^{1}H NMR (500 MHz, $CDCl_3$): 7.16−7.29 (11H, m, aromatic), 5.41 (1H, dt, H7), 4.57 (1H, s, H1), 4.58 (1H, d, J_{gem} = 12 Hz, CH_2Ph), 4.52 (2H, ABq, J_{gem} = 6.6 Hz, CH_2Ph), 4.44 (1H, d, J_{gem} = 11.4 Hz, CH_2Ph), 4.32 (1H, bs, H3), 3.61 (2H, ABq, J_{gem} = 11.4 Hz, H5, H5′), 3.25 (3H, s, OCH_3), 3.20 (1H, dd, $J_{2,3}$ = 1.2 Hz, $J_{2,7}$ = 4.2 Hz, H2), 2.49 (1H, dd, J_{gem} = 13.2 Hz, $J_{6,7}$ = 4.2 Hz, H6′),

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2.08 (1H, dd, J_{gem} = 13.8 Hz, $J_{6',7}$ = 10.8 Hz, H6′). ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.7, 137.8 (aromatic), 128.9, 128.7, 128.6, 128.3, 127.8 (aromatic), 100.7 (C1), 86.9 (C4), 82.5 (C3), 73.9 (CH_2Ph), 72.6 (CH_2Ph), 68.2 (C5), 66.8 (C8), 55.4 (OCH_3), 46.1 (C2), 32.0 (C6). MALDI-TOF *m*/*z* calcd for $C_{22}H_{25}NO_5Na$ $[M + Na]^+$ 406.163; found 406.163.

Oxime *E*-**8b**: ^{1}H NMR (600 MHz, DMSO-d_6): δ 10.66 (1H, s, NO*H*), 7.24−7.36 (13H, m, aromatic), 4.67 (1H, s, H1), 4.48 (1H, d, J_{gem} = 12 Hz, CH_2Ph), 4.53 (2H, d, J_{gem} = 12.5 Hz, CH_2Ph), 4.58 (1H, d, J_{gem} = 12 Hz, CH_2Ph), 4.28 (1H, s, H3), 3.66 (2H, ABq, J_{gem} = 11.4 Hz, H5, H5′), 3.25 (3H, s, OCH_3), 3.13 (1H, bs, H2), 2.37 (1H, d, J_{gem} = 16.8 Hz, H6), 2.37 (1H, d, J_{gem} = 15 Hz, H6′). ^{13}C NMR (150 MHz, DMSO): δ 157.4 (C7), 138.7, 138.2 (aromatic), 128.6, 127.9, 127.8, 127.7 (aromatic), 102.9 (C1), 86.2 (C4), 80.5 (C3), 72.7 (CH_2Ph), 71.4 (CH_2Ph), 54.6 (OCH_3), 50.5 (C2), 34.8 (C6). MALDI-TOF *m*/*z* calcd for $C_{22}H_{25}NO_5Na$ $[M + Na]^+$ 406.163; found 406.163.

(3*S*,5*S*)-4-(Benzyloxy)-5-[(1*R*,2*E*/*Z*)-2-(benzyloxy)imino-1-[(4-methoxyphenyl)methoxy]ethyl]-3-[(benzyloxy)methyl]oxolan-3-ol (*E*/*Z*-13). Compound **11** (7.42 g, 15.1 mmol) was dissolved in acetone (110 mL). OsO_4 (4.93 mL, 0.76 mmol), NMO (2.65 g, 19.66 mmol), and H_2O (16.7 mL) were added at room temperature. The reaction mixture was stirred at rt overnight and then partitioned between EtOH and H_2O. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give the crude aldehyde. The crude aldehyde (1.16 g, 2.36 mmol) was dissolved in dry dichloromethane (55 mL), and pyridine (1.2 mL) and *O*-benzylhydroxylamine hydrochloride (960 mg, 4.72 mmol) were added at room temperature. The reaction mixture was stirred at reflux for 2 h and then cooled to room temperature, and saturated aqueous $NaHCO_3$ was added. The organic layer was separated, dried over $MgSO_4$, and evaporated. The residue was subjected to short column chromatography over silica gel (10%−30% EtOAc/petroleum ether) to give a mixture of *E*-**13** and *Z*-**13** (621 mg, 1.04 mmol, ∼3:1 *E*:*Z*, 44%).

Z-**13**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40−7.17 (17H, m, aromatic), 6.9 (1H, d, $J_{8,1}$= 6 Hz, H8), 6.82 (2H, d, J_{gem} = 8.5 Hz, PMB), 5.15 (2H, ABq, J_{gem} = 12 Hz, NOCH_2Ph), 4.67 (1H, dd, $J_{1,2}$ = 3.5 Hz, H1), 4.63 (2H, q, CH_2Bn), 4.53 (1H, d, *J* = 11.5 Hz, CH_2PMB), 4.37 (2H, q, J_{gem} = 12 Hz, 3OCH_2Ph), 4.31 (1H, d, CH_2PMB), 4.14 (1H, t, $J_{2,3}$ = 2.8 Hz, H2), 3.86 (1H, d, *J* = 9.5 Hz, H6), 3.81−3.76 (6H, m, OCH_3, H3, H6′, H5), 3.67 (1H, d, *J* = 9.5 Hz, H5′), 2.72 (1H, d, O*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.6 (C4-PMB), 150.8 (C8), 138.1, 137.6, 137.2, 130.2, 128.5, 128.46, 128.4, 128.4, 128.38, 128.3, 127.8, 127.76, 127.7, 113.9 (aromatic), 85.2 (C3), 84.9 (C2), 81.2 (C4), 76.6 (NOCH_2Ph), 75.8 (C6), 73.9 (5OCH_2Bn), 72.2 (3OCH_2Bn), 72.0 (CH_2PMB), 71.1 (C1), 69.8 (C5), 55.3 (CH_3). MALDI-TOF *m*/*z* calcd for $C_{36}H_{39}NO_7Na$ $[M + Na]^+$ 620.262; found 620.262.

E-**13**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.5 (1H, d, $J_{8,1}$ = 6 Hz, H8), 7.41−7.29 (13H, m, aromatic), 7.19−7.16 (4H, m), 6.85 (2H, d, J_{gem} = 8.8 Hz, PMB), 5.15 (2H, s, CH_2Ph), 4.63 (2H, q, *J* = 12 Hz, 5OCH_2Ph), 4.56 (1H, d, J_{gem} = 11.4 Hz, CH_2PMB), 4.45 (1H, d, *J* = 11.7 Hz, 3OCH_2Ph), 4.36 (H, d, 3OCH_2Ph), 4.29 (1H, d, CH_2PMB), 3.99−3.95 (2H, m, H3, H1), 3.88 (1H, d, *J* = 9.1 Hz, H6), 3.85−3.78 (6H, m, OCH_3, H2, H6′, H5), 3.73 (1H, bs, O*H*), 3.67 (1H, d, *J* = 9.5 Hz, H5′). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5 (C4-PMB), 148.6 (C8), 138.0, 137.6, 137.5, 130.2, 128.8, 128.4, 128.3, 128.0, 127.8, 127.79, 127.8, 113.8 (aromatic), 85.8 (C2), 85.4 (C3), 81.2 (C4), 76.1 (NOCH_2Ph), 75.7 (C6), 75.1 (C1), 73.9 (5OCH_2Bn), 72.6 (3OCH_2Bn), 70.5 (CH_2PMB), 70.0 (C5), 55.3 (CH_3). MALDI-TOF *m*/*z* calcd for $C_{36}H_{39}NO_7Na$ $[M + Na]^+$ 620.262; found 620.262.

(1*R*,2*E*/*Z*,3*S*,5*S*)-4-(Benzyloxy)-5-[2-[(benzyloxy)imino]-1-[(4-methoxyphenyl)methoxy]ethyl]-3-[(benzyloxy)methyl]oxolan-3-yl methyl oxalate (*E*/*Z*-14). The mixture of *E*-**13** and *Z*-**13** (3.99 g, 6.68 mmol) was dissolved in dry pyridine (190 mL), and methyloxalyl chloride (2.8 mL, 30 mmol) was added at room temperature. The reaction mixture was stirred at 50 °C overnight, after which it was quenched with saturated $NaHCO_3$ solution and extracted with DCM. The organic phase was dried over anhydrous sodium sulfate, filtered, and evaporated. The crude product was purified by silica gel column chromatography (5−25% EtOAc/petroleum ether) to yield a mixture of *E*-**14** and *Z*-**14** (3.1 g, 4.53 mmol, 3:1 *E*:*Z*, 68%).

E-**14**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (1H, d, $J_{8,1}$ = 8 Hz, H8), 7.40−7.14 (17H, m, aromatic), 6.87 (2H, d, *J* = 8.8 Hz, PMB), 5.14 (2H, s, NOCH_2Ph), 4.63 (1H, d, J_{gem} = 11 Hz, CH_2Ph), 4.55 (1H, d, *J* = 12 Hz, CH_2Ph), 4.51 (1H, d, *J* = 11.7 Hz, CH_2PMB), 4.50 (1H, d, *J* = 12 Hz, CH_2Ph), 4.43 (1H, d, $J_{6,6'}$ = 11 Hz, H6), 4.27 (2H, 2 × d, J_{gem} = 11 Hz, CH_2Ph, $J_{3,2}$ = 6.3 Hz, H3), 4.21 (1H, d, $J_{5,5'}$ = 10.7 Hz, H5), 4.20 (1H, d, CH_2PMB), 4.01 (1H, dd, $J_{1,2}$ = 4.7 Hz, H1), 3.94 (1H, d, H5′), 3.91 (1H, d, H6′), 3.87 (3H, s, oxalyl-CH_3), 3.86 (1H, m, H2), 3.79 (3H, s, OCH_3-PMB). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.4 (C4-PMB), 157.9 (*C*(O)OMe), 156.6 (*C*(O)), 148.3 (C8), 137.6, 137.5, 137.4, 130.1, 128.42, 128.4, 128.36, 128.0, 127.9, 127.8, 127.7 (aromatic), 113.8 (C3-PMB), 92.3 (C4), 85.1 (C2), 83.5 (C3), 76.2 (NOCH_2), 74.3 (C1), 74.2 (C6), 73.6 (CH_2Ph), 73.5 (CH_2Ph), 70.5 (CH_2PMB), 66.5 (C5), 55.2 (OCH_3), 53.5 (CH_3-oxalyl). MALDI-TOF *m*/*z* calcd for $C_{39}H_{41}NO_{10}K$ $[M + K]^+$ 722.237; found 722.235.

Z-**14**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.59 (m, 1H, H1), 4.18 (m, 1H, H3), 3.81 (m, 1H, H2).

(1*R*,4*R*,5*S*,6*R*,7*R*)-*N*,7-Bis(benzyloxy)-4-[(benzyloxy)methyl]-6-[(4-methoxyphenyl)methoxy]-2-oxabicyclo[2.2.1]heptan-5-amine (15). The mixture of *E*-**14** and *Z*-**14** (910 mg, 1.24 mmol) was dissolved in anhydrous toluene (130 mL), and then the solution was purged with N_2 for 40 min. The mixture was refluxed, and Bn_3SnH (0.8 mL in 20 mL in dry toluene) and AIBN (40 mg in 10 mL in dry toluene) were added dropwise over 5 h; then the mixture continued to reflux for 1 h. The mixture was cooled to room temperature, and the solvent was evaporated. The residue was chromatographed on silica gel (5−30% EtOAc in petroleum ether) to give **15** (433 mg, 60%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29−7.08 (17H, m, aromatic), 6.84 (2H, d, *J* = 8.4 Hz, PMB), 6.0 (1H, d, *J* = 4.8 Hz, NH), 4.69 (2H, ABq, J_{gem} = 11.4 Hz, CH_2Ph), 4.61 (1H, d, *J* = 12 Hz, CH_2Ph), 4.54−4.44 (4H, m, CH_2Ph × 2, CH_2PMB), 4.36 (1H, d, *J* = 11.4 Hz, CH_2Ph), 4.08 (1H, s, H2), 3.95 (1H, d, *J* = 7.5 Hz, H6), 3.93 (1H, s, H3), 3.80 (3H, s, OCH_3), 3.69− 3.63 (3H, m, H6′, H5, H5′), 3.46 (1H, d, $J_{8,1}$ = 3.6 Hz, H8), 3.38 (1H, s, H1). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.6 (C-PMB), 138.6, 138.2, 130.8, 129.6, 128.8, 128.1, 127.9, 127.8 (aromatic), 114.2 (C-PMB), 82.0 (C1), 81.9 (C3), 78.1 (C2), 76.9 (NOCH_2), 73.9 (CH_2Ph), 72.3 (CH_2Ph), 71.0 (CH_2Ph), 68.2 (C5), 67.1 (C6), 55.69 (OCH_3), 52.9 (C4). MALDI-TOF *m*/*z* calcd for $C_{36}H_{40}NO_6$ $[M + H]^+$ 582.286; found 582.286.

(1*R*,4*R*,5*S*,6*R*,7*R*)-7-(Benzyloxy)-4-[(benzyloxy)methyl]-6-[(4-methoxyphenyl)methoxy]-5-nitroso-2-oxabicyclo[2.2.1]-heptane (16) and *N*-[(1*R*,4*R*,5*Z*/*E*,6*R*,7*R*)-7-(Benzyloxy)-4-(benzyloxy)methyl-6-[(4-methoxyphenyl)methoxy]-2-oxabicyclo[2.2.1]heptan-5-ylidene]hydroxylamine (*E*/*Z*-17). To compound **15** (1.74 g, 2.99 mmol) were added *m*CPBA (840 mg, 3.65 mmol) and K_2CO_3 (994 mg, 7.2 mmol). The reaction mixture was stirred at rt for 1 h, after which it was diluted with EtOAc and extracted with saturated aqueous $NaHCO_3$. The organic phase was dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (5−35% in ethyl acetate in petroleum ether) to give **16** (290 mg, 20%) and *E*/*Z*-**17** (415 mg, 28%).

E-**17**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.78 (1H, s, OH), 7.38−7.26 (12H, m, aromatic), 6.89 (2H, d, *J* = 8.5 Hz, PMB), 4.76 (2H, ABq, J_{gem} = 12 Hz, CH_2Ph), 4.66−4.57 (5H, m, CH_2Ph, CH_2PMB), 4.28 (1H, d, $J_{3,2}$ = 1.5 Hz, H3), 4.22 (1H, s, H1), 4.09 (1H, d, $J_{2,3}$ = 1.5 Hz, H2), 4.05 (1H, d, J_{gem} = 6.5 Hz, H6), 3.83 (3H, s, OCH_3), 3.81 (2H, s, H5, H5′), 3.67 (1H, d, J_{gem} = 6.5 Hz, H6′). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.5 (C8), 159.5 (C-PMB), 138.2, 137.9, 129.7, 129.6, 127.8, 127.6, 127.6, 127.5 (aromatic), 113.8 (C-PMB), 81.4 (C1), 78.0 (C2), 75.2 (C3), 73.7 (CH_2Ph), 73.6 (CH_2PMB), 72.3 (CH_2Ph), 71.9 (CH_2Ph), 70.9 (C6), 65.1 (C5), 55.3 (OCH_3), 54.2 (C4). MALDI-TOF *m*/*z* calcd for $C_{29}H_{32}NO_6$ $[M + H]^+$ 490.223; found 490.223.

Z-**17**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.38 (1H, s, H1), 4.22 (1H, d, $J_{2,3}$ = 2 Hz, H3), 4.05 (1H, m, H2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 81.13 (C1), 77.8 (C3), 78.1 (C2).

16: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.8 (1H, s, OH), 7.32−7.07 (12H, m, aromatic), 6.81 (2H, d, *J* = 8.5 Hz, PMB), 5.81 (1H, d,

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$J_{8,1}$ = 2 Hz, H8), 4.66 (2H, ABq, J_{gem} = 12 Hz, CH_2Ph), 4.49 (1H, d, J = 12 Hz, CH_2Ph), 4.44 (2H, ABq, J = 11.5 Hz, CH_2PMB), 4.36 (1H, m, $J_{1,2}$ = 3 Hz, H1), 4.25 (1H, d, J = 11.5 Hz, CH_2Ph), 4.15 (1H, s, H2), 4.11 (1H, d, J = 7.5 Hz, H6), 4.05 (1H, s, H3), 3.76 (3H, s, OCH_3), 3.54 (2H, m, H6′, H5), 3.35 (1H, d, J = 9.5 Hz, H5′). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9 (C-PMB), 138.3, 138.2, 130.0, 129.4, 128.9, 128.7, 128.2, 127.9 (aromatic), 114.3 (C-PMB), 81.5 (C3), 78.6 (C1), 77.8 (C2), 74.1 (CH_2Ph), 72.5 (CH_2PMB), 72.5 (CH_2Ph), 71.5 (CH_2Ph), 71.1 (C8), 66.6 (C5), 66.5 (C6), 56.1 (C4), 55.6 (OCH_3). MALDI-TOF m/z calcd for $C_{29}H_{32}NO_6$ $[M + H]^+$ 490.223, found 490.224.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR, COSY, HMQC, and HMBC spectra for compounds **2b**, **4b**, **5b**, **6b**, **7**, *E*-**8b**, and *Z*-**8b** (in part I) and *E*-**13**, *Z*-**13**, *E*-**14**, *Z*-**14**, **15**, **16**, *E*-**17**, *Z*-**17**, and **23** (in part II); 1D NOE spectra for compounds **6b** and **7** (in part I) and **15** and **16** (in part II); and molecular structures based on molecular mechanics and semiempirical calculations for compounds **6b** and **7** (in part I) and **15** and **16** (in part II). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This work is dedicated to Professor C. B. Reese (FRS) on the occasion of his 84th birthday.

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