JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

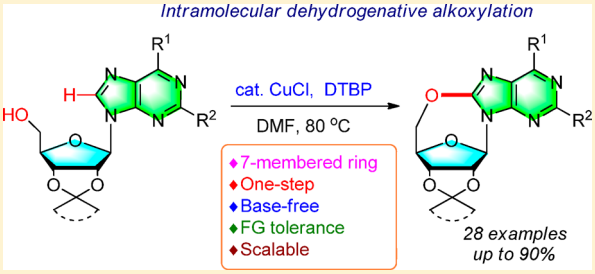
Copper-Catalyzed Intramolecular Alkoxylation of Purine Nucleosides: One-Step Synthesis of 5′-*O*,8-Cyclopurine Nucleosides

Mingwu Yu, Zhiqian Wang, Junbin Hu, Shunlai Li, and Hongguang Du*

Faculty of Science, Beijing University of Chemical Technology, Beijing 100029, People's Republic of China

Supporting Information

ABSTRACT: A novel copper-catalyzed intramolecular dehydrogenative alkoxylation of purine nucleosides has been developed successfully, providing the 5′-*O*,8-cyclopurine nucleosides in one-step with a yield up to 90%. The method, which utilized an inexpensive CuCl catalyst and a di-*tert*-butyl peroxide (DTBP) oxidant was suitable in a broad substrate scope and proceeded well even in gram scale.



INTRODUCTION

5′-*O*,8-Cyclopurine nucleosides with an additional large seven-membered ring between the sugar ring and the purine base through a C−O−C bridge have attracted increasing attention from medicinal and synthetic chemists for their variety of potential bioactivities, such as antiplatelet aggregation,[1] rhodopsin kinase nucleoside inhibition,[2] and equilibrative nucleoside transporter 1 (ENT1) inhibition[3] (Figure 1). Due

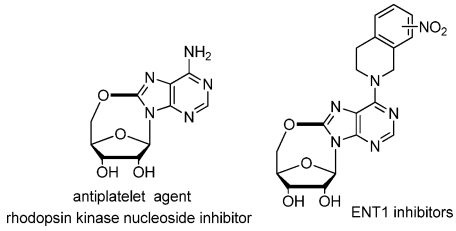
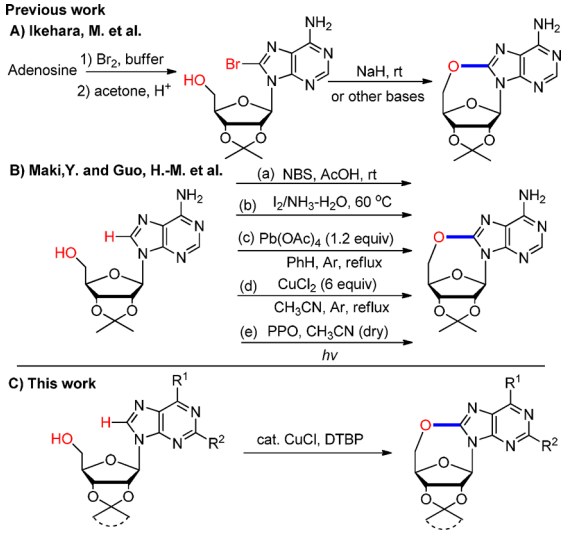


Figure 1. Selected examples of 5′-*O*,8-cyclopurine nucleosides with bioactivities.

to their unique molecular structure, these cyclopurine nucleosides were also an essential tool for nucleoside conformational studies and key intermediates in the synthesis of the heterocyclic moieties of nucleosides.[4]

Despite 5′-*O*,8-cyclopurine nucleosides playing important roles in biological and synthetic areas, the synthetic approaches are still limited to date. One of the most used methods is intramolecular nucleophilic substitution of 8-bromo-2′,3′-*O*-isopropylidenepurine nucleosides (Scheme 1, route A), but multiple steps were involved, and strong bases were required.[5] The cyclization of 2′,3′-*O*-isopropylidenepurine nucleosides by oxidation with I_2−NH_3,[6] NBS−AcOH,[7] or stoichiometric amounts of Lewis acid, such as lead tetraacetate[8] and cupric chloride[9] could be alternative methods for the synthesis of 5′-*O*,8-cyclopurine nucleosides (Scheme 1, route B, a−d). Although the substrate scope was very narrow, the photo-

Scheme 1. Strategies for Synthesis of 5′-*O*,8-Cyclopurine Nucleosides



chemical oxidation of 2′,3′-*O*-isopropylidenepurine nucleosides with pyrimido[5,4-*g*]pteridinetetraone N-oxide (PPO) could also lead to the corresponding 5′-*O*,8-cyclopurine nucleosides[10] (Scheme 1, route B, e). Thus, the development of a more efficient route to synthesize 5′-*O*,8-cyclopurine nucleosides is quite necessary but challenging.

Till now, various transition-metal-catalyzed C−H functionalization/C−O cyclizations have been a powerful tool for constructing intramolecular C−O bonds in synthetic chemistry.[11] To our best knowledge, transition-metal-catalyzed intramolecular alkoxylation is still unexplored for purine

Received: June 16, 2015
Published: September 4, 2015

DOI: 10.1021/acs.joc.5b01360
J. Org. Chem. 2015, 80, 9446−9453

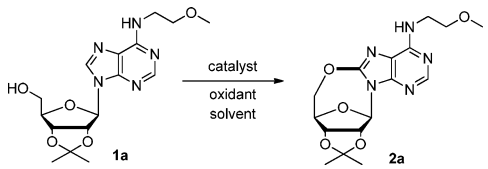
nucleosides. Herein, we will report a novel copper-catalyzed intramolecular alkoxylation of purine nucleosides to construct the additional large seven-membered ring between the 5′-OH group and the 8-C atom, which provides an efficient one-step method to synthesize 5′-*O*,8-cyclopurine nucleosides under neutral conditions (Scheme 1, route C).

RESULTS AND DISCUSSION

The synthesis study was first carried out with 2′,3′-*O*-isopropylidene-6-(2-methoxyethyl)aminoadenosine, **1a**, in the presence of $CuCl_2$ (0.1 equiv) and di-*tert*-butyl peroxide (DTBP; 2 equiv) in CH_3CN at 80 °C (Table 1, entry 1). To our delight, the desired 5′-*O*,8-cycloadenosine derivative **2a** was successfully obtained in a yield of 41%. Then replacing the catalyst $CuCl_2$ with other metal salts (Table 1, entries 2−6) showed that other first-row transition metal chlorides ($CoCl_2$, $NiCl_2$) could not promote the alkoxylation (Table 1, entries 2−3) but CuCl (Table 1, entry 4) was the most effective catalyst. Because the oxidant was very important to the transition-metal-catalyzed alkoxylation reaction, we tried other various oxidants (THBP, BPO, $K_2S_2O_8$, etc.), and the results indicated that DTBP was still the best oxidant (Table 1, entries 7−11). After identifying the catalyst and oxidant, the effect of solvents was next tested, and the results showed that DMF was more effective than the other solvents including dichloroethane (DCE), 1,4-dioxane, toluene, and CH_3CN (Table 1, entries 4 and 12−15). After screening the ratio of DTBP and CuCl, we successfully found that the best yield of **2a** was obtained by employing 0.5 equiv of CuCl and 3 equiv of DTBP in DMF at 80 °C (Table 1, entries 15−20). Moreover, when the temperature was reduced to 60 °C, the yield dropped to 79% from 95%, but a higher temperature could not improve the yield any further (Table 1, entries 21−22).

With the optimized reaction conditions in hand, a series of C-6-substituted adenosines were tested (Table 2). To our delight, the most products were obtained in moderate to good isolated yields. Furthermore, various functional groups such as aryl halides (**2h**, **2i**), ether (**2o**−**2q**), alkylamino (**2c**−**2n**), arylamino (**2j**), amino (**2b**), and hydroxyl (**2l**) survived under the oxidizing conditions. Notably, the results showed that substrate with aliphatic cyclic amine substituted gave a slightly higher yield than those with aliphatic amine groups substituted (**2n** vs **2c**−**2l**).The results also indicated that substrates with C-6 alkylamino groups were more reactive than those with C-6 alkyoxyl or alkythio groups (**2e** vs **2p**, **2q**; **2c** vs **2o**). It was worth mentioning that 2′,3′-*O*-isopropylidene-6-(2-hydroxyethyl)-aminoadenosine (**1l**) was cyclized in DMF to give **2m** but not **2l** in 14% yield possibly because of the esterification of the hydroxyl group with DMF. After replacing DMF with CH_3CN, the desired product **2l** was successfully synthesized only in a yield of 22%, which might indicate that the hydroxyl group was

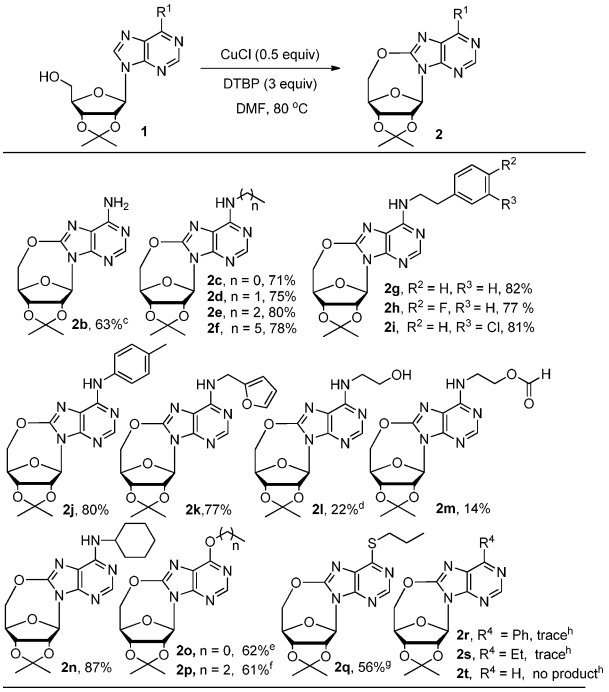
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (equiv)	oxidant (equiv)	solvent	yield[b] (%)
1	$CuCl_2$(0.1)	DTBP (2)	CH_3CN	41
2	$CoCl_2$ (0.1)	DTBP (2)	CH_3CN	0[c]
3	$NiCl_2$ (0.1)	DTBP (2)	CH_3CN	0[c]
4	CuCl (0.1)	DTBP (2)	CH_3CN	51
5	CuBr (0.1)	DTBP (2)	CH_3CN	46
6	CuI (0.1)	DTBP (2)	CH_3CN	23
7	CuCl (0.1)	THBP (2)	CH_3CN	13
8	CuCl (0.1)	$K_2S_2O_8$ (2)	CH_3CN	trace[c]
9	CuCl (0.1)	DLP (2)	CH_3CN	trace[c]
10	CuCl (0.1)	BPO (2)	CH_3CN	16
11	CuCl (0.1)	AgOAc(2)	CH_3CN	21
12	CuCl (0.1)	DTBP (2)	DCE	36
13	CuCl (0.1)	DTBP (2)	1,4-dioxane	26
14	CuCl (0.1)	DTBP (2)	toluene	34
15	CuCl (0.1)	DTBP (2)	DMF	62
16	CuCl (0.1)	DTBP (3)	DMF	68
17	CuCl (0.1)	DTBP (4)	DMF	65
18	CuCl (0.2)	DTBP (3)	DMF	72
19	CuCl (0.4)	DTBP (3)	DMF	92
20	CuCl (0.5)	DTBP (3)	DMF	95(86)[d]
21	CuCl (0.5)	DTBP (3)	DMF	79[e]
22	CuCl (0.5)	DTBP (3)	DMF	94[f]

[a]Reaction conditions: Unless otherwise noted, reactions were carried out with **1a** (0.35 mmol) in solvent (3 mL) at 80 °C for 12 h. DTBP, di-*tert*-butyl peroxide; THBP, *tert*-butyl hydroperoxide, 70% solution in water; DLP, dilauroyl peroxide; BPO, benzoyl peroxide. [b]Yield was determined by ^{1}H NMR. [c]Yield was determined by TLC. [d]Isolated yield based on **1a**. [e]At 60 °C. [f]At 100 °C.

Table 2. Effect of C-6-Substituent in Purine Base[a]



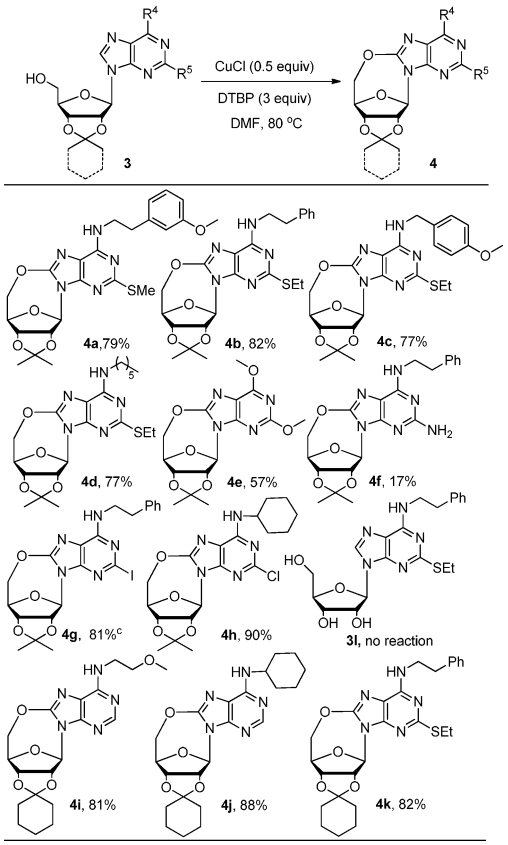
[a]Unless otherwise specified, all rections were carried out with purine nucleosides (**1**, 0.35 mmol), CuCl (0.5 equiv), and DTBP (3 equiv) at 80 °C in 3 mL of DMF for 12 h. [b]Isolated yields. [c]The solvent was 6 mL of CH_3CN. [d]The solvent was 3 mL of CH_3CN. [e]Recovery of staring material was 27%. [f]Recovery of staring material was 25%. [g]Recovery of staring material was 27%. [h]Products **2r**−**2t** were detected by HPLC-MS. Recovery of staring material (**2r**) was 86%. Recovery of staring material (**2s**) was 90%. Recovery of staring material (**2t**) was 91%.

DOI: 10.1021/acs.joc.5b01360
J. Org. Chem. 2015, 80, 9446−9453

harmful to the catalyst−oxidation system. To our surprise, only trace or no products **2r**, **2s**, and **2t** were generated when substrates **1r**, **1s**, and **1t** were applied to the experiments under standard conditions, and most raw materials were recovered. This result implied that the C6-heteroatoms might promote the reaction. Besides, the larger functional groups (Et or Ph) attached to C-6 may affect the coordination between the catalyst and 7-N atom in the purine structure, which could lead to only trace products. It is worth mentioning that there was still no product for substrate **1t**, although only one small hydrogen atom was attached to the C-6. The reason might be that the 1-N atom was much easier to coordinate with the catalyst than the 7-N atom, which caused the deactivation of catalyst when there was no steric hindrance in the C-6 position in the purine base.

To explore the electronic and steric effects of C-2 substituents in the purine ring, a further substrate scope study was performed, and the results are shown in Table 3. To

Table 3. Electronic and Steric Effects of C-2-Substitutent in Purine Base[a]



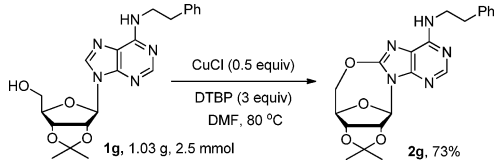
[a]Unless otherwise specified, all rections were carried out with purine nucleosides (**1**, 0.35 mmol), CuCl (0.5 equiv), and DTBP (3 equiv) at 80 °C in 3 mL of DMF for 12 h. [b]Isolated yields. [c]The solvent was 3 mL of CH_3CN.

our delight, most of the substrates could afford the desired products in moderate to good yields, even in the presence of electron-withdrawing halogen atoms (Cl, I) or electron-donating groups (SMe, SEt, OMe) on the 2-position of the purine ring. Notably, an amino group at C-2 position in purine ring led to an obvious decrease of the yield (**4f**, 17%), possibly because the amino group coordinated with the copper catalyst and reduced the activity. Meanwhile, the brief screening disclosed that the steric hindrance of C-2 substituents in the purine ring had no noticeable effect on the reaction.

On the other hand, 2′,3′-*O*-cyclohexylidene-5′-*O*,8-cyclopurine nucleosides (Table 3, **4i**−**4k**) were also successfully obtained under the reaction conditions in good yields (82−88%), which were similar to those of 2′,3′-*O*-isopropylidene protected products. It is worth mentioning that the unprotected nucleoside **3l** gave no product even after prolonged reaction time under the standard conditions. This phenomenon also happened when other methods and other substrates were used.[6] The reason might be that the isopropylidene group could force the furanose ring into a conformation that favored the proximity of the hydroxyl group to the C-8 atom in purine base, which resulted in the formation of an internal C(5′)−O−C(8) linkage.[12]

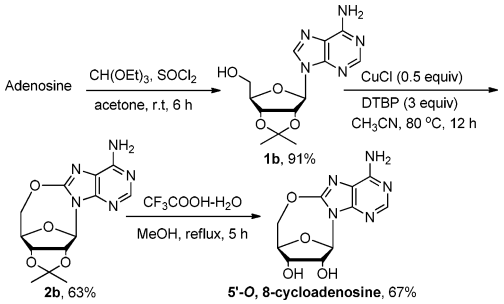
To demonstrate the practicality of the present method, a scale-up experiment was conducted. To our delight, the corresponding product could be obtained in 73% yield in gram scale (Scheme 2).

Scheme 2. Gram-Scale Synthesis of 2′,3′-*O*-Isopropylidene-6-phenethylamino-5′-*O*,8-cycloadenosine (2g)



The optimized methodology was applied to the total synthesis of 5′-*O*,8-cycloadenosine, a rhodopsin kinase nucleoside inhibitor (Scheme 3). Protection of 2′,3′-hydroxyl groups

Scheme 3. Synthesis of 5′-*O*,8-Cycloadenosine

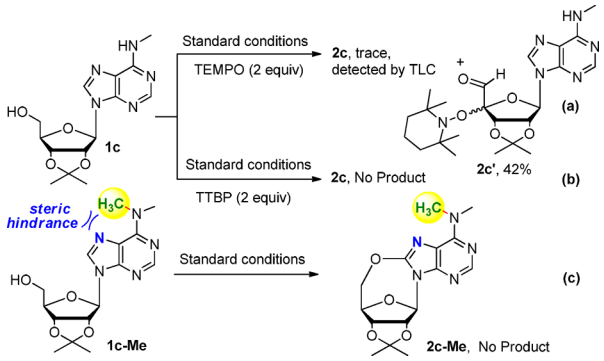


of adenosine was achieved with $SOCl_2$−$CH(OEt)_3$ in acetone. Subsequently, a intramolecular cyclization of 2′,3′-*O*-isopropylideneadenosine (**1b**) in the presence of CuCl (0.5 equiv) and DTBP (3 equiv) gave the intermediate (**2b**). Finally, the deprotection of **2b** promoted by CF_3COOH afforded the 5′-*O*,8-cycloadenosine in 67% yield, of which the spectral data were identical with those reported in the literature.[5b,13] Moreover, the present strategy was more efficient (three steps and 38% overall yield) compared with the previously reported methods (four steps and 5% overall yield).[13]

To gain some insights into the reaction mechanism, several control experiments were carried out (Scheme 4). First, a radical trapping experiment was carried out in the presence of a radical scavenger 2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO, Scheme 4a). As a result, only trace of **2c** was generated, and the major product was **2c′** in yield of 42%, which might be formed by oxidation of **1c** under the TEMPO−

DOI: 10.1021/acs.joc.5b01360
J. Org. Chem. 2015, 80, 9446−9453

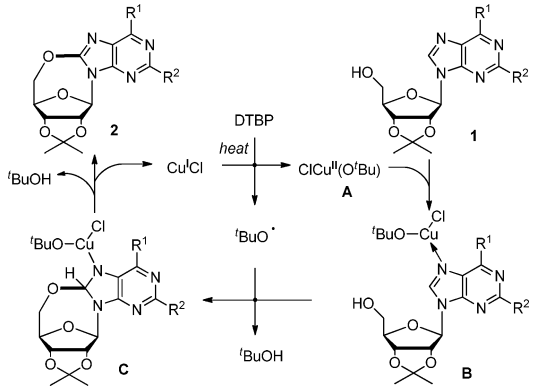
Scheme 4. Experiments for Preliminary Mechanistic Study



CuCl system.[14] The reaction with addition of another radical inhibitor 2,4,6-tri-*tert*-butylphenol (TTBP) afforded no product (Scheme 4b), which implied that the reaction might include a radical process. To our surprise, the reaction failed to give any desired product when substrate **1c-Me** was applied to the standard conditions (Scheme 4, c). The reason might be that the methyl group prevented the catalyst from coordinating with the 7-N atom in the purine structure. Subsequently, a ^{1}H NMR study between **1a** and CuCl−DTBP was carried out, and the downfield shift of the resonance for the C-8-H proton of **1a** was observed. Meanwhile, the peak of C-8-H became very broad (see, Supporting Information).

Based on the experimental results above and literatures,[7−9,11f,g] a proposed reaction pathway is described in Scheme 5. Initially, the oxidation of CuCl with DTBP under heating

Scheme 5. Plausible Mechanism



generated the copper species **A** and radical *t*-BuO$^\bullet$.[15] After that, purine nucleosides **1** coordinated with **A** and formed the 7-N−copper complex **B**.[7−9,16] Subsequently, intramolecular nucleophilic addition of 5′-OH to C-8 provided an intermediate **C** with *t*-BuOH leaving assisted by *t*-BuO$^\bullet$ radical.[17] Finally, reductive elimination of intermediate **C** afforded the desired products **2** and regenerated copper catalyst with leaving of *t*-BuOH.

CONCLUSION

In summary, we have successfully developed an efficient one-step copper-catalyzed reaction for the synthesis of 5′-*O*,8-cyclopurine nucleosides. This method could directly construct the large seven-membered ring between the sugar ring and the purine base through a C−O−C bridge, which avoided multiple steps. The cheap and readily available catalyst−oxidation (CuCl−DTBP) system made this method very promising for the synthesis of more 5′-*O*,8-cyclopurine nucleosides. Notably, this protocol provided a useful tool for convenient synthesis of rhodopsin kinase nucleoside inhibitor 5′-*O*,8-cycloadenosine.

EXPERIMENTAL SECTION

General Information. Commercially available reagents were used without further purification. Melting points were determined on a hot stage melting point apparatus (uncorrected). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with TMS as an internal standard, and the chemical shifts (δ) are reported in parts per million (ppm). The obtained signal multiplicities were distinguished with the common abbreviations s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), br s (broad singlet), quint (quintet), sext (sextet), and m (multiplet). IR spectra were recorded on a FT-IR instrument. HRMS measurements were carried out on an LC/MSD QTOF mass spectrometer.

2′,3′-*O*-Protected-2,6-disubtitued purine nucleosides **1a**, **1c−1t**, **1c-Me**, and **3a−3k** were prepared according to the method in previous reports.[18]

General Procedure for the Copper-Catalyzed Intramolecular Alkoxylation of 2′,3′-*O*-Protected 2,6-Disubstituted Purine Nucleosides 2a−2q and 4a−4k. Under ambient atmosphere, substrate **1** (0.35 mmol) and CuCl (0.175 mmol, 0.5 equiv) were suspended in DMF (3 mL) in a 15 mL vial. DTBP (1.05 mmol, 3 equiv) was then added to the mixture. The vial was sealed with a Teflon lined cap, and the reaction was heated at 80 °C for 12 h. Then, the reaction mixture was diluted with ethyl acetate−H_2O (100:15 mL). HCl (1 M, 0.1 mL) was added to the mixture. The organic and the aqueous layers were separated, and the organic layer was washed with brine (3 × 25 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The resulting oil was purified by chromatography on silica gel to afford products **2a−2q** and **4a−4k**. as semisolid or colorless crystals.

*2′,3′-O-Isopropylidene-6-(2-methoxyethyl)amino-5′-O,8-cycloadenosine (**2a**).* Yield 110 mg, 86%; white solid, mp 82−84 °C; R_f = 0.16 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H), 6.36 (s, 1H), 5.85 (br s, 1H), 5.06 (d, J = 5.6 Hz, 1H), 4.74 (d, J = 5.6 Hz, 1H), 4.67 (s, 1H), 4.47 (d, J = 12.8 Hz, 1H), 4.17 (d, J = 12.8 Hz, 1H), 3.80 (br s, 2H), 3.57 (t, J = 4.6 Hz, 2H), 3.35 (s, 3H), 1.53 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 153.2, 152.6, 147.7, 115.4, 113.2, 86.6, 85.8, 85.7, 81.4, 74.4, 71.2, 58.8, 40.5, 26.1, 24.7. FTIR (film, cm^{-1}): 3310, 2985, 2935, 2870, 1625, 1583, 1560, 1501, 1382, 1350, 1277. ESI-HRMS [M + H]$^+$ calcd for $C_{16}H_{22}N_5O_5$ m/z 364.1615, found 364.1611.

*2′,3′-O-Isopropylidene-5′-O,8-cycloadenosine (**2b**).* Yield 67 mg, 63%; white solid, mp 228−230 °C; R_f = 0.21 (EA). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.13 (s, 1H), 7.10 (br s, 2H), 6.04 (s, 1H), 5.11 (d, J = 5.6 Hz, 1H), 4.90 (d, J = 5.6 Hz, 1H), 4.75 (s, 1H), 4.64 (dd, J = 2.0, 12.8 Hz, 1H), 4.14 (d, J = 12.8 Hz, 1H), 1.47 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.7, 153.1, 151.9, 147.6, 114.5, 111.9, 85.8, 85.2, 84.8, 80.9, 74.3, 25.9, 24.3. FTIR (neat, cm^{-1}): 3425, 3178, 2990, 2930, 1641, 1608, 1578, 1550, 1451, 1382, 1091, 1066. ESI-HRMS [M + H]$^+$ calcd for $C_{13}H_{16}N_5O_4$ m/z 306.1197, found 306.1203.

*2′,3′-O-Isopropylidene-6-methylamino-5′-O,8-cycloadenosine (**2c**).* Yield 79 mg, 71%; white solid, mp 205−206 °C; R_f = 0.20 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 6.39 (s, 1H), 5.68 (br s, 1H), 5.09 (d, J = 5.6 Hz, 1H), 4.76 (d, J = 5.6 Hz, 1H), 4.70 (s, 1H), 4.50 (dd, J = 1.6, 12.8 Hz, 1H), 4.20 (d, J = 12.8 Hz, 1H), 3.18 (d, J = 4.4 Hz, 3H), 1.56 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.4, 153.2, 152.7, 147.4, 115.4, 113.3, 86.6, 85.8, 85.7, 81.4, 74.4, 27.8, 26.1, 24.7. FTIR (film, cm^{-1}): 3297, 2989, 2940, 1630, 1583, 1562, 1508, 1378, 1321, 1278, 1094. ESI-HRMS [M + H]$^+$ calcd for $C_{14}H_{18}N_5O_4$ m/z 320.1353, found 320.1351.

*2′,3′-O-Isopropylidene-6-ethylamino-5′-O,8-cycloadenosine (**2d**).* Yield 87 mg, 75%; white solid, mp153−154 °C; R_f = 0.36 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 6.39 (s, 1H), 5.56 (br s, 1H), 5.09 (d, J = 5.6 Hz, 1H), 4.77 (d, J = 5.6 Hz,

DOI: 10.1021/acs.joc.5b01360
J. Org. Chem. 2015, 80, 9446−9453

1H), 4.70 (s, 1H), 4.49 (d, J = 12.8 Hz, 1H), 4.20 (d, J = 12.8 Hz, 1H), 3.67 (br s, 2H), 1.56 (s, 3H), 1.36 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 153.2, 152.7, 147.5, 115.2, 113.3, 86.6, 85.8, 85.7, 81.3, 74.4, 35.9, 26.1, 24.7, 15.1. FTIR (film, cm^{-1}): 3297, 2989, 2940, 1630, 1583, 1562, 1508, 1378, 1321, 1278, 1094, 1039. ESI-HRMS $[M + H]^+$ calcd for $C_{15}H_{20}N_5O_4$ m/z 334.1510, found 334.1512.

2′,3′-O-Isopropylidene-6-propylamino-5′-O,8-cycloadenosine (**2e**). Yield 97 mg, 80%; white solid, mp 104−105 °C; R_f = 0.44 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 6.39 (s, 1H), 5.50 (br s, 1H), 5.09 (d, J = 5.6 Hz, 1H), 4.76 (d, J = 5.6 Hz, 1H), 4.70 (s, 1H), 4.49 (dd, J = 2.0, 12.8 Hz, 1H), 4.19 (d, J = 12.8 Hz, 1H), 3.59 (br s, 2H), 1.69 (sext, J = 7.2 Hz, 2H), 1.56 (s, 3H), 1.36 (s, 3H), 1.00 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 153.1, 152.7, 147.5, 115.2, 113.3, 86.6, 85.8, 85.7, 81.4, 74.4, 42.7, 26.1, 24.7, 23.1, 11.4. FTIR (film, cm^{-1}): 3285, 2960, 2934, 2872, 1624, 1583, 1559, 1500, 1379, 1322, 1277, 1065. ESI-HRMS $[M + H]^+$ calcd for $C_{16}H_{22}N_5O_4$ m/z 348.1666, found 348.1664.

2′,3′-O-Isopropylidene-6-hexylamino-5′-O,8-cycloadenosine (**2f**). Yield 107 mg, 78%; white solid, mp 76−78 °C; R_f = 0.59 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 6.40 (s, 1H), 5.53 (br s, 1H), 5.09 (d, J = 5.6 Hz, 1H), 4.76 (d, J = 5.6 Hz, 1H), 4.70 (s, 1H), 4.49 (d, J = 12.8 Hz, 1H), 4.18 (d, J = 12.8 Hz, 1H), 3.61 (br s, 2H), 1.63 (quint, J = 7.2 Hz, 2H), 1.56 (s, 3H), 1.40−1.25 (m, 11H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 153.3, 152.7, 148.0, 115.4, 113.3, 86.7, 85.8, 85.7, 81.4, 74.4, 41.0, 31.5, 29.8, 26.5, 26.1, 24.7, 22.6, 14.0. FTIR (film, cm^{-1}): 3295, 2960, 2930, 2857, 1624, 1583, 1560, 1501, 1381, 1322, 1277, 1065. ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{28}N_5O_4$ m/z 390.2136, found 390.2131.

2′,3′-O-Isopropylidene-6-phenethylamino-5′-O,8-cycloadenosine (**2g**). Yield 118 mg, 82%; white solid, mp 73−74 °C; R_f = 0.50 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.32−7.20 (m, 5H), 6.39 (s, 1H), 5.48 (br s, 1H), 5.08 (d, J = 5.6 Hz, 1H), 4.75 (d, J = 5.6 Hz, 1H), 4.69 (s, 1H), 4.47 (dd, J = 2.0, 12.8 Hz, 1H), 4.17 (d, J = 12.8 Hz, 1H), 3.92 (br s, 2H), 2.96 (t, J = 7.2 Hz, 2H), 1.56 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 153.1, 152.7, 147.6, 138.9, 128.8, 128.6, 126.4, 115.3, 113.3, 86.6, 85.8, 85.7, 81.3, 74.4, 42.1, 36.0, 26.1, 24.7. FTIR (film, cm^{-1}): 3292, 3027, 2989, 2939, 2857, 1632, 1584, 1561, 1497, 1382, 1231, 1065. ESI-HRMS $[M + H]^+$ calcd for $C_{21}H_{24}N_5O_4$ m/z 410.1823, found 410.1827.

2′,3′-O-Isopropylidene-6-(4-fluorophenethyl)amino-5′-O,8-cycloadenosine (**2h**). Yield 116 mg, 77%, white solid, mp 82−84 °C; R_f = 0.45 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.20−7.16 (m, 2H), 6.99−6.94 (m, 2H), 6.39 (s, 1H), 5.64 (br s, 1H), 5.08 (d, J = 5.6 Hz, 1H), 4.75 (d, J = 5.6 Hz, 1H), 4.69 (s, 1H), 4.48 (dd, J = 2.0, 12.8 Hz, 1H), 4.18 (d, J = 12.8 Hz, 1H), 3.88 (br s, 2H), 2.93 (t, J = 7.0 Hz, 2H), 1.56 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 160.3, 153.6, 153.2, 152.6, 147.7, 134.60, 134.57, 130.2, 130.1, 115.4, 115.2, 113.2, 86.6, 85.8, 85.7, 81.3, 74.4, 42.1, 35.2, 26.1, 24.6. FTIR (film, cm^{-1}): 3281, 2987, 2939, 2871, 1623, 1584, 1559, 1508, 1382, 1220, 1065, 865. ESI-HRMS $[M + H]^+$ calcd for $C_{21}H_{23}FN_5O_4$ m/z 428.1729, found 428.1726.

2′,3′-O-Isopropylidene-6-(3-chlorophenethyl)amino-5′-O,8-cycloadenosine (**2i**). Yield 126 mg, 81%; white solid, mp 85−86 °C; R_f = 0.44 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 7.21−7.08 (m, 4H), 6.39 (s, 1H), 5.96 (br s, 1H), 5.07 (d, J = 5.6 Hz, 1H), 4.75 (d, J = 5.6 Hz, 1H), 4.69 (s, 1H), 4.47 (d, J = 12.8 Hz, 1H), 4.18 (d, J = 12.8 Hz, 1H), 3.89 (br s, 2H), 2.93 (t, J = 6.8 Hz, 2H), 1.55 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 153.2, 152.6, 147.7, 141.1, 134.2, 129.8, 128.9, 127.0, 126.6, 115.2, 113.3, 86.6, 85.8, 85.7, 81.3, 74.4, 41.8, 35.7, 26.1, 24.7. FTIR (film, cm^{-1}): 3280, 3051, 2980, 2926, 2852, 1624, 1583, 1558, 1501, 1403, 1382, 1210, 1064, 865, 756. ESI-HRMS $[M + H]^+$ calcd for $C_{21}H_{23}ClN_5O_4$ m/z 444.1433, found 444.1432.

2′,3′-O-Isopropylidene-6-(4-methylphenyl)amino-5′-O,8-cycloadenosine (**2j**). Yield 110 mg, 80%; white solid, mp 105−108 °C; R_f = 0.56 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.37 (br s, 1H), 7.17 (d, J = 8.0 Hz, 2H), 6.43 (s, 1H), 5.09 (d, J = 5.6 Hz, 1H), 4.78 (d, J = 5.6 Hz, 1H), 4.72 (s, 1H), 4.50 (dd, J = 2.0, 12.8 Hz, 1H), 4.20 (d, J = 12.8 Hz, 1H), 2.33 (s, 3H), 1.57 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 152.3, 151.2, 147.8, 136.0, 133.1, 129.5, 120.8, 116.0, 113.3, 86.7, 85.8, 85.7, 81.3, 74.4, 26.1, 24.7, 20.9. FTIR (film, cm^{-1}): 3369, 3058, 2986, 2938, 2855, 1624, 1587, 1556, 1514, 1446, 1379, 1209, 1063. ESI-HRMS $[M + H]^+$ calcd for $C_{20}H_{22}N_5O_4$ m/z 396.1666, found 396.1666.

2′,3′-O-Isopropylidene-6-(furan-2-yl-methyl)amino-5′-O,8-adenosine (**2k**). Yield 104 mg, 77%; white solid, mp 74−76 °C; R_f = 0.45 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H), 7.36−7.34 (m, 1H), 6.40 (s, 1H), 6.32−6.30 (m, 1H), 6.28−6.27 (m, 1H), 5.76 (t, J = 5.4 Hz, 1H), 5.08 (d, J = 5.6 Hz, 1H), 4.84 (m, 2H), 4.75 (d, J = 5.6 Hz, 1H), 4.70 (m, 1H), 4.48 (dd, J = 2.5, 12.8 Hz, 1H), 4.18 (d, J = 12.8 Hz, 1H), 1.56 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 153.2, 152.6, 151.8, 147.8, 142.1, 115.4, 113.3, 110.4, 107.3, 86.6, 85.8, 85.7, 81.3, 74.4, 37.8, 26.1, 24.7. FTIR (film, cm^{-1}): 3289, 3021, 2986, 2929, 2872, 1622, 1558, 1503, 1445, 1379, 1209, 1063. ESI-HRMS $[M + H]^+$ calcd for $C_{18}H_{20}N_5O_5$ m/z 386.1459, found 386.1462.

2′,3′-O-Isopropylidene-6-(2-hydroxyethyl)amino-5′-O,8-cycloadenosine (**2l**). Yield 27 mg, 22%; white solid, mp 194−195 °C; R_f = 0.05 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 6.36 (s, 1H), 6.33 (br s, 1H), 5.07 (d, J = 5.6 Hz, 1H), 4.75 (d, J = 5.6 Hz, 1H), 4.71 (d, J = 0.8 Hz, 1H), 4.49 (dd, J = 2.0, 12.8 Hz, 1H), 4.26 (d, J = 12.8 Hz, 1H), 3.88 (br s, 2H), 3.76 (br s, 2H), 1.56 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 153.2, 152.3, 147.3, 115.1, 113.3, 86.7, 85.7, 81.3, 74.5, 62.3, 44.1, 26.1, 24.7. FTIR (film, cm^{-1}): 3407, 3300, 2991, 2936, 2870, 1621, 1563, 1503, 1374, 1215, 1060. ESI-HRMS $[M + H]^+$ calcd for $C_{15}H_{20}N_5O_5$ m/z 350.1459, found 350.1459.

2′,3′-O-Isopropylidene-6-(2-(formyloxy)ethyl)amino-5′-O,8-cycloadenosine (**2m**). Yield 19 mg, 14%; white solid, mp:86−88 °C; R_f = 0.20 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 8.07 (s, 1H), 6.40 (s, 1H), 5.85 (t, J = 5.6 Hz, 1H), 5.09 (d, J = 5.6 Hz, 1H), 4.76 (d, J = 5.6 Hz, 1H), 4.71(s, 1H), 4.51 (dd, J = 2.0, 12.8 Hz, 1H), 4.40 (t, J = 5.6 Hz, 1H), 4.20 (d, J = 12.8 Hz, 1H), 3.97 (br s, 2H), 1.56 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 153.5, 153.4, 152.5, 147.9, 115.4, 113.3, 86.7, 85.8, 85.7, 81.3, 74.5, 62.9, 39.6, 26.1, 24.7. FTIR (film, cm^{-1}): 3340, 2986, 2926, 2846, 1725, 1624, 1561, 1447, 1380, 1161, 1065. ESI-HRMS $[M + H]^+$ calcd for $C_{16}H_{20}N_5O_6$ m/z 378.1408, found 378.1406.

2′,3′-O-Isopropylidene-6-cyclohexylamino-5′-O,8-cycloadenosine (**2n**). Yield 118 mg, 87%. white solid, mp 172−174 °C; R_f = 0.52 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 6.38 (s, 1H), 5.39 (d, J = 8.0 Hz, 1H), 5.08 (d, J = 5.6 Hz, 1H), 4.76 (d, J = 5.6 Hz, 1H), 4.70 (s, 1H), 4.49 (d, J = 12.6 Hz, 1H), 4.18 (d, J = 12.6 Hz, 1H), 4.15 (m, 1H), 2.08−2.05 (m, 2H), 1.78−1.75 (m, 2H), 1.67−1.64 (m, 1H), 1.56 (s, 3H), 1.50−1.41 (m, 2H), 1.35 (s, 3H), 1.30−1.21 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 153.0, 152.7, 147.5, 115.1, 113.2, 86.6, 85.8, 85.7, 81.3, 74.4, 49.2, 33.4, 26.1, 25.6, 24.8, 24.7. FTIR (film, cm^{-1}): 3416, 2989, 2930, 2855, 1619, 1582, 1493, 1381, 1161, 1066. ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{26}N_5O_4$ m/z 388.1979, found 388.1980.

2′,3′-O-Isopropylidene-6-methoxyl-5′-O,8-cycloinosine (**2o**). Yield 70 mg, 62%; white solid, mp:184−185 °C; R_f = 0.43 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (s, 1H), 6.45 (s, 1H), 5.11 (d, J = 5.6 Hz, 1H), 4.78 (d, J = 5.6 Hz, 1H), 4.73 (s, 1H), 4.55 (dd, J = 2.0, 13.2 Hz, 1H), 4.22 (d, J = 13.2 Hz, 1H), 4.15 (s, 3H), 1.57 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 154.9, 151.6, 150.3, 117.6, 113.4, 86.9, 85.8, 85.7, 81.3, 74.5, 54.2, 26.1, 24.6. FTIR (film, cm^{-1}): 2989, 2942, 2867, 1610, 1580, 1548, 1481, 1452, 1376, 1199, 1062. ESI-HRMS $[M + H]^+$ calcd for $C_{14}H_{17}N_4O_5$ m/z 321.1193, found 321.1195.

2′,3′-O-Isopropylidene-6-propoxyl-5′-O,8-cycloinosine (**2p**). Yield 75 mg, 61%; white solid, mp 116−118 °C; R_f = 0.69 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1H), 6.45 (s, 1H), 5.11 (d, J = 5.6 Hz, 1H), 4.78 (d, J = 5.6 Hz, 1H), 4.73 (s, 1H), 4.55−4.49 (m, 3H), 4.22 (d, J = 13.2 Hz, 1H), 1.89 (sext, J = 7.2 Hz, 2H), 1.57 (s, 3H), 1.36 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 154.8, 151.6, 150.4, 117.5, 113.3, 86.9, 85.78, 85.76, 81.3, 74.5, 68.8, 26.1, 24.6, 22.2, 10.4. FTIR (film, cm^{-1}): 2969, 2938,

DOI: 10.1021/acs.joc.5b01360
J. Org. Chem. 2015, 80, 9446−9453

1608, 1579, 1547, 1376, 1318, 1187, 1061. ESI-HRMS $[M + H]^+$ calcd for $C_{16}H_{21}N_4O_5$ m/z 349.1506, found 349.1501.

*2′,3′-O-Isopropylidene-6-propylthio-5′-O,8-cycloinosine (**2q**).* Yield 71 mg, 56%; white solid, mp 140−141 °C; R_f = 0.80 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (s, 1H), 6.44 (s, 1H), 5.10 (d, J = 5.6 Hz, 1H), 4.75 (d, J = 5.6 Hz, 1H), 4.73 (s, 1H), 4.55 (dd, J = 2.0, 13.2 Hz, 1H), 4.24 (d, J = 13.2 Hz, 1H), 3.35 (dt, J = 7.2, 13.2 Hz, 1H), 3.31 (dt, J = 7.2, 13.2 Hz, 1H), 1.79 (sext, J = 7.2 Hz, 2H), 1.56 (s, 3H), 1.35 (s, 3H), 1.07 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 155.3, 151.5, 146.9, 128.1, 113.4, 86.7, 85.75, 85.73, 81.3, 74.7, 30.6, 26.1, 24.6, 22.9, 13.4. FTIR (film, cm^{-1}): 2964, 2963, 2873, 1585, 1530, 1431, 1382, 1184, 1105. ESI-HRMS $[M + H]^+$ calcd for $C_{16}H_{21}N_4O_4S$ m/z 365.1278, found 365.1279.

*2′,3′-O-Isopropylidene-2-methoxythio-6-(3-methoxyphenethyl)-amino-5′-O,8-cyclo adenosine (**4a**).* Yield 121 mg, 79%; white solid, mp:73−74 °C; R_f = 0.48 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (t, J = 8.0 Hz, 1H), 6.79−6.70 (m, 3H), 6.33 (s, 1H), 5.90 (br s, 1H), 5.04 (d, J = 5.6 Hz, 1H), 4.74 (d, J = 5.6 Hz, 1H), 4.65 (s, 1H), 4.43 (dd, J = 1.6, 13.2 Hz, 1H), 4.13 (d, J = 13.2 Hz, 1H), 3.86 (br s, 2H), 3.76 (s, 3H), 2.90 (t, J = 7.2 Hz, 2H), 2.57 (s, 3H), 1.55 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 158.7, 152.0, 151.2, 147.1, 139.6, 128.5, 120.1, 113.5, 112.1, 111.3, 110.5, 85.4, 84.7, 84.6, 80.3, 73.3, 54.1, 40.8, 35.0, 25.1, 23.6, 13.5. FTIR (film, cm^{-1}): 3294, 2989, 2935, 2825, 1619, 1584, 1561, 1443, 1382, 1220, 1064. ESI-HRMS $[M + H]^+$ calcd for $C_{23}H_{28}N_5O_5S$ m/z 486.1806, found 486.1804.

*2′,3′-O-Isopropylidene-2-ethylthio-6-phenethylamino-5′-O,8-cycloadenosine (**4b**).* Yield 134 mg, 82%; white solid, mp =85−86 °C; R_f = 0.55 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30−7.18 (m, 5H), 6.35 (s, 1H), 5.62 (br s, 1H), 5.05 (d, J = 5.6 Hz, 1H), 4.73 (d, J = 5.6 Hz, 1H), 4.66 (s, 1H), 4.43 (d, J = 12.6 Hz, 1H), 4.13 (d, J = 12.6 Hz, 1H), 3.87 (br s, 2H), 3.20 (dt, J = 7.2, 14.2 Hz, 1H), 3.15 (dt, J = 7.2, 14.2 Hz, 1H), 2.92 (t, J = 7.2 Hz, 2H), 1.56 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 153.1, 152.3, 148.3, 139.0, 128.8, 128.6, 126.4, 113.1, 112.4, 86.4, 85.8, 85.7, 81.3, 74.4, 42.0, 36.0, 26.1, 25.6, 24.6, 15.0. FTIR (film, cm^{-1}): 3292, 3062, 2989, 2930, 2870, 1600, 1559, 1495, 1444, 1357, 1065. ESI-HRMS $[M + H]^+$ calcd for $C_{23}H_{28}N_5O_4S$ m/z 470.1857, found 470.1859.

*2′,3′-O-Isopropylidene-2-ethylthio-6-(3-methoxybenzyl)amino-5′-O,8-cycloadeno- sine (**4c**).* Yield 131 mg, 77%; white solid, mp 78−79 °C; R_f = 0.54 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 6.31 (s, 1H), 6.03 (br s, 1H), 5.02 (d, J = 5.6 Hz, 1H), 4.72 (m, 2H), 4.70 (d, J = 5.6 Hz, 1H), 4.64 (s, 1H), 4.38 (d, J = 12.8 Hz, 1H), 4.09 (d, J = 12.8 Hz, 1H), 3.77 (s, 3H), 3.16 (dq, J = 7.2, 14.4 Hz, 1H), 3.10 (dq, J = 7.2, 14.4 Hz, 1H), 1.54 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 158.9, 152.9, 152.3, 148.4, 130.9, 128.9, 113.9, 113.1, 112.4, 86.4, 85.8, 85.7, 81.3, 74.4, 55.3, 44.0, 26.1, 25.5, 24.6, 14.9. FTIR (film, cm^{-1}): 3303, 2995, 2930, 2870, 1615, 1582, 1560, 1511, 1443, 1381, 1246, 1064. ESI-HRMS $[M + H]^+$ calcd for $C_{23}H_{28}N_5O_5S$ m/z 486.1806, found 486.1806.

*2′,3′-O-Isopropylidene-2-ethylthio-6-hexylamino-5′-O,8-cycloadenosine (**4d**).* Yield 122 mg, 77%; semisolid; R_f = 0.68 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.33 (s, 1H), 5.44 (br s, 1H), 5.07 (d, J = 5.6 Hz, 1H), 4.75 (d, J = 5.6 Hz, 1H), 4.67 (s, 1H), 4.46 (dd, J = 2.0, 12.8 Hz, 1H), 3.59 (br s, 2H), 3.18 (dq, J = 7.2, 14.0 Hz, 1H), 3.12 (dq, J = 7.2, 14.0 Hz, 1H), 1.60 (quint, J = 7.2 Hz, 2H), 1.56 (s, 3H), 1.42−1.30 (m, 12H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 153.3, 152.2, 148.2, 113.1, 112.3, 86.4, 85.8, 85.7, 81.3, 74.4, 40.8, 31.5, 29.8, 26.6, 26.1, 25.5, 24.6, 22.6, 14.9, 14.0. FTIR (film, cm^{-1}): 3305, 2962, 2929, 2857, 1619, 1584, 1562, 1497, 1444, 1374, 1221, 1065. ESI-HRMS $[M + H]^+$ calcd for $C_{21}H_{32}N_5O_4S$ m/z 450.2170, found 450.2170.

*2′,3′-O-Isopropylidene-2,6-dimethoxy-5′-O,8-cycloguanosine (**4e**).* Yield 70 mg, 57%; white solid, mp 81−82 °C; R_f = 0.40 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.35 (s, 1H), 5.10 (d, J = 5.6 Hz, 1H), 4.80 (d, J = 5.6 Hz, 1H), 4.70 (s, 1H), 4.49 (dd, J = 2.0, 12.8 Hz, 1H), 4.18 (d, J = 12.8 Hz, 1H), 4.12 (s, 3H), 4.02 (s, 3H), 1.58 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 161.0, 153.5, 151.4, 113.2, 112.5, 86.7, 85.8, 85.7, 81.4, 74.4, 55.1, 54.3, 26.1, 24.6. FTIR (film, cm^{-1}): 2988, 2941, 2870, 1613, 1560, 1479, 1390, 1365, 1218, 1061. ESI-HRMS $[M + H]^+$ calcd for $C_{15}H_{19}N_4O_6$ m/z 351.1299, found 351.1297.

*2′,3′-O-Isopropylidene-2-amino-6-phenethylamino-5′-O,8-cycloguanosine (**4f**).* Yield 25 mg, 17%; white solid, mp 219−220 °C; R_f = 0.38 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.26 (m, 2H), 7.23−7.16 (m, 3H), 6.20 (s, 1H), 5.34 (br s, 1H), 5.05 (d, J = 5.6 Hz, 1H), 4.74 (d, J = 5.6 Hz, 1H), 4.68 (s, 2H), 4.64 (s, 1H), 4.40 (dd, J = 2.0, 12.8 Hz, 1H), 4.10 (d, J = 12.8 Hz, 1H), 3.82 (br s, 2H), 2.92 (t, J = 7.0 Hz, 2H), 1.54 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 154.2, 151.2, 149.5, 139.0, 128.8, 128.6, 126.4, 113.1, 109.1, 86.3, 85.8, 85.7, 81.5, 74.2, 42.0, 36.1, 26.1, 24.7. FTIR (film, cm^{-1}): 3387, 3320, 3018, 2987, 2930, 2854, 1603, 1565, 1497, 1455, 1394, 1218, 1065. ESI-HRMS $[M + H]^+$ calcd for $C_{21}H_{25}N_6O_4$ m/z 425.1932, found 425.1935.

*2′,3′-O-Isopropylidene-2-iodo-6-phenethylamino-5′-O,8-cycloadenosine (**4g**).* Yield 151 mg, 81%; white solid, mp 116−118 °C; R_f = 0.60 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.20 (m, 5H), 6.35 (s, 1H), 5.62 (br s, 1H), 5.04 (d, J = 5.6 Hz, 1H), 4.72 (d, J = 5.6 Hz, 1H), 4.68 (s, 1H), 4.45 (d, J = 12.8 Hz, 1H), 4.15 (d, J = 12.8 Hz, 1H), 3.86 (br s, 2H), 2.93 (t, J = 7.2 Hz, 2H), 1.54 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 152.7, 138.5, 128.8, 128.7, 126.6, 119.1, 114.9, 113.4, 86.7, 85.8, 85.7, 81.3, 74.6, 42.1, 35.8, 26.1, 24.7. FTIR (film, cm^{-1}):3286, 3018, 2987, 2938, 2870, 1620, 1566, 1495, 1376, 1300, 1275, 1218, 1064. ESI-HRMS $[M + H]^+$ calcd for $C_{21}H_{23}IN_5O_4$ m/z 536.0789, found 536.0791.

*2′,3′-O-Isopropylidene-2-choloro-6-cyclohexylamino-5′-O,8-cycloadenosine (**4h**).* Yield 133 mg, 90%; white solid, mp > 250 °C; R_f = 0.68 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.35 (s, 1H), 5.44 (d, J = 8.0 Hz, 1H), 5.07 (d, J = 5.6 Hz, 1H), 4.69 (s, 1H), 4.48 (dd, J = 2.0, 12.8 Hz, 1H), 4.17 (d, J = 12.8 Hz, 1H), 4.16 (m, 1H), 2.06−2.03 (m, 2H), 1.77−1.66 (m, 2H), 1.65−1.63 (m, 1H), 1.54 (s, 3H), 1.50−1.41 (m, 2H), 1.35 (s, 3H), 1.29−1.21 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 153.1, 147.8, 113.8, 113.3, 86.7, 85.8, 85.7, 81.3, 74.5, 49.2, 33.2, 26.1, 25.5, 24.7, 24.6. FTIR (film, cm^{-1}): 3403, 2974, 2932, 2853, 1621, 1566, 1497, 1445, 1380, 1247, 1066. ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{25}ClN_5O_4$ m/z 422.1590, found 422.1588.

*2′,3′-O-cyclohexylidene-6-methoxyethylamino-5′-O,8-cycloadenosine (**4i**).* Yield 115 mg, 81%; white solid, mp 158−159 °C; R_f = 0.25 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 6.36 (s, 1H), 5.85 (t, J = 5.2 Hz, 1H), 5.06 (d, J = 5.6 Hz, 1H), 4.73 (d, J = 5.6 Hz, 1H), 4.68 (s, 1H), 4.46 (dd, J = 1.6, 12.8 Hz, 1H), 4.16 (d, J = 12.8 Hz, 1H), 3.80 (br s, 2H), 3.57 (t, J = 5.2 Hz, 2H), 3.35 (s, 3H), 1.77−1.73 (m, 2H), 1.66−1.62 (m, 2H), 1.57−1.54 (m, 4H), 1.39−1.37 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 153.2, 152.6, 147.5, 115.4, 114.1, 86.7, 85.8, 85.4, 80.9, 74.4, 71.2, 58.8, 40.5, 35.8, 34.2, 24.9, 23.9, 23.7. FTIR (film, cm^{-1}): 3305, 2936, 2860, 1624, 1583, 1560, 1499, 1379, 1238, 1114, 1058. ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{26}N_5O_5$ m/z 404.1928, found 404.1926.

*2′,3′-O-cyclohexylidene-6-cyclohexylamino-5′-O,8-cycloadenosine (**4j**).* Yield 131 mg, 88%; white solid, mp 210−211 °C; R_f = 0.60 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 6.39 (s, 1H), 5.38 (d, J = 8.4 Hz, 1H), 5.08 (d, J = 5.6 Hz, 1H), 4.75 (d, J = 5.6 Hz, 1H), 4.70 (s, 1H), 4.49 (dd, J = 1.6, 13.0 Hz, 1H), 4.18 (d, J = 13.0 Hz, 1H), 4.17 (m, 1H), 2.08−2.06 (m, 2H), 1.78−1.21 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 153.0, 152.7, 147.5, 115.1, 114.0, 86.7, 85.8, 85.4, 80.9, 74.4, 49.2, 35.8, 34.2, 33.4, 25.6, 24.9, 24.8, 23.9, 23.7. FTIR (film, cm^{-1}): 3418, 2987, 2931, 2855, 1619, 1558, 1493, 1448, 1367, 1239, 1058. ESI-HRMS $[M + H]^+$ calcd for $C_{22}H_{30}N_5O_4$ m/z 428.2292, found 428.2290.

*2′,3′-O-cyclohexylidene-2-ethylthio-6-phenethylamino-5′-O,8-cycloadenosine (**4k**).* Yield 146 mg, 82%; white solid, mp 121−122 °C; R_f = 0.68 (PE/EA = 1:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30−7.18 (m, 5H), 6.33 (s, 1H), 5.70 (br s, 1H), 5.04 (d, J = 5.6 Hz, 1H), 4.71 (d, J = 5.6 Hz, 1H), 4.66 (s, 1H), 4.42 (d, J = 12.8 Hz, 1H), 4.12 (d, J = 12.8 Hz, 1H), 3.86 (br s, 2H), 3.22 (dq, J = 7.2, 14.4 Hz, 1H), 3.14 (dq, J = 7.2, 14.4 Hz, 1H), 2.93 (t, J = 7.0 Hz, 2H), 1.77 (m, 2H), 1.66−1.65 (m, 2H), 1.56 (m, 4H), 1.44−1.40 (m, 5H). ^{13}C

DOI: 10.1021/acs.joc.5b01360
J. Org. Chem. 2015, 80, 9446−9453

NMR (100 MHz, $CDCl_3$): δ 164.5, 153.1, 152.3, 148.5, 139.0, 128.8, 128.6, 126.4, 113.9, 112.5, 86.6, 85.8, 85.4, 80.9, 74.4, 42.0, 36.0, 35.8, 34.1, 25.6, 25.0, 24.0, 23.7, 15.0. FTIR (film, cm^{-1}): 3304, 3031, 2960, 2937, 2863, 1619, 1584, 1562, 1496, 1448, 1359, 1222, 1057. ESI-HRMS $[M + H]^+$ calcd for $C_{26}H_{32}N_5O_4S$ m/z 510.2170, found 510.2164.

Preparation of 2′,3′-*O*-Isopropylideneadenosine (1b). Triethyl orthoformate (1 mL) and $SOCl_2$ (5.4 g, 0.045 mol) were subsequently and slowly added into the solution of adenosine (4 g, 0.015 mol) in acetone (80 mL). The resulting mixture was stirred at room temperature overnight. After neutralization with a solution of sodium carbonate, the solution was cooled to crystallize. After filtration, 2′,3′-*O*-isopropylideneadenosine (**1b**) was obtained as a white solid (4.2 g, 91% yield). Mp 215−216 °C; R_f = 0.26 (EA/CH_3OH = 1:15, v/v). ^1H NMR (400 MHz, DMSO-d_6): δ 8.37 (s, 1H), 8.19 (s, 1H), 7.39 (br s, 2H), 6.16 (d, J = 2.8 Hz, 1H), 5.37 (dd, J = 2.8, 6.0 Hz, 1H), 5.28 (t, J = 6.0 Hz, 1H), 4.99 (dd, J = 2.4, 6.0 Hz, 1H), 4.25 (m 1H), 3.63−3.52 (m, 2H), 1.56 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.1, 152.6, 148.8, 139.7, 119.1, 113.0, 89.6, 86.3, 83.2, 81.3, 61.6, 27.0, 25.1. FTIR (neat, cm^{-1}): 3297, 2989, 2940, 1630, 1583, 1562, 1508, 1445, 1318, 1208, 1064. ESI-HRMS $[M + H]^+$ calcd for $C_{13}H_{18}N_5O_4$ m/z 308.1353, found 308.1352.

Preparation of 5′-*O*,8-cycloadenosine. 2′,3′-*O*-Isopropylidene-5′-*O*,8-cycloadenosine (**2b**, 200 mg, 0.66 mmol) was dissolved in the solvent mixture $CH_3OH-H_2O-CF_3COOH$ (20:10:10 mL) and refluxed for 5 h. Then, the reaction mixture was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 10/1). The desired 5′-*O*,8-cycloadenosine was finally obtained as a white solid (116 mg, 67%). Mp > 250 °C; R_f = 0.26 (EA/CH_3OH = 1:5, v/v). ^1H NMR (400 MHz, DMSO-d_6): δ 8.12 (s, 1H), 7.07 (s, 2H), 5.98 (s, 1H), 5.65 (d, J = 6.4 Hz, 1H), 5.35 (d, J = 5.2 Hz, 1H), 4.59 (d, J = 12.8 Hz, 1H), 4.56 (s, 1H), 4.46 (dd, J = 5.6, 5.2 Hz, 1H), 4.25 (dd, J = 5.6, 6.4 Hz), 4.09 (d, J = 12.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.7, 153.3, 151.9, 147.6, 114.3, 88.7, 88.1, 77.2, 74.7, 71.1. FTIR (neat, cm^{-1}): 3421, 3300, 2960, 2926, 2855, 1648, 1552, 1413, 1327, 1207, 1086. ESI-HRMS $[M + H]^+$ calcd for $C_{10}H_{12}N_5O_4$ m/z 266.0884, found 266.0880.

Radical Trapping Experiment. Under ambient atmosphere, substrate **1c** (112 mg, 0.35 mmol), CuCl (17.3 mg, 0.175 mmol), and TEMPO (109.4 mg, 0.7 mmol) were suspended in DMF (3 mL) in a 15 mL vial. DTBP (154 mg, 1.05 mmol) was then added to the mixture. The vial was sealed with a Teflon lined cap, and the reaction was heated at 80 °C for 12 h. Then, the reaction mixture was diluted with ethyl acetate−H_2O (100:15 mL). HCl (1 M, 0.1 mL) was added to the mixture. The organic and the aqueous layers were separated, and the organic layer was washed with brine (3 × 25 mL).The organic layer was dried over $MgSO_4$, filtered, and concentrated. The resulting oil was purified by chromatography on silica gel to afford a white solid, 2′,3′-*O*-isopropylidene-6-methylamino-5′-oxo-4′-(2,2,6,6-tetramethyl piperidin-1-yl)-oxyladenosine (**2c′**, 68 mg, 42%). Mp 180 °C; R_f = 0.37 (PE/EA = 1:2, v/v). ^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.41 (s, 1H), 7.94 (s, 1H), 6.33 (s, 1H), 5.95 (d, J = 5.6 Hz, 1H), 5.90 (m, 1H), 5.68 (d, J = 5.6 Hz, 1H), 3.20 (br s, 3H), 1.50−1.48 (m,1H), 1.44 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.37−1.31 (m, 2H), 1.31−1.25 (m, 2H), 1.22−1.20 (m, 1H), 0.93 (s, 3H), 0.91 (s, 3H), 0.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.5, 155.5, 153.1, 148.3, 140.0, 120.1, 114.6, 114.0, 90.1, 87.0, 82.8, 61.5, 60.9, 39.96, 39.86, 33.4, 31.8, 27.6, 25.8, 25.1, 20.4, 19.8, 16.6. FTIR (film, cm^{-1}): 3440, 3287, 3110, 2978, 2934, 2872, 2854, 1741, 1625, 1579, 1536, 1445, 1377, 1215, 1074. ESI-HRMS $[M + H]^+$ calcd for $C_{23}H_{35}N_6O_5$, m/z 475.2663, found 475.2665.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01360.

Copies of ^1H and ^{13}C NMR spectra for the products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dhg@mail.buct.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National Natural Science Foundation of China (Grant 21272022).

■ REFERENCES

(1) Kikugawa, K.; Iizuka, K.; Higuchi, Y.; Hirayama, H.; Ichino, M. *J. Med. Chem.* **1972**, *15*, 387.

(2) Palczewski, K.; Kahn, N.; Hargrave, P. A. *Biochemistry* **1990**, *29*, 6276.

(3) Zhu, Z.; Buolamwini, J. K. *Bioorg. Med. Chem.* **2008**, *16*, 3848.

(4) (a) Haromy, T. P.; Raleigh, J.; Sundaralingam, M. *Biochemistry* **1980**, *19*, 1718. (b) Fuciarelli, A. F.; Shum, F. Y.; Raleigh, J. A. *Biochem. Biophys. Res. Commun.* **1986**, *134*, 883. (c) Karpeisky, A.; Zavgorodny, S.; Hotokka, M.; Oivanen, M.; Lönnberg, H. *J. Chem. Soc., Perkin Trans. 2* **1994**, *4*, 741. (d) Sako, M.; Saito, T.; Kameyama, K.; Hirota, K.; Maki, Y. *J. Chem. Soc., Chem. Commun.* **1987**, *17*, 1298. (e) Anzai, K.; Uzawa, J. *J. Org. Chem.* **1984**, *49*, 5076. (f) Ikehara, M. *Acc. Chem. Res.* **1969**, *2*, 47.

(5) (a) Ikehara, M.; Kaneko, M. *J. Am. Chem. Soc.* **1968**, *90*, 497. (b) Ikehara, M.; Kaneko, M.; Okano, R. *Tetrahedron* **1970**, *26*, 5675. (c) Naka, T.; HonJo, M. *Chem. Pharm. Bull.* **1976**, *24*, 2052. (d) Butora, G.; Schmitt, C.; Levorse, D. A.; Streckfuss, E.; Doss, G. A.; MacCoss, M. *Tetrahedron* **2007**, *63*, 3782. (e) Jamison, M. T.; Boddy, C. N.; Molinski, T. F. *J. Org. Chem.* **2014**, *79*, 9992. (f) Gunji, H.; Vasella, A. *Helv. Chim. Acta* **2000**, *83*, 1331. (g) Janeba, Z.; Masojídková, M.; Holý, A. *Collect. Czech. Chem. Commun.* **2010**, *75*, 371.

(6) Qu, G.-R.; Ren, B.; Niu, H.-Y.; Mao, Z.-J.; Guo, H.-M. *J. Org. Chem.* **2008**, *73*, 2450.

(7) Maki, Y.; Sako, M.; Saito, T.; Hirota, K. *Heterocycles* **1988**, *27*, 347.

(8) (a) Kameyama, K.; Sako, M.; Hirota, K.; Maki, Y. *J. Chem. Soc., Chem. Commun.* **1984**, *24*, 1658. (b) Kitade, Y.; Makino, T.; Hirota, K.; Maki, Y. *Nucleosides Nucleotides* **1992**, *11*, 365. (c) Janeba, Z.; Holy, A.; Votavova, H.; Masojidkova, M. *Collect. Czech. Chem. Commun.* **1996**, *61*, 442.

(9) Kitade, Y.; Nakanishi, R.; Sako, M.; Hirota, K.; Maki, Y. *Chem. Pharm. Bull.* **1991**, *39*, 1902.

(10) (a) Kameyama, K.; Sako, M.; Hirota, K.; Maki, Y. *J. Chem. Soc., Chem. Commun.* **1984**, *24*, 1658. (b) Sako, M.; Shimada, K.; Hitota, K.; Maki, Y. *J. Chem. Soc., Chem. Commun.* **1986**, *23*, 1704.

(11) For selected examples, see: (a) Eom, D.; Jeong, Y.; Kim, Y. R.; Lee, E.; Choi, W.; Lee, P. H. *Org. Lett.* **2013**, *15*, 5210. (b) Wang, X.; Lu, Y.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 12203. (c) Cheng, X.-F.; Li, Y.; Su, Y.-M.; Yin, F.; Wang, J.-Y.; Sheng, J.; Vora, H. U.; Wang, X.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 1236. (d) Wei, Y.; Yoshikai, N. *Org. Lett.* **2011**, *13*, 5504. (e) Xiao, B.; Gong, T.-J.; Liu, Z.-J.; Liu, J.-H.; Luo, D.-F.; Xu, J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 9250. (f) Takemura, N.; Kuninobu, Y.; Kanai, M. *Org. Lett.* **2013**, *15*, 844. (g) Takemura, N.; Kuninobu, Y.; Kanai, M. *Org. Biomol. Chem.* **2014**, *12*, 2528. (h) Zhao, J.; Wang, Y.; He, Y.; Liu, L.; Zhu, Q. *Org. Lett.* **2012**, *14*, 1078. (i) Tang, L.; Pang, Y.; Yan, Q.; Shi, L.; Huang, J.; Du, Y.; Zhao, K. *J. Org. Chem.* **2011**, *76*, 2744. (j) Gallardo-Donaire, J.; Martin, R. *J. Am. Chem. Soc.* **2013**, *135*, 9350. (k) Dai, J.-J.; Xu, W.-T.; Wu, Y.-D.; Zhang, W.-M.; Gong, Y.; He, X.-P.; Zhang, X.-Q.; Xu, H.-J. *J. Org. Chem.* **2015**, *80*, 911. (l) Wang, Y.; Gulevich, A. V.; Gevorgyan, V. *Chem. - Eur. J.* **2013**, *19*, 15836. (m) Luo, S.; Luo, F.-X.; Zhang, X.-S.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2013**, *52*, 10598. (n) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411. (o) Yeh, M.-C. P.; Tsao, W.-C.; Tu, L.-H. *Organometallics* **2005**, *24*, 5909. (p) Murayama, H.; Nagao, K.; Ohmiya, H.; Sawamura, M. *Org.*

DOI: 10.1021/acs.joc.5b01360
J. Org. Chem. 2015, 80, 9446−9453

Lett. **2015**, *17*, 2039. (q) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. *Chem. Rev.* **2015**, *115*, 1622. (r) Miller, Y.; Miao, L.; Hosseini, A. S.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 12149. (s) Kawai, J.; Chikkade, P. K.; Shimizu, Y.; Kanai, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7177. (t) Bovino, M. T.; Liwosz, T. W.; Kendel, N. E.; Miller, Y.; Tyminska, N.; Zurek, E.; Chemler, S. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 6383. (u) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (v) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *134*, 1298.

(12) (a) Mieczkowski, A.; Roy, V.; Agrofoglio, L. A. *Chem. Rev.* **2010**, *110*, 1828. (b) Reist, E. J.; Beniter, A.; Goodman, L. *J. Org. Chem.* **1964**, *29*, 554.

(13) Capon, R. J.; Trotter, N. S. *J. Nat. Prod.* **2005**, *68*, 1689.

(14) (a) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Org. Biomol. Chem.* **2003**, *1*, 3232. (b) Hoover, J. M.; Ryland, B. L.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 2357. (c) Hoover, J. M.; Ryland, B. L.; Stahl, S. S. *ACS Catal.* **2013**, *3*, 2599. (d) Paderes, M. C.; Chemler, S. R. *Eur. J. Org. Chem.* **2011**, *2011* (20), 3679.

(15) Similar examples, see: (a) Jang, E. S.; McMullin, C. L.; Käß, M.; Meyer, K.; Cundari, T. R.; Warren, T. H. *J. Am. Chem. Soc.* **2014**, *136*, 10930. (b) Wang, C.-Y.; Song, R.-J.; Wei, W.-T.; Fan, J.-H.; Li, J.-H. *Chem. Commun.* **2015**, *51*, 2361. (c) Bunescu, A.; Wang, Q.; Zhu. *Org. Lett.* **2015**, *17*, 1890. (d) Xia, R.; Niu, H.-Y.; Qu, G.-R.; Guo, H.-M. *Org. Lett.* **2012**, *14*, 5546.

(16) Similar examples, see: (a) Xia, R.; Xie, M.-S.; Niu, H.-Y.; Qu, G.-R.; Guo, H.-M. *Org. Lett.* **2014**, *16*, 444. (b) Lu, J.; Jin, Y.; Liu, H.; Jiang, Y.; Fu, H. *Org. Lett.* **2011**, *13*, 3694. (c) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233. (d) Li, J.-P.; Huang, Y.; Xie, M.-S.; Qu, G.-R.; Niu, H.-Y.; Wang, H.-X.; Qin, B.-W.; Guo, H.-M. *J. Org. Chem.* **2013**, *78*, 12629. (e) Storr, T. E.; Baumann, C. G.; Thatcher, R. J.; De Ornellas, S.; Whitwood, A. C.; Fairlamb, I. J. S. *J. Org. Chem.* **2009**, *74*, 5810. (f) Scott, M.; Sud, A.; Boess, E.; Klussmann, M. *J. Org. Chem.* **2014**, *79*, 12033.

(17) Similar examples, see: (a) Liu, L.-W.; Wang, Z.-Z.; Zhang, H.-H.; Wang, W.-S.; Zhang, J.-Z.; Tang, Y. *Chem. Commun.* **2015**, *51*, 9531. (b) Boess, E.; Schmitz, C.; Klussmann, M. *J. Am. Chem. Soc.* **2012**, *134*, 5317. (c) Boess, E.; Sureshkumar, D.; Sud, A.; Wirtz, C.; Farès, C.; Klussmann, M. *J. Am. Chem. Soc.* **2011**, *133*, 8106. (d) Xie, J.; Huang, Z.-Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 10181. (e) Wan, C.; Zhang, J.; Wang, S.; Fan, J.; Wang, Z. *Org. Lett.* **2010**, *12*, 2338. (f) Kawade, R. K.; Huple, D. B.; Lin, R.-J.; Liu, R.-S. *Chem. Commun.* **2015**, *51*, 6625. (g) Xia, Q.; Chen, W. *J. Org. Chem.* **2012**, *77*, 9366.

(18) (a) Neres, J.; Labello, N. P.; Somu, R. V.; Boshoff, H. I.; Wilson, D. J.; Vannada, J.; Chen, L.; Barry, C. E., III; Bennett, E. M.; Aldrich, C. C. *J. Med. Chem.* **2008**, *51*, 5349. (b) Lukkarila, J. L.; da Silva, S. R.; Ali, M.; Shahani, V. M.; Xu, G. W.; Berman, J.; Roughton, A.; Dhe-Paganon, S.; Schimmer, A. D.; Gunning, P. T. *ACS Med. Chem. Lett.* **2011**, *2*, 577. (c) Spitale, R. C.; Heller, M. G.; Pelly, A. J.; Wedekind, J. E. *J. Org. Chem.* **2007**, *72*, 8551. (d) Liu, G.; Xu, J.; Chen, N.; Zhang, S.; Ding, Z.; Du, H. *Eur. J. Med. Chem.* **2012**, *53*, 114. (e) Mathew, S. C.; Ghosh, N.; By, Y.; Berthault, A.; Virolleaud, M.-A.; Carrega, L.; Chouraqui, G.; Commeiras, L.; Condo, J.; Attolini, M.; Gaudel-Siri, A.; Ruf, J.; Parrain, J.-L.; Rodriguez, J.; Guieu, R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6736. (f) Hocek, M.; Holý, A.; Votruba, I.; Dvořáková, H. *J. Med. Chem.* **2000**, *43*, 1817. (g) Xia, R.; Xie, M.-S.; Niu, H.-Y.; Qu, G.-R.; Guo, H.-M. *Org. Lett.* **2014**, *16*, 444.

DOI: 10.1021/acs.joc.5b01360
J. Org. Chem. 2015, 80, 9446−9453