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Unusual Strain-Releasing Nucleophilic Rearrangement of a Bicyclo[2.2.1]heptane System to a Cyclohexenyl Derivative

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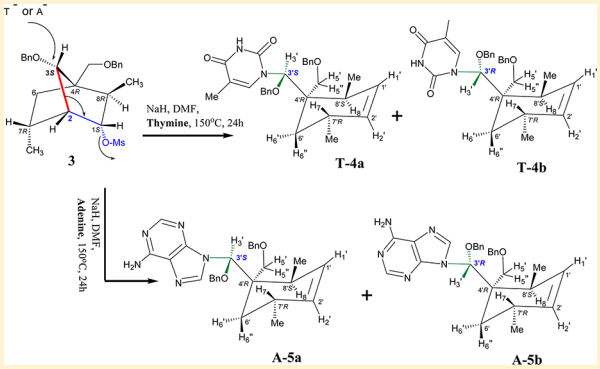
Supporting Information

ABSTRACT: We report an unusual strain-releasing reaction of 1-mesyloxy-8,7-dimethylbicyclo[2.2.1]heptane (**3**) by a base-promoted substitution at the chiral C3 followed by spontaneous concerted ring opening involving the most strained C2−C3−C4 bonds (with bond angle 94°) and the C2 bridgehead leading to *anti*−*endo* elimination of the C1-mesyloxy group by the conjugate base of adenine or thymine to give two diastereomeric C3′(*S*) and C3′(*R*) derivatives of 1-thyminyl and 9-adeninyl cyclohexene: **3** → **T-4a** + **T-4b** and **3** → **A-5a** + **A-5b**. These products have been unambiguously characterized by detailed 1D and 2D NMR (*J*-coupling constants and nOe analysis), mass, and UV spectroscopy. Evidence has been presented suggesting that the origin of these diastereomeric C3′(*S*) and C3′(*R*) derivatives of 1-thyminyl and 9-adeninyl cyclohexene from **3** is most probably a rearrangement mechanism of a trigonal bipyramidal intermediate formed in the S_N2 displacement-ring-opening reaction.



INTRODUCTION

Recently, we have completed the synthesis of the conformationally locked dimethylbicyclo[2.2.1]heptane (**1**)[1] to transform it to the corresponding carbocyclic nucleosides for incorporating them into oligo-DNA or -RNA to study their biochemical properties as antisense agent[2a−i] and small interfering RNAs.[2j−l] This led us to attempt coupling of thymine and adenine base to the dimethylbicyclo[2.2.1]heptane system (**2** or **3** in Scheme 1) both through Mitsunobu coupling condition[3a−h] and by direct displacement[4a−c] of a triflate or mesylate at C1 at various temperatures and solvent conditions, but none of these worked.

We would like to report here an elusive strain-releasing reaction[5a−c] of the bicyclo[2.2.1]heptane derivative [1-mesyloxy-8,7-dimethylbicyclo[2.2.1]heptane (**3**)] under our coupling conditions (DMF, NaH, reflux for 24 h under N_2) by a concerted base-promoted nucleophilic attack at the *chiral* C3 by the conjugate base of adenine (A) or thymine (T), followed by spontaneous ring opening of the most strained C2−C3−C4 (Scheme 1 for numbering) bonds leading to elimination of the C1-mesylate group to give two diastereomeric products of C3′(*S*) and C3′(*R*) derivatives of 1-thyminyl or 9-adeninyl cyclohexene: **3** → **T-4a** + **T-4b** and **3** → **A-5a** + **A-5b**. It is noteworthy that the first example of the cleavage of the C2−C3 bond releasing the angular strain of the C2−C3−C4 angle is found in the solvolysis (AcOH/25 °C) of 2-tosyl-bicyclo[2.1.1]-hexenes involving a nonclassical carbonium ion.[6a,b]

In contrast, we herein show the base-promoted cleavage of the C2−C3 bond, releasing the angular strain of the C2−C3−C4 angle,[5a−c] which is devoid of a "keto" functionality.[6a,8] The X-ray structure[7] shows that there is considerable angular strain built in the system, and all bond angles are less than the tetrahedral, particularly the C2−C3−C4 angle which is only 94° and most strained. Despite this angular strain, the nucleophilic attack at C3 without a "keto" is unprecedented.[6a,8] The base-induced bimolecular nucleophilic displacements involving a C3 bridge-carbon can occur only with inversion of configuration (S_N2) which has been known to be rare,[6a,8] except in 7-halonorbornane,[9] 7-halo-2-norbornanones,[10] and 7-halo-2,3-norbornadiones,[11] simply because all groups involved in this system cannot be planar in the trigonal bipyramidal transition state[8] owing to, first, angular constraints and, second, to the *exo* C8-methyl and C1-hydrogen in compound **3** which sterically hinder the approach of the incoming nucleophile.[6a,8−11] In contradistinction, the base-promoted 1,2-elimination from both *endo*- and *exo*-2-bicyclo[2.2.1]heptyl halides and arenesulfonates has been studied[12a,b] which gives competitive *syn*−*endo* and *anti*−*exo*-H 1,2-elimination products along with a small amount of solvolytic elimination product (nortricyclene).

We argued that since the approach of the nucleophile 1-thyminyl (i.e., T^-) or 9-adeninyl (i.e., A^-) for any back-side attack is sterically *not* likely in compound **3** the only possible way for the T^-/A^- nucleophile to approach is the "in-line attack" from the front-side to C3, i.e., 180° for the $Nu^-\cdots C3\cdots C2$ bond angle (i.e., opposite to C8-methyl and C1-hydrogen in compound **3**); hence, it is far from clear as to why two

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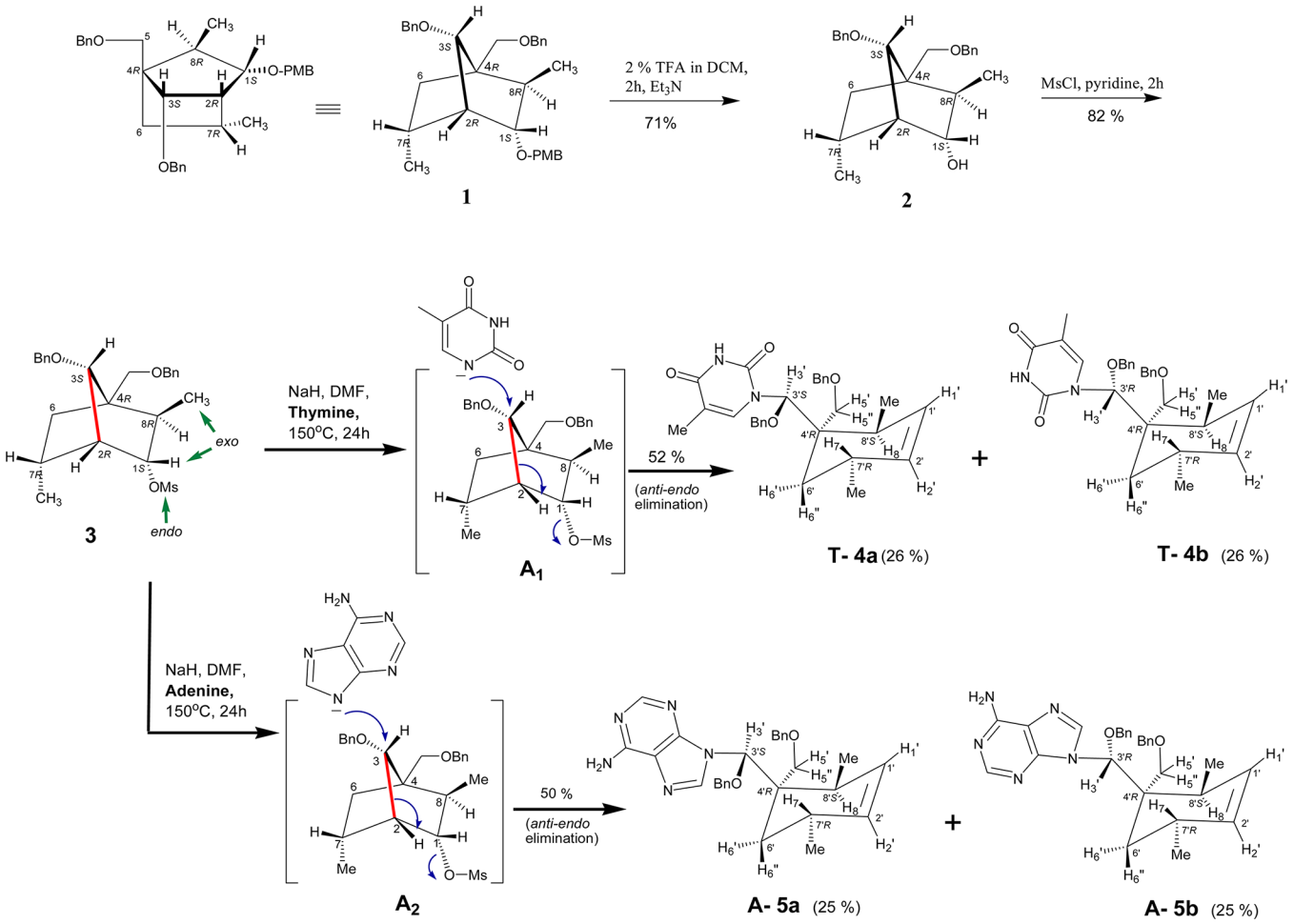
Scheme 1. Syntheses of 1-((4*R*,7*R*,8*S*)-(*S*)-Benzyloxy(4-benzyloxymethyl-7,8-dimethylcyclohex-1-en-4-yl)methyl)thymine (T-4a), 1-((4*R*,7*R*,8*S*)-(*R*)-Benzyloxy(4-benzyloxymethyl-7,8-dimethylcyclohex-1-en-4-yl)methyl)thymine (T-4b), 9-((4*R*,7*R*,8*S*)-(*S*)-Benzyloxy(4-benzyloxymethyl-7,8-dimethylcyclohex-1-en-4-yl)methyl)adenine (A-5a), 9-((4*R*,7*R*,8*S*)-(*R*)-Benzyloxy(4-benzyloxymethyl-7,8-dimethylcyclohex-1-en-4-yl)methyl)adenine (A-5b)[a]



[a]Intermediate (A_1) shows the "in-line front-side attack" by the conjugate base of thymine, whereas Intermediate (A_2) shows an identical S_N2 attack by the conjugate base of adenine, followed by the concerted cleavage of the C2−C3 bond and elimination of mesylate.

diastereomeric C3′(*S*) and C3′(*R*) products in ca. 1:1 ratio were obtained in our reaction unless the C3 center was racemized before or after the ring-opening reaction. These are the reasons why we considered it important to rigorously characterize the reaction products and establish this unusual reaction course of the bicyclo[2.2.1]heptane chemistry and discuss briefly a plausible mechanistic outcome.

RESULTS AND DISCUSSION

1.0. Reaction of 1-Mesyloxy-8,7-dimethylbicyclo-[2.2.1]heptane (3) with Thymine (T). *1.1. Preparation of 1-Mesyloxy-8,7-dimethylbicyclo[2.2.1]heptane (3).* Appropriately protected (1*S*,2*R*,3*S*,4*R*,7*R*,8*R*)-3-(benzyloxy)-4-[benzyloxymethyl]-1-mesyloxy-8,7-dimethylbicyclo[2.2.1]heptane (**3**) was prepared from (1*S*,2*R*,3*S*,4*R*,7*R*,8*R*)-3-(benzyloxy)-4-[benzyloxymethyl]-1-[(4-methyloxyphenyl)methoxy]-8,7-dimethylbicyclo[2.2.1]heptane (**1**) (Scheme 1). Deprotection of the *p*-methoxybenzyl (PMB) group at C1 from **1** using 2% trifluoroacetic acid (TFA) in dichloromethane (DCM) at room temperature afforded the intermediate **2** (71%, $[\alpha]_D^{25\ °C} = 31°$).

1.2. Stereochemical Assignment of (1S,2R,3S,4R,7R,8R)-3-(Benzyloxy)-4-[benzyloxymethyl]-1-hydroxyl-8,7-dimethyl-bicyclo[2.2.1]heptane (2). Accurate determination of the stereochemistry of the chiral centers in the hydroxy precursor, compound **2**, is important in view of the rearrangement that takes place on its mesylate **3** upon treatment with the 9-adenylate or 1-thyminalate ion. This has been determined by nOe experiments and coupling constant analysis: irradiation of H1 [Figure S6, Panel A_1, SI (Supporting Information)] showed strong nOe enhancements for H3 (3.0%, $d_{H1,H3(calc)} \approx 2.4$ Å), 8-Me (2.7%, $d_{H1,8Me(calc)} \approx 2.6$ Å), and H2 (2.4%, $d_{H1,H2(calc)} \approx 2.5$ Å), which proved that 8Me is on the same face of the 2,4-fused carbocycle as the H3-(*S*) and H2-(*R*), which indicated that the C8 center has (*R*) configuration. On the other hand, the weak nOe enhancement for H8 (0.6%, $d_{H1,H8} \approx 3$ Å) upon H1 irradiation showed that H1 and H8 are *trans* oriented.

In addition, irradiation of 8Me (Figure S6, Panel A_2, SI) showed 1.3% nOe enhancement for H5 ($d_{8Me,H5} \approx 2.4$ Å) which confirmed that 8Me and H5 are located on the same face. So, these assignments confirmed the (*R*)-configuration at the C8 center and (*S*)-configuration at the C1 center, which means that the C1-hydroxy group in **2** is in *endo* orientation. The assignment of these configurations for **2** is also consistent with what has been assigned for the precursor: 3-(benzyloxy)-4-[benzyloxymethyl]-

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1-[(4-methyloxyphenyl)methoxy]-8,7-dimethylbicyclo[2.2.1]-heptane (**1**).[1] Quiet expectedly, the nOe assignments confirmed the preservation of the configuration at the C1 center during the deprotection of the *p*-methoxybenzyl (PMB) group **1** (**1** → **2**). These results have been further evidenced by the observed coupling constants in that the $^{3}J_{H2,H3}$ = 3.5 ± 0.2 Hz for compound **2** corresponded to the torsion angle $\phi_{H2-C2-C3-H3}$ = 60 ± 2°, thereby confirming the H2 and H3 have *cis* orientation with 1(*S*) configuration. On the other hand, the $^{3}J_{H1,H8}$ = 4.8 ± 0.2 Hz (Figure S7, SI), corresponding to a torsion for $\phi_{H1-C1-C8-H8}$ of 132 ± 2°, thereby indicating a *transoid* orientation between H1 and H8, which confirms the C1(*S*) and C8(*R*) configurations

After esterification of the 1-hydroxyl group of (1*S*,2*R*,3*S*,4*R*,7*R*,8*R*)-3-(benzyloxy)-4-(benzyloxymethyl)-1-hydroxy-8,7-dimethylbicyclo[2.2.1]heptane (**2** → **3**) with methylsulfonyl chloride in dry pyridine at 0 °C, the key intermediate **3** (82%, $[\alpha]_D^{25\ °C}$ = 28.5°) was obtained, which was also confirmed by NMR (Figure S8−S13, SI) and mass spectroscopy.

*1.3. Reaction of 1-Mesyloxy-8,7-dimethylbicyclo[2.2.1]-heptane (**3**) with Thymine or Adenine.* The key precursor **3** was subjected to the coupling reaction with thymine or adenine in anhydrous DMF in the presence of NaH as a base at 150 °C for ∼24 h. The products formed in the reaction mixture were separated by silica gel chromatography into pure components with an isolated yield of 26% each for **T-4a** and **T-4b** in a yield of 25% each for **A-5a** and **A-5b**. The NMR assignments showed unexpected thymine (T)−N1 or adenine (A)−N9 nucleophilic attack at C3′ (Scheme 1) with cleavage of the most strained C2−C3 bond and concomitant elimination of C1′-mesylate to give a diastereomerically pure C1′−C2′ double bond containing **T-4a** and **T-4b** or **A-5a** and **A-5b**, respectively.

The NMR evidence that proves the proposed structure of the two isolated diastereomeric olefinic products **T-4a** ($[\alpha]_D^{25\ °C}$ = 14.5°) and **T-4b** ($[\alpha]_D^{25\ °C}$ = 19.3°), on one hand, and **A-5a** ($[\alpha]_D^{25\ °C}$ = 16°) and **A-5b** ($[\alpha]_D^{25\ °C}$ = 23.3°), on the other hand, is based on *J*-coupling, HMBC, and nOe data as well as on UV and high-resolution mass spectrometry. Comparison of $[\alpha]_D^{25\ °C}$ values shows that **T-4a** and **A-5a** have a lower value compared to those of **T-4b** and **A-5b**. Immediate inspection of the chemical shifts (δ) and coupling constants (Table 1) gave a clear hint that **T-4a**, **T-4b** and **A-5a**, **A-5b** (for atom numbering, see Scheme 1 and legend) are likely to be similar because of the fact that in all four compounds their H1′, H2′ double triplet (olefinic system) and H3′ singlets appear with very similar chemical shifts (Table 1). The fact that the δ *H3′* of all four compounds, **T-4a** (δ 5.90), **T-4b** (δ 5.86) and **A-5a** (δ 5.98), **A-5b** (δ 5.97), appear as a sharp singlet which has moved downfield by ∼2.51 ppm in comparison with the parent 1-mesyloxy-8,7-dimethylbicyclo[2.2.1]heptane (**3**) $^{3}J_{H2,H3}$ ≈ 3 Hz suggested quite early that the C2′−C3′ covalent bond is broken as a result of a new C3′−N bond formation owing to the nucleophilic attack by the conjugate base of the 1-thyminyl and 9-adeninyl moiety (see below). Further detailed comparison of 500 and 600 MHz NMR properties (Table 1) for thyminylcyclohexenyl derivatives **T-4a** and **T-4b** and adeninylcyclohexenyl derivatives **A-5a** and **A-5b** shows that the dispersion of the chemical shifts of H5′, H5″ in **T-4a** [$\Delta\delta_{(H5'-H5'')}$ = 0.16 ppm] and **A-5a** [$\Delta\delta_{(H5'-H5'')}$ = ∼0 ppm] is very small, whereas the corresponding chemical shifts in the case of **T-4b** [$\Delta\delta_{(H5'-H5'')}$ = 0.87 ppm] and **A-5b** [$\Delta\delta_{(H5'-H5'')}$ = 1.0 ppm] are more dispersed, thereby showing that the anisotropic effects of the nucleobase on H5′/5″ in **T-4a**/**A-5a** are very similar because they experience very similar diamagnetic

Table 1. Relevant Chemical Shifts (δ) and Coupling Constants (*J* in Hz) of Rearranged Products T-4a, T-4b, A-5a, and A-5b (Figures S14−S57, SI for All 1 and 2D Spectra as Well as Decoupling Studies)

	H1′	H2′	H3′	H5′, H5″	H6′, H6″	H7′	H8′	other protons
(T-4a)	5.32 (1H, dt, $J_{1',2'}$ = 10, $J_{1',7'}$ = 2, $J_{1',8'}$ = 2.5)	5.47 (1H, dt, $J_{1',2'}$ = 10, $J_{2',8'}$ = 1.83, $J_{2',7'}$ = 2.4)	5.90 (1H, s)	3.23 (1H, d, J_{gem} = 9.5, H5′), 3.39 (1H, *d*, J_{gem} = 9.5, H5″)	2.03 (1H, dd, J_{gem} = 14.5, $J_{6',7'}$ = 5.5, H6), 1.21 (1H dd, J_{gem} = 14.5, $J_{6'',7''}$ = 10.7, H6″), "W" coupling: $^{4}J_{2',6'}$ = 1.53; "U" coupling: $^{4}J_{6'',8'} \approx 1$ (broad) (Figures S22−S25, SI)	2.33 (2H, m, H7′ & H8′)	2.33 (2H, m, H7′ & H8′)	1.78 (3H, s, T-Me), 0.94 (3H, d, $J_{8',Me}$ = 7.5, 8′Me), 0.91 (3H, d, $J_{7',Me}$ = 6.6, 7′Me), 7.12 (1H, d, *J* = 1, H6-T′)
(T-4b)	5.33 (1H, dt, $J_{1',2'}$ = 9.6, $J_{1',7'}$ = 1.8, $J_{1',8'}$ = 2.4)	5.51 (1H, dt, $J_{1',2'}$ = 10.2, $J_{2',8'}$ = 2.4, $J_{2',7'}$ = 2.4)	5.86 (1H, s)	3.18 (1H, d J_{gem} = 9 Hz, H5′), 4.06 (1H, d, J_{gem} = 9, H5″)	1.88 (1H, dd, J_{gem} = 13.8, $J_{6',7'}$ = 6.6, H6′), 1.13 (1H, dd, J_{gem} = 13.8, $J_{6'',7''}$ = 7.8, H6″), "W" coupling: $^{4}J_{2',6'}$ = 0.61; "U" coupling: $^{4}J_{6',8'} \approx 0.5$ (broad) (Figures S33−S37, SI)	1.91 (1H, m)	2.14 (1H, m)	1.36 (3H, s, T-Me) 0.97 (3H, d, $J_{8',Me}$ = 7.8, 8′Me), 0.91 (3H, d, $J_{7',Me}$ = 6.5, 7′Me), 7.76 (1H, d, *J* = 1.2, H6-T′)
(A-5a)	5.37 (1H, dt, $J_{1',2'}$ = 10.38, $J_{1',7'}$ = 1.89, $J_{1',8'}$ = 2.21)	5.51 (1H, dt, $J_{1',2'}$ = 10.38, $J_{2',8'}$ = 1.58, $J_{2',7'}$ = 1.89)	5.98 (1H, s)	3.23 (2H, s, H5′, H5″)	2.03 (1H, dd, J_{gem} = 14.5, $J_{6',7'}$ = 4.5, H6′), 1.25 (1H, H6″), "W" coupling: $^{4}J_{2',6'}$ = 1.5; "U" coupling: $^{4}J_{6'',8'} \approx 1$ (broad) (Figures S45−S46, SI)	2.51 (2H, m, H7′/H8′)	2.51 (2H, m, H7′/H8′)	0.91 (6H, t $J_{8',Me}$ = 8, $J_{7',Me}$ = 6.6, 8′Me, 7′Me), 8.29 (1H, s, H2-A), 7.96 (1H, s, H8-A)
(A-5b)	5.37 (1H, dt, $J_{1',2'}$ = 9.5, $J_{1',7'}$ = 2.14, $J_{1',8'}$ = 2.44)	5.50 (1H, dt, $J_{1',2'}$ = 9.5, $J_{2',8'}$ = 2.44)	5.97 (1H, s)	3.23 (1H, d, J_{gem} = 9, H5′), 4.23 (1H, d, J_{gem} = 9, H5″)	1.78 (1H, dd, J_{gem} = 14.5, $J_{6',7'}$ = 5.5 Hz, H6′), 1.08 (1H, 1H, dd, J_{gem} = 14.5, $J_{6'',7''}$ = 7.5, H6″), "W" coupling: $^{4}J_{2',6'}$ = 0.9; "U" coupling: $^{4}J_{6'',8'} \approx$ 0.8 (broad) (Figures S54−S57, SI)	1.46 (1H, m)	2.24 (1H, m)	1.04 (3H, d, $J_{8',Me}$ = 7.5, 8′Me), 0.65 (3H, d, $J_{7',Me}$ = 7, 7′Me), 8.58 (1H, s, H8-A), 8.30 (1H, s, H2-A)

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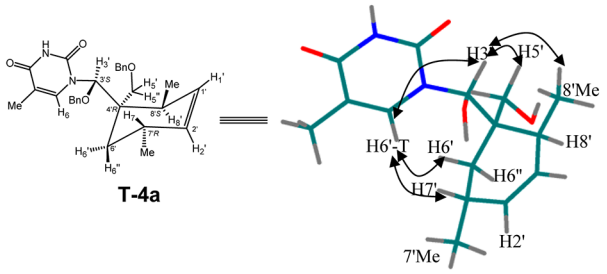
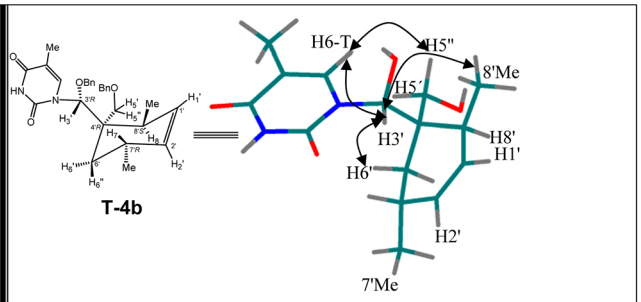
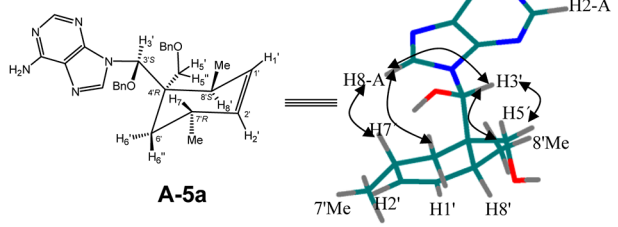
Table 2. Determination of Various Interproton Distances as Well as of Glycosyl Conformation Based on 1D nOe Experiments of Compounds T-4a/T-4b/A-5a and A-5b (Actual 1D nOe Experiments Have Been Summarized in SD_1)

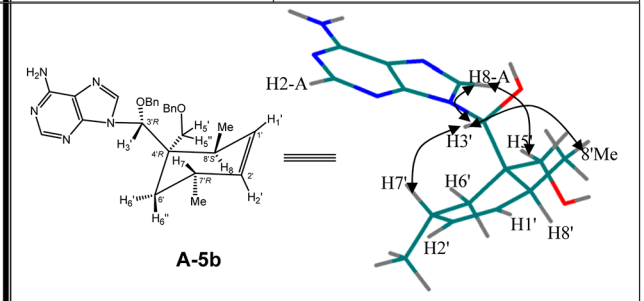




H3' Irradiation in (4a) /calc. distance/Observed nOe supporting the C3'(*S*) Configuration	H5' Irradiation in (4a) /distance/Observed nOe supporting the C3'(*S*) Configuration	H3' Irradiation in (4b) /distance/Observed nOe supporting the C3'(*R*) Configuration	H5' Irradiation in (4b) /distance/Observed nOe supporting the C3'(*R*) Configuration
$d_{H3',8'Me}$ = 2.2 Å, 4.1 %	$d_{H5',H3'}$ = 2.8 Å, 1.4 %	$d_{H3',8'Me}$ = 2.6 Å, 3.9 %	$d_{H5',8'Me}$ = 2.3Å, 2.3 %
$d_{H3',H5'}$ =2.8 Å, 1.7 %	$d_{H5',H8'}$ = 2.5 Å, 4.2 %	$d_{H3',H6'}$ = 3.2 Å, 2.4 %	$d_{H5',H6\text{-}T}$ = 2.5 Å, 1.8 %
$d_{H3',H5''}$ = 3.1 Å, 1.0 %	$d_{H5',8'Me}$ = 3.1 Å, 1.3 %	$d_{H3',H5''}$ = 3.7 Å, 0.3 %	$d_{H5',H3'}$ = 4.0Å, n.o
$d_{H3',H8'}$ = 3.5 Å, 1.9 %		$d_{H3',H6\text{-}T}$ = 3.6 Å, 0.7 %	$d_{H5',H8'}$ = 3.1 Å, 1.6 %
$d_{H3',CH2Ph}$ = 2.4 Å, 3.7 %		$d_{H3',CH2Ph}$ = 2.8 Å, 3.2 %	

H6'-T Irradiation in (4a) /calc. distance/Observed nOe	Glycosyl Conformation Assignment	H6'-T Irradiation in (4b) /distance/Observed nOe	Glycosyl Conformation Assignment
$d_{H6\text{-}T,H7'}$ = 2.1Å, 4.2 %	H6-T-*syn*-H7'	$d_{H6\text{-}T,H3'}$ = 3.6Å, 0.4 %	H6-T-*anti*-H3'
$d_{H6\text{-}T,H6'}$ = 2.3Å, 2.3%	H6-T-*syn*-H6'	$d_{H6\text{-}T,8'Me}$= 2.5Å, 2.2 %	H6-T-*syn*-8'Me
$d_{H6\text{-}T,H3'}$ = 3.6Å, 0.8 %	H6-T-*anti*-H3'	$d_{H6\text{-}T,H5'}$= 2.5Å, 1.4 %	H6-T-*syn*-H5'
$d_{H6\text{-}T,H5'}$ = 3.4Å, 1.0 %	H6-T-*anti*-H5'	$d_{H6\text{-}T,H7'}$ = 4.9Å, n.o	H6-T-*anti*-H7'





H3' Irradiation in (5a) /calc. distance/Observed nOe supporting the C3'(*S*) Configuration	H5' Irradiation in (5a) /distance/Observed nOe supporting the C3'(*S*) Configuration	H3' Irradiation in (5b) /distance/Observed nOe supporting the C3'(*R*) Configuration	H5' Irradiation in (5b) /distance/Observed nOe supporting the C3'(*R*) Configuration
$d_{H3',8'Me}$ = 2.2 Å, 3.7 %	$d_{H5',H3'}$ = 2.6 Å, 2.9 %	$d_{H3',8'Me}$ = 2.5 Å, 3.8 %	$d_{H5',8'Me}$ = 2.1 Å, 4 %
$d_{H3',H5'}$ = 2.6 Å, 2.2 %	$d_{H5',8Me'}$ = 3.2Å, 1.8%	$d_{H3',H5'}$ = 3.7 Å, n.o	$d_{H5',H3'}$ = 3.7Å, n.o
$d_{H3',H8\text{-}A}$ = 3.8 Å, 0.52 %	$d_{H5',H8'}$ = 2.8Å, 2.9%	$d_{H3',H6'}$ = 3.2 Å, 0.8 %	$d_{H5',H8'}$ = 2.9Å, 2.4%
$d_{H3',H8'}$ = 3.1 Å, 2.1 %		$d_{H3',H8'}$ = 3.8 Å, n.o	

H8'-A Irradiation in (5a) /calc. distance/Observed nOe	Glycosyl Conformation Assignment	H6'-T Irradiation in (5b) /distance/Observed nOe	Glycosyl Conformation Assignment
$d_{H8\text{-}A,H7'}$= 2.3 Å, 2.5 %	H8-A-*syn*-H7'	$d_{H8\text{-}A,H5'}$ = 2.8 Å, 1.8 %,	H8-A-*syn*-H5'
$d_{H8\text{-}A,H6'}$ = 2.4 Å, 1.8 %	H8-A-*syn*-H6'	$d_{H8\text{-}A,H6'}$ = 3.1 Å, 1.7 %	H8-A-*syn*-H6'
$d_{H8\text{-}A,H3'}$ = 3.8 Å, n.o	H8-A-*anti*-H3'	$d_{H8\text{-}A,H3'}$ = 3.8 Å, 0.9 %,	H8-A-*anti*-H3'

effect owing to the fact that they are spatially just under the nucleobase (see the nOe effect), which tentatively settles the configuration at C3′ to be (*S*). In addition, δ H7′ and δ H8′ have isochronous chemical shifts in **T-4a** (δ 2.33) and **A-5a** (δ 2.51),

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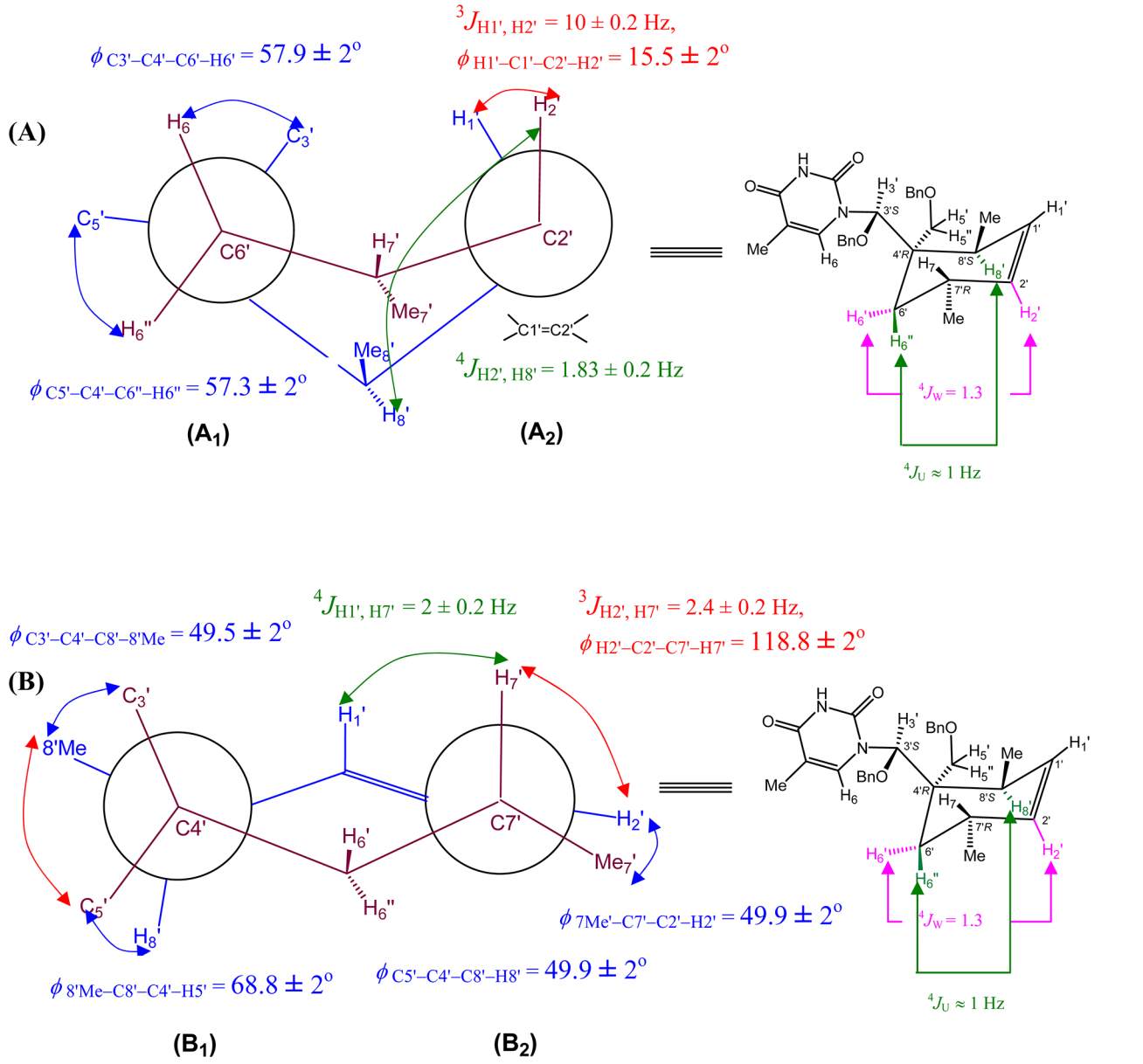

Figure 1. Panel A: Newman projections across the C1′−C2′ (A_2) and C4′−C6′ (A_1) bonds in **T-4a** are shown (for all other compounds, see Table S1 (SI) for coupling constants and corresponding dihedral angles). Projection A_2 through the C1′−C2′ bond shows an experimental $^3J_{H1',H2'}$ = 10 ± 0.2 Hz, giving torsion, $\phi_{H1'-C1'-C2'-H2'}$ = 15.5 ± 2°, and allylic, $^4J_{H2',\ H8'}$ = 1.83 ± 0.2 Hz, which in turn shows in projection A_1 that $\phi_{C3'-C4'-C6''-H6''}$ = 57.9 ± 2° and $\phi_{C5'-C4'-C6'-H6'}$ = 57.3 ± 2°. Panel B: Newman projections across the C7′−C2′ (A_2) and C4′−C8′ (A_1) bonds in **T-4a** are shown. Projection A_2 through the C2′−C7′ bond shows an experimental $^3J_{H2',H7'}$ = 2.4 ± 0.2 Hz, giving torsion, $\phi_{H2'-C2'-C7'-H7'}$ = 118.8 ± 2°, and allylic, $^4J_{H1',\ H7'}$ = 2 ± 0.2 Hz, which in turn shows in projection A_1 that the $\phi_{C3'-C4'-C8'-8'Me}$ = 49.5 ± 2°, $\phi_{8'Me-C8'-C4'-C5'}$ = 68.8 ± 2°, and $\phi_{C5'-C4'-C8'-H8'}$ = 49.9 ± 2°.

whereas the corresponding chemical shifts are relatively more dispersed in **T-4b** (δ 1.91 for H7′ and δ 2.14 for H8′) and **A-5b** (δ 1.46 for H7′ and δ 2.24 for H8′).

Our detailed NMR studies on all of these four compounds have allowed us to assign the chemical shift of each proton resonance and their *J*-coupled multiplicities (Table 1), which in turn have allowed us to ascertain steric proximities of each proton by detailed nOe studies. This information showed that the only difference between **T-4a** and **T-4b** isomers on one hand and **A-5a** and **A-5b**, on the other, arises from the configuration differences at the C3′ center. The detailed nOe studies have led us to assign 3′(*S*) configuration for **T-4a** and **A-5a** and 3′(*R*) configuration for **T-4b** and **A-5b**.

Since the NMR and nOe assignments are very closely similar for **T-4a** and **A-5a** and **T-4b** and **A-5b**, we restrict the discussion of our NMR observations and resulting arguments for unambiguous characterization only for pure **T-4a**, as an example, which also apply for the other compounds. Full NMR assignments for all of the other products (**T-4b**, **A-5a**, and **A-5b** in comparison with **T-4a**) are given in Table 1 based on actual spectra for all diastereomers of A and T which can be found in the SI.

*NMR of Compound Thyminylcyclohexen Derivative **T-4a**.*

(a) An important observation is the disappearance of a broad $^3J_{H2,H3} \approx 3$ Hz coupling constant between H2 and H3, found in the starting 1-mesyloxy-8,7-dimethylbicyclo-[2.2.1]heptane (**3**) and the appearance of a sharp singlet

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at δ 5.90 in the ^{1}H NMR spectrum (500 MHz) for H3′ in the product **T-4a** (Figure S14, SI): It should be noted that a *cisoid* orientation of H2 and H3 with $\phi_{[H2-C2-C3-H3]}$ of 60 ± 5° corresponds to a $^3J_{H2,H3} \approx 3$ Hz, whereas a *transoid* H2 and H3 corresponds to $\phi_{[H2-C2-C3-H3]}$ = 180 ± 5°, which corresponds to a $^3J_{H2,H3}$ = 11.16 ± 0.2 Hz. Since a clean singlet for H3′ is only observed (see SI), it clearly suggests that the vicinal H2′ is absent, which in turn leads us to conclude that there is no covalent carbon−carbon bond between C2′−C3′, thereby explaining the absence of vicinal $^3J_{H2',H3'}$ coupling.

(b) On the other hand, the absorption of H2′ was evident from its *J*-coupling with H1′, $^3J_{H1',H2'}$ = 10 ± 0.2 Hz corresponding to a torsion [$\phi_{H1'-C1'-C2'-H2'}$ = 15.5 ± 2°], suggesting a *cis* orientation between H1′ and H2′. These were further corroborated by the COSY spectrum (Figure S21, Panel A_1, SI) which showed a clear correlation between H1′ and H2′, but no correlation was found between H2′ and H3′.

(c) The presence of allylic H1′ and H7′ coupling [$^4J_{H1',H7'}$ = 2 ± 0.2 Hz] and also of the allylic H2′ and H8′ coupling [$^4J_{H2',H8'}$ of 1.83 ± 0.2 Hz], as evidenced by detailed decoupling experiments (Figure S23, SI), also shows the covalent connectivity in the backbone C8′(H)−C1′(H)═C2′(H)−C7′(H).

(d) The presence of a three-bond *J*-coupling between H6′ and H7′, $^3J_{H6',H7'}$ of 5.5 ± 0.2 Hz, [$\phi_{H6'-C6'-C7'-H7'}$ = 46 ± 2°], furthermore extends the backbone connectivity to C6′(H2′)−C7′(H)−C2′(H)═C1′(H)−C8′(H).

(e) Furthermore, we have observed two four-bond ″W″-couplings,[13] one between H2′ and H6′ ($^4J_{H2',H6'}$ = 1.53 Hz) (Figure S24, SI), as well as a ″U″-type coupling[14,15] between H6″ and H8′ ($^4J_{H6'',H8'} \approx 1$ Hz) (Figure S25, SI), thereby showing that H2′ and H6′ are oriented on the β-face, whereas H6″ and H8′ are on the α-face because the H6′−C6′−C7′ and C7′−C2′−H2′ fragments in the former and the H6″−C6′−C4′ and C4′−C8′−H8′ fragments in the latter are close to coplanar in an *anti*- and *cis*-arrangement in ″W″ and ″U″ orientation, respectively, which are prerequisites for proper orbital alignment for the HCCCH fragments. The latter ″U″-type coupling between H6″ and H8′ is particularly noteworthy because it simply shows that the C4′ center is part of the cyclohexene ring. Furthermore, the large allylic H2′−C2′═C1′−C8′−H8′ coupling of 1.83 ± 0.2 Hz as well as the allylic H1′−C1′═C2′−C7′−H7′ coupling of 2 ± 0.2 Hz show that both allylic C−H bonds are perpendicular to the plane of the vinyl C−H group in the C1′═C2′ double bond, which altogether suggests that C6′−C4′−C8′−C1′−C2′−C7′ constitutes a closed conformationally constrained cyclohexene ring in **T-4a**.

(f) The long-range ^{13}C−^{1}H connectivities (HMBC) of H3′ with C6-T and C2═O(T) (Figure S21, Panel A_3, SI) confirm that the 1-thyminyl has formed a covalent bond from its N1 to C3′ of the cyclohexene ring, as shown in **T-4a**. On the other hand, the ^{1}H−^{13}C correlation in the HMQC spectrum shows the connection between H1′ and C1′ at δ 130.6 as well as between H2′ and C2′ at δ 131.6 (Figure S21, Panel A_4, SI), thereby confirming the presence of the olefinic bond, C1′═C2′, as in compound **T-4a**.

(g) pH-dependent UV studies corroborated the presence of an N1 attached base since the UV spectra of neither **T-4a** nor **T-4b** showed the bathochromic shift of the absorption maxima expected for N3-alkylated pyrimidinones upon increase of the pH[16] (Figure S27, SI).

*(1.4). Determination of C3′ Configuration in Diastereomeric 1-(Benzyloxy(4-benzyloxymethyl-7,8-dimethylcyclohex-1-en-4-yl)methyl)thymine (**T-4a** and **T-4b**), 9-(Benzyloxy-(4-benzyloxymethyl-7,8-dimethylcyclohex-1-en-4-yl)methyl)-adenine (**A-5a** and **A-5b**), and Glycosyl Conformation Assignment Through nOe Analysis.* The stereochemistries of all chiral centers in compounds **T-4a**, **T-4b** and **A-5a**, **A-5b** have been determined by 1D nOe experiments which have been summarized in Table 2. The detailed procedure, results, and discussions of 1D nOe experiments can be however found in the SI (see discussions for the nOe assignments under SD_1 based on Figures S26, S38, S47, and S58).

1.5. Determination of Dihedral Angles through Analysis of Three-Bond $^3J_{HH}$ by the Karplus Equation and the Newman Projection for Rearranged Products. Since there are no vicinal protons in the proximity of H3′, and it resonates as a singlet, thereby proving the cleavage of the C2′−C3′ bond. On the basis of the key observable *J*-coupling network, we describe here a general proton−proton torsional framework, which is very closely similar to all diastereomers (**T-4a**/**T-4b**/**A-5a** and **A-5b**) using the Newman projection, taking compound **T-4a** as an example, whereas the individual *J*-coupling network and the corresponding dihedral angles for each of the isomers (**T-4b**, **A-5a** and **A-5b**) are shown in Table S1 (SI) (for comparison), including the Newman projections (Figure S22−S24, S33−S35, and S45−S46, SI). In rearranged compound **T-4a**, the Newman projections across the C1′−C2′ (projection A_2) and C4′−C6′ (projection A_1) are shown (Figure 1, Panel A). The experimentally derived $^3J_{H1',H2'}$ = 10 ± 0.2 Hz gives the dihedral angle for the corresponding torsion, $\phi_{H1'-C1'-C2'-H2'}$ = 15.5 ± 2°, and the allylic H2′ and H8′ coupling $^4J_{H2',H8'}$ of [$^4J_{H2',H8'}$ = 1.83 ± 0.2 Hz]. With these torsion angles fixed, we could calculate the other significant torsions through modeling in HyperChem (MM/Amber and semiempirical/AM1) which in turn shows through projection A_1 that the $\phi_{C3'-C4'-C6'-H6'}$ = 57.9 ± 2° and $\phi_{C5'-C4'-C6'-H6''}$ = 57.3 ± 2°. In addition, projection B shows the Newman projection across the C7′−C2′ (projection B_2 in Figure 1) and C4′−C8′ (projection B_1 in Figure 1) bonds. The experimentally derived $^3J_{H2',H7'}$ = 2.4 ± 0.2 Hz, which gives the dihedral angle for the corresponding torsion, $\phi_{H2'-C2'-C7'-H7'}$ = 118.8 ± 2°, and the allylic H2′ and H8′ coupling [$^4J_{H2',H8'}$ = 1.83 ± 0.2 Hz]. So, with these torsion angles fixed, we could successfully calculate the other torsions through projection B_1 that the $\phi_{C3'-C4'-C8'-8'Me}$ = 49.5 ± 2°, $\phi_{8'Me-C8'-C4'-C5'}$ = 68.8 ± 2°, and $\phi_{C5'-C4'-C8'-H8'}$ = 49.9 ± 2°.

Mechanism. Since the above NMR, UV, and mass characterizations show that in each of the reactions two diastereomers at the C3′ position are formed, we have performed two sets of blank experiments to examine the origin of intramolecular isomerization:

1. Treatment of pure **T-4a** or **A-5a** in an identical basic condition (i.e., NaH in dry DMF, reflux for 24 h under N_2), followed by usual workup, as used for **3** → **T-4a** + **T-4b** or **3** → **A-5a** + **A-5b**, gave us a full recovery of starting material **T-4a** or **A-5a** without any contamination by other isomers **T-4b** or **A-5b**. This suggests that no racemization took place at C3′ after the nucleophilic ring-opening reaction.

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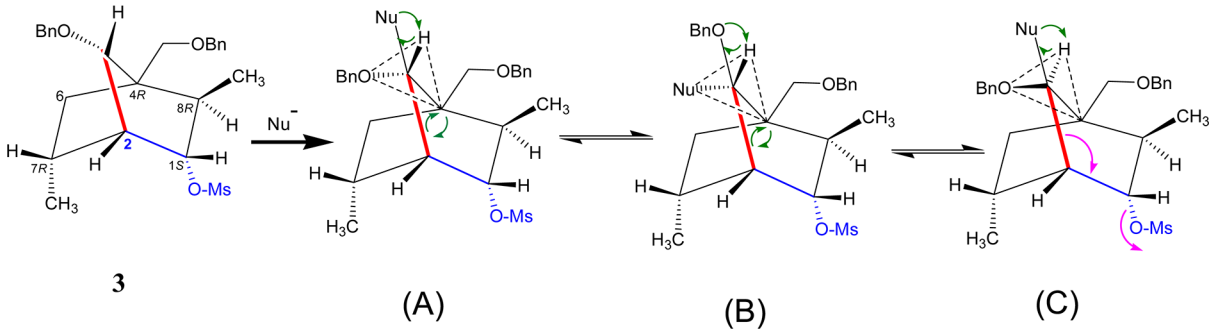

Figure 2. Mechanistic rationale for the S_N2 transition state, in which, upon nucleophilic attack at C3′ in compound **3** a putative trigonal bipyramidal intermediate (A) is formed. The C2′−C3′ bond breaking is slower than the pseudorotation of the resulting pentavalent carbon in the transition state (A) because of distorted geometry across C2−C3−C4 bonds, leading to scrambling at the chiral C3′ center (B). When the Nu⁻···C3···C2 bond forms "in-line attack" geometry, i.e., 180° bond angle, the scission of the departing C2′−C3′ bond takes place with the scrambled chirality at C3′ to give racemic mixtures, **T-4a** + **T-4b** or **A-5a** + **A-5b**.

2. Treatment of 1-mesyloxy-8,7-dimethylbicyclo[2.2.1]-heptane (**3**) in an identical basic condition (i.e., NaH in dry DMF, reflux for 24 h under N_2), but in the absence of adenine or thymine, followed by usual workup, as used for **3** → **T-4a** + **T-4b** or **3** → **A-5a** + **A-5b**, did not give the expected *anti*−*endo* 1,2-elimination product at C1−C8, since no *syn*−*exo* product is possible in our system, as in **3**. Noteworthy is also the fact that no other product was formed in the above reaction, thereby ruling out any carbocation intermediate after fragmentation. The absence of any 1,2-elimination product is not perhaps surprising in view of the fact that there is only one report[12a] of base-promoted 1,2-elimination for *endo*-2-bicyclo[2.2.1]heptyl halides and sulfonates, in which: (i) no methyl substituent was present on either of the carbons involved in the elimination reaction!; (ii) a strong soluble base *t*-BuOK in DMSO or triglyme was used at a high temperature;[12a] (iii) since the 8-Me substituent in our system in compound **3** is *exo*, as evident from the nOe contacts as well as from the $^3J_{H1,H8} = 4.8 \pm 0.2$ Hz (Figure S7, SI) corresponding to a *transoid* torsion for $\phi_{H1-C1-C8-H8}$ of 132 ± 2°, the H8 on the C8 center is sterically hindered for a potential 1,2-elimination reaction in our chemical framework, as in **3**. This means, first, the conjugate base of 1-thyminyl (i.e., T^-) or 9-adeninyl (i.e., A^-) formed under our reaction condition, which attacks at C3′ as a nucleophile to give the trigonal−bipyramidal intermediate, and, second, the cleavage of the most strained C2−C3 bond takes place. It is clear that the trigonal bipyramidal intermediate for carbon is well-known for its stereochemical rigidity and high inversion barrier and that the bond breaking has always been assumed to take place before any inversion.[17a,b] We may have however a unique case here in that we have observed full recovery of starting material in all of our starting molecules with their chiral centers intact, i.e., either from **3** or **T-4a** or **T-4b** or **A-5a** or **A-5b**, which means that in the *absence* of T^- or A^- in the reaction mixture *no* racemization event takes place under the present alkaline reaction conditions.

Clearly, given the above facts, it is likely that after the attack of T^- or A^- at the C3 carbon center we have a trigonal−bipyramidal intermediate, in which the racemization at C3 is likely to have taken place through the formation of a species,[17a,b] which does not have a chiral center any longer with a low energy barrier of intramolecular exchange (rearrangement)[17d] with "sufficient lifetime" relative to dissociation of the C2−C3 bond to give the pair of diastereomers at C3.[17a] The nucleophilic attack takes place from the apical position to form the trigonal bipyramidal intermediate (A) in which the departing C2−C3 bond takes up only a distorted apical geometry which prevents an actual bond breaking process from taking place because of the angular strain through the C2−C3−C4 bonds (Figure 2). This in turn initiates shape changes to take place just as in the trigonal bipyramidal shaped pentavalent phosphorus compounds, in which two equatorial groups become apical and two apical groups become equatorial because of the low energy barrier, through a concerted shortening of apical bonds and lengthening of equatorial bonds until the leaving group takes up an apical position. This means that the bond-breaking process involving the departing C2−C3 bond is slower than the inversion, and the relatively lower inversion barriers of substituents make the interconversions possible. So far, unlike other second and higher row elements which show higher coordination number, carbon has been assumed[17c] to have the stereochemical rigidity and high inversion barrier for substituent rearrangement in the transition state of a trigonal bipyramidal geometry resisting any displacement.[17a−c] The present scrambling of chirality during the base-induced rearrangement provides further evidence supporting some recent work on the hypervalent carbon atom in the context of the rigid, ball-in-a-box model in the S_N2 transition state,[17e] penta- and hexacoordinated carbon by experimental electron density distribution analysis,[17f] as well as some other theoretical and experimental evidence that points to the transient formation of pentavalent carbon.[17g]

■ CONCLUSIONS

An unusual nucleophilic substitution at the chiral C3 leads to the release of angular strain of C2−C3−C4 bonds (with bond angle 94°) of conformationally locked 1-mesyloxy-8,7-dimethylbicyclo[2.2.1]heptane (**3**). The nucleophilic attack at the C3 leads to *anti*−*endo* 1,2-elimination of the C1-mesyloxy group by the conjugate base of adenine or thymine to give two diastereomeric C3′(*S*) and C3′(*R*) derivatives of 1-thyminyl and 9-adeninyl cyclohexene: **3** → **T-4a** + **T-4b** and **3** → **A-5a** + **A-5b**. These products have been unambiguously characterized by detailed 1D and 2D NMR (*J*-resolved coupling constants and nOe analysis), mass, and UV spectroscopy. The origin of these diastereomeric C3′(*S*) and C3′(*R*) derivatives of 1-thyminyl and 9-adeninyl cyclohexene from **3** has been traced to a plausible

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rearrangement mechanism of the trigonal bipyramidal intermediate formed in the S_N2 displacement−ring-opening reaction.

EXPERIMENTAL SECTION

General Procedures. All reagents were the highest commercial quality and were used without further purification. All nonaqueous 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 as visualizing agent and/or cerium−ammonium−molybdate. Flash chromatography was performed using silica gel 60 (230−400 mesh). ^{1}H and ^{13}C NMR were obtained using 500 and 600 MHz instruments for ^{1}H and 125 and 150 MHz for ^{13}C. The same spectrometers were used for the acquisition of the ^{1}H−^{1}H homonuclear (COSY and nOe) and ^{1}H−^{13}C heteronuclear (HMQC and HMBC) correlations. Optical rotations were recorded on a polarimeter, and values are reported as follows: $[\alpha]_\lambda^T$ (c (g/100 mL), solvent). The molecular modelings have been performed using HyperChem Pro 6.0[18] using MM (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 have been obtained using the Karplus equation[19] through the coupling constants (NMR data) input, whereas HyperChem was used where no coupling constant could be obtained. High-resolution mass spectra (HRMS) with correct masses have been obtained by MALDI-TOF mass spectroscopy.

(1*S*,2*R*,3*S*,4*R*,7*R*,8*R*)-3-(Benzyloxy)-4-[benzyloxymethyl]-1-hydroxyl-8,7-dimethylbicyclo[2.2.1]heptane (2). Compound **1** (100 mg, 0.20 mmol) was dissolved in 6 mL of dichloromethane and 2% of trifluoroacetic acid. The solution was stirred at rt for 2 h, and then it was neutralized with 0.05 mL of Et_3N. Solvent was evaporated, and the concentrate was purified by silica gel column chromatography (0−15% EtOAc in petroleum ether, v/v) to give compound **2** as a colorless oil (50.2 mg, 71%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18−7.23 (10H, m, aromatic), 4.38 (3H, ABq, J_{gem} = 12 Hz, CH_2Ph), 4.27 (1H, d, J_{gem} = 12 Hz, CH_2Ph), 3.61 (1H, m, H1), 3.49 (1H, d, J_{gem} = 9 Hz, H5), 3.41 (1H, d, J_{gem} = 9 Hz, H5′), 3.40 (1H, d, $J_{3,2}$ = 3.5 Hz, H3), 2.46 (1H, m, H7), 2.20 (1H, t, $J_{1,2}$ = 3 Hz, $J_{2,3}$ = 3.5 Hz, H2), 2.11 (1H, t, J_{gem} = 11.5 Hz, H6), 1.48 (1H, m, H8), 1.23 (3H, d, J = 7.5 Hz, 7-CH_3), 1.13 (1H, dd, J_{gem} = 12 Hz, $J_{6,7}$ = 5.5 Hz, H6′), 0.94 (3H, d, J = 7.0 Hz, 8-CH_3). ^{13}C NMR (125 MHz): δ 138.8, 128.3, 128.2, 127.5, 127.4, 127.1 (aromatic), 84.0 (C3), 81.1 (C1), 73.4 (CH_2Ph), 71.2 (CH_2Ph), 70.8 (C5), 53.5 (C4), 48.7 (C2), 47.3 (C8), 42.1 (C6), 31.2 (C7), 18.4 (7-CH_3), 13.6 (8-CH_3). MALDI-TOF m/z [M + Na]$^+$ calcd for $C_{24}H_{30}O_3$ Na 389.209, found 389.208.

(1*S*,2*R*,3*S*,4*R*,7*R*,8*R*)-3-(Benzyloxy)-4-[benzyloxymethyl]-1-mesyloxy-8,7-dimethylbicyclo[2.2.1]heptane (3). Compound **2** (50 mg, 0.14 mmol) was dissolved in dry pyridine (2 mL). Methanosulfonyl chloride (16.2 μL, 0.21 mmol) was added at 0 °C. The reaction was stirred at room temperature for 1 h. The reaction mixture was partitioned between EtOAc and H_2O. The organic layer was washed with brine twice and dried over $MgSO_4$, filtered, and concentrated.

The concentrate was purified by silica gel column chromatography (0−10% EtOAc/petroleum ether, v/v) to give **3** as a colorless oil (53 mg, 82%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.18−7.24 (15H, m, aromatic), 4.37 (3H, m, J_{gem} = 12 Hz, CH_2Ph, H1), 4.27 (1H, d, J_{gem} = 12 Hz, CH_2Ph), 3.47 (1H, bs, $J_{2,3} \approx$ 3 Hz, H3), 3.48 (1H, d, J_{gem} = 9 Hz, H5), 3.41 (1H, d, J_{gem} = 9 Hz, H5′), 2.93 (3H, s, Me), 2.53 (1H, m, H7), 2.50 (1H, t, H2), 2.12 (1H, t, J_{gem} = 11.4 Hz, H6), 1.80 (1H, t, $J_{1,8}$ = 5.4 Hz, H8), 1.18 (3H, d, J = 7.2 Hz, 7-CH_3), 1.14 (1H, dd, J_{gem} = 12 Hz, $J_{6',7}$ = 6.6 Hz, H6′), 0.99 (3H, d, J = 7.2 Hz, 8-CH_3). ^{13}C NMR (150 MHz): δ 138.9, 138.6, 128.8, 128.7, 128.0, 127.9, 127.6 (aromatic), 87.9 (C1), 83.3 (C3), 73.8 (CH_2Ph), 71.8 (CH_2Ph), 70.6 (C5), 53.5 (C4), 48.1 (C2), 44.9 (C8), 42.0 (C6), 38.6 (CH_3-Ms), 31.4 (C7), 18.3 (7-CH_3), 16.7 (8-CH_3). MALDI-TOF m/z [M + Na]$^+$ calcd for $C_{25}H_{32}O_5$ SNa 467.187, found 467.188.

1-((4*R*,7*R*,8*S*)-(*S*)-Benzyloxy-(4-benzyloxymethyl-7,8-dimethylcyclohex-1-en-4-yl)methyl)-thymine (T-4a) and 1-((4*R*,7*R*,8*S*)-(*R*)-Benzyloxy-(4-benzyloxymethyl-7,8-dimethylcyclohex-1-en-4-yl)methyl)-thymine (T-4b). The compound **3** (20 mg, 45 μmol) was dissolved in anhydrous *N*,*N*-dimethylformamide (2 mL) and thymine (34.0 mg, 0.27 mmol), and NaH (9.6 mg, 0.4 mmol) was added at room temperature. The reaction was stirred at 150 °C for 24 h. The mixture was dissolved in EtOAc and H_2O and washed with brine twice. The organic layer was separated, dried over $MgSO_4$, and concentrated. The crude product was chromatographed over silica gel (0−40% EtOAc in petroleum ether, v/v) to give compound **4** as a colorless oil (11.1 mg, 52%) as a separable mixture of **T-4a** (5.5 mg, 26%) and **T-4b** (5.5 mg, 26%).

T-4a: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (1H, bs, NH), 7.12−7.21 (14H, m, aromatic), 7.12 (1H, d, J = 1 Hz, H6-T), 5.90 (1H, s, H3′), 5.47 (1H, dt, $J_{1',2'}$ = 10 Hz, $J_{H2',\ H7'}$ = 2.4, $^4J_{H2',\ H8'}$ = 1.83, H2′), 5.32 (1H, dt, $J_{1',2'}$ = 10 Hz, $J_{H1',\ H8'}$ = 2.5, $J_{1',7'}$ = 2 Hz, H1′), 4.40 (1H, d, J_{gem} = 12 Hz, CH_2Ph), 4.34 (1H, d, J_{gem} = 12 Hz, CH_2Ph), 4.28 (2H, d, J_{gem} = 12 Hz, CH_2Ph), 3.39 (1H, d, J_{gem} = 9.5, H5′), 3.23 (1H, d, J_{gem} = 9.5, H5″), 2.33 (2H, m, H7′ & H8′), 2.03 (1H, dd, J_{gem} = 14.5, $J_{6',7'}$ = 5.5, H6′), 1.78 (3H, s, T-CH_3), 1.21 (1H, dd, J_{gem} = 14.5, $J_{6'',7'}$ = 10.7, H6″), 0.94 (3H, d, $J_{8',Me}$ = 7.5, 8′-CH_3), 0.91 (3H, d, $J_{7',Me}$ = 6.6, 7′-CH_3). ^{13}C NMR (125 MHz): δ 163.2 (C4-T), 151.4 (C2-T), 138.0 (C6-T), 137.3, 136.6 (aromatic), 131.6 (C2′), 130.6 (C1′), 128.4, 128.3, 127.9, 127.6, 127.4, 127.2 (aromatic), 109.7 (C5-T), 87.6 (C3′), 74.9 (C5′), 73.3 (CH_2Ph), 71.4 (CH_2Ph), 45.2 (C4′), 35.6 (C8′), 35.1 (C6′), 28.4 (C7′), 22.2 (8′-CH_3), 15.4 (7′-CH_3), 12.7 (T-CH_3). MALDI-TOF m/z [M + Na]$^+$ calcd for $C_{29}H_{34}N_2O_4$ Na 497.242, found 497.242.

T-4b: ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.08 (1H, bs, NH), 7.76 (1H, d, J = 1.2 Hz, H6-T), 7.17−7.27 (14H, m, aromatic), 5.86 (1H, s, H3′), 5.51 (1H, dt, $J_{1',2'}$ = 10.2 Hz, $J_{H2',\ H7'}$ = 2.4, $^4J_{H2',\ H8'}$ = 2.4, H2′), 5.33 (1H, dt, $J_{1',2'}$ = 10.2 Hz, $^3J_{H1',\ H8'}$ = 2.4, $J_{1',7'}$ = 1.8 Hz, H1′), 4.47 (1H, d, J_{gem} = 12 Hz, CH_2Ph), 4.37 (2H, ABq, J_{gem} = 12 Hz, CH_2Ph), 4.25 (2H, d, J_{gem} = 12 Hz, CH_2Ph), 4.06 (1H, d, J_{gem} = 9 Hz, H5′), 3.18 (1H, d, J_{gem} = 9 Hz, H5″), 2.14 (1H, m, H8′), 1.9 (1H, m, H7′), 1.88 (1H, dd, J_{gem} = 13.8, $J_{6',7'}$ = 6.6, H6′), 1.36 (3H, s, T-CH_3), 1.13 (1H, dd, J_{gem} = 13.8, $J_{6'',7'}$ = 7.8, H6″), 0.97 (3H, d, $J_{H8',Me}$ = 7.8 Hz, 8′-CH_3), 0.91 (3H, d, $J_{H7',Me}$ = 6.5 Hz, 7′-CH_3). ^{13}C NMR (150 MHz): δ 163.2 (C4-T), 152.4 (C2-T), 139.4 (C6-T), 132.2 (C2′), 129.5 (C1′), 132.2, 129.5, 128.4, 127.9, 127.8, 127.6, 127.5 (aromatic), 109.5 (C5-T), 86.5 (C3′), 73.5 (CH_2Ph), 73.3 (C5′), 70.7 (CH_2Ph), 45.7 (C4′), 36.2 (C8′), 34.3 (C6′), 27.1 (C7′), 22.2 (7′-CH_3), 16.4 (8′-CH_3), 11.9 (T-CH_3). MALDI-TOF m/z [M+Na]$^+$ calcd for $C_{29}H_{34}N_2O_4$ Na 497.242, found 497.243.

9-((4*R*,7*R*,8*S*)-(*S*)-Benzyloxy-(4-benzyloxymethyl-7,8-dimethylcyclohex-1-en-4-yl)methyl)-adenine (A-5a) and 9-((4*R*,7*R*,8*S*)-(*R*)-Benzyloxy-(4-benzyloxymethyl-7,8-dimethylcyclohex-1-en-4-yl)methyl)-adenine. Compound **3** (20 mg, 45 μmol) was dissolved in anhydrous *N*,*N*-dimethylformamide (2 mL) and adenine (36.0 mg, 0.27 mmol), and NaH (9.6 mg, 0.4 mmol) was added at room temperature. The reaction was stirred at 150 °C for 24 h. The mixture was dissolved in EtOAc and H_2O and washed with brine twice. The organic layer was separated, dried over $MgSO_4$, and concentrated. The crude product was chromatographed over silica gel (0−70% EtOAc in petroleum ether, v/v) to give compound **5** as a colorless oil (10.9 mg, 50%) as a separable mixture of **A-5a** (5.45 mg, 25%) and **A-5b** (5.45 mg, 25%).

A-5a: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (1H, s, H2-A), 7.96 (1H, s, H8-A), 7.01−7.20 (15H, m, aromatic), 5.98 (1H, s, H3′), 5.69 (2H, bs, NH_2), 5.51 (1H, dt, $J_{1',2'}$ = 10.38, Hz, $J_{2',8'}$ = 1.58 Hz, $J_{2',7'}$ = 1.89 Hz, H2′), 5.37 (1H, dt, $J_{1',2'}$ = 10.38 Hz, $J_{1',7'}$ = 1.89 Hz, $J_{1',8'}$ = 2.21 Hz, H1′), 4.30 (1H, d, J_{gem} = 11.5 Hz, CH_2Ph), 4.26 (1H, d, J_{gem} = 11.5 Hz, CH_2Ph), 4.16 (1H, d, J_{gem} = 12 Hz, CH_2Ph), 4.03 (1H, d, J_{gem} = 12 Hz, CH_2Ph), 3.23 (2H, s, H5′, H5″), 2.51 (2H, m, H7′ & H8′), 2.03 (1H, dd, J_{gem} = 14.5, $J_{6',7'}$ = 4.5, $^4J_{2',6'}$ = 1.5, H6′), 1.25 (1H, H6″), 0.91 (6H, t, $J_{8',Me}$ = 8, $J_{7',Me}$ = 6.6, 8′-CH_3, 7′-CH_3). ^{13}C NMR (125 MHz): δ 155.2 (C6-A), 152.6 (C2-A), 140.9 (C8-A), 138.3, 136.9 (aromatic), 132.2 (C2′), 131.3 (C1′), 128.6, 127.9, 127.7, 127.1, 127.6, 127.2 (aromatic), 87.6 (C3′), 75.2 (C5′), 73.7 (CH_2Ph), 71.5 (CH_2Ph), 45.5 (C4′), 36.0 (C6′), 35.6 (C8′), 30.0 (C7′), 28.6 (7′-CH_3), 15.9 (8′-CH_3). MALDI-TOF m/z [M + H]$^+$ calcd for $C_{29}H_{34}N_5O_2$ 484.271, found 484.271.

A-5b :^{1}H NMR (500 MHz, $CDCl_3$): δ 8.58 (1H, s, H8-A), 8.30 (1H, s, H2-A), 7.15−7.22 (15H, m, aromatic), 6.16 (2H, bs, NH_2), 5.97 (1H,

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s, H3′), 5.50 (1H, dt, $J_{1',2'}$ = 9.5 Hz, $^4J_{2',8'}$ = 2.44 Hz, H2′), 5.37 (1H, dt, $J_{1',2'}$ = 9.5 Hz, $J_{1',7'}$ = 2.14 Hz, $J_{1',8'}$ = 2.44 Hz, H1′), 4.53 (2H, s, CH_2Ph), 4.42 (1H, d, J_{gem} = 11.5 Hz, CH_2Ph), 4.23 (1H, d, J_{gem} = 9.5, H5′), 3.92 (1H, d, J_{gem} = 11.5 Hz, CH_2Ph), 3.23 (1H, d, J_{gem} = 9.5, H5″), 2.24 (1H, m, H8′), 1.78 (1H, dd, J_{gem} = 14.5, $J_{6',7'}$ = 5.5, $^4J_{2',6'}$ = 0.9, H6′), 1.46 (1H, m, H7′), 1.08 (1H, dd, J_{gem} = 14.5, $J_{6',7'}$ = 7.5, H6″), 1.04 (3H, d, $J_{8',Me}$ = 7.5, 8′-CH_3), 0.65 (3H, d, $J_{8',Me}$ = 7, 7′-CH_3). ^{13}C NMR (125 MHz): δ 151.1 (C2-A), 144.0 (C8-A), 132.6 (C2′), 129.8 (C1′), 128.5, 128.2, 127.8, 127.7, 127.3 (aromatic), 85.3 (C3′), 73.6 (C5′), 70.7 (CH_2Ph), 45.4 (C4′), 37.1 (C8′), 36.2 (C6′), 26.8 (C7′), 21.9 (7′-CH_3), 16.9 (8′-CH_3). MALDI-TOF m/z $[M + H]^+$ calcd for $C_{29}H_{34}N_5O_2$ 484.271, found 484.270.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H, ^{13}C NMR, COSY, HMQC, and HMBC spectra for compounds **2**, **3**, **T-4a**, **T-4b**, **A-5a**, and **A-5b** (SI); ^{1}H-homodecoupling for compounds **T-4a**, **T-4b**, **A-5a**, and **A-5b**; 1D nOe spectra for compounds **2** and $^3J_{HH}$ vicinal coupling constant of compounds **T-4a**, **T-4b**, **A-5a**, and **A-5b** along with Newman projections of these compounds; molecular structures based on MM and semiempirical calculations for compounds **T-4a**, **T-4b**, **A-5a**, and **A-5b**. UV spectra of compound **T-4a**, **T-4b**, **A-5a**, and **A-5b** in various pH. 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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