Notes

Oxidative Conversion of Isoxazolidines to Isoxazolines

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Isoxazolines, are versatile synthetic intermediates in the preparation of a variety of compounds with 1,3-difunctional groups and are readily constructed via the 1,3-dipolar cycloaddition of nitrile oxides **1** to olefins **2**.[1] Although these cycloadditions display high regioselectivity,[2] it remains challenging to form optically pure isoxazolines via asymmetric cycloadditions.[3] For example, the isoxazoline nucleoside **3** (R = CH_2OH, Y = 6-chloropurine), which exhibits moderate anti-HIV-1 activity,[4] has been prepared only in racemic form via [2 + 3]-dipolar cycloaddition of nitrile oxide **1** (R = CH_2OTHP) with vinyl nucleoside bases **2** (Y = 6-chloropurine). An attempt to use optically active materials **1** (R = CH_2OR^*) for asymmetric induction in **3** furnished a diastereomeric mixture of cycloadducts.[5] To circumvent this problem we have developed a method for the conversion of isoxazolidines such as **4**−**6** to the corresponding isoxazolines **3**, as these will retain the optical integrity of **4**−**6** gained in the synthesis.

If the desired target **3** is to be formed from compounds **4**−**6**, then a method for the selective cleavage of the N−R′ bond is necessary. In the pursuit of such a cleavage, we have investigated alkylative, reductive, and oxidative pathways. Initially, we encountered difficulties in removing the methyl group of **4** by using the chloroformate procedure which was reported to dealkylate tertiary amines to secondary amine hydrochlorides in high yield.[6] Next, the hydrogenolysis of **5** was tested for the selective removal of the benzyl group, but the N−O bond was preferentially cleaved to furnish the corresponding amine.[7] Oxidative cleavage of the N-protected *p*-methoxybenzyl group (pMB) in isoxazolidines **6** was able to affect conversion to the desired isoxazolines **3**.

Although oxidative removal of the pMB group from *nitrogen* atoms is uncommon,[8i] it is well documented that the pMB group can be used as a protecting group for alcohols and removed by oxidative cleavage with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[8] Several solvent systems, including aqueous acetonitrile, benzene, tetrahydrofuran, dichloroethane, and dichloromethane, were investigated for the DDQ conversion of **6** to **3**. The combination of aqueous dichloromethane and DDQ gives good results (Table 1). This condition is sufficiently mild that various functional groups such as nitriles, esters, and benzyl moieties are unaffected (entries 1−10). On the basis of decreased yields of acetal compounds (entries 11, 13, and 15), we speculated that the acetal moieties of starting materials or products may be hydrolyzed under these aqueous conditions and that the yield of the reaction may be improved by decreasing the acidity of the reaction mixture.[9] The use of base in the DDQ oxidation appeared to be questionable because it has been reported that "addition of triethylamine or sodium bi-

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(3) For selected diastereo- and enantioselective syntheses of isoxazolidines or isoxazolines via dipolar cycloaddition reactions, see: (a) Kozikowski, A. P.; Ghosh, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 5788. (b) Deshong, P.; Leginus, J. M.; *J. Am. Chem. Soc.* **1983**, *105*, 1686. (c) Yuan, C.; Li, C. *Tetrahedron Lett.* **1993**, *34*, 5959. (d) Bravo, P.; Bruche, L.; Diliddo, D.; Resnati, G. *J. Chem. Res., Synop.* **1993**, 346. (e) Blake, A. J.; Gould, R. O.; Paton, R. M.; Yong, A. A. *J. Chem. Res., Synop.* **1993**, 482. (f) Ukaji, Y.; Sada, K.; Inomata, K. *Chem. Lett.* **1993**, 1847. (g) Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc.* **1994**, *116*, 2324 (h) Fisera, L.; Sauter, F.; Froehlich, J.; Feng, Y.; Ertl, P.; Mereiter, K. *Monatsh. Chem.* **1994**, *125*, 553. (i) Blake, A. J.; Kirkpatrick, G.; McGhie, K. E.; Paton, R. M.; Penman, K. J. *J. Carbohydr. Chem.* **1994**, *13*, 409. (j) Boa, A. N.; Dawkins, D. A.; Hergueta, A. R.; Jenkins, P. R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 953. (k) de Blas, J.; Carretero, J. C.; Dominguez, E. *Tetrahedron: Asymmetry* **1995**, *6*, 1035. (l) Schreiner, E. P.; Gstach, H. *Synlett* **1996**, 1131. (m) Curran, D. P.; Yoon, M.-H. *Tetrahedron* **1997**, *53*, 1971.

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(5) The nitrile oxide, which was generated from 1-(2-nitroethyl)-2,3,4,6-pentaacetyl glucopyranoside by using phenyl isocyanate, gave a mixture of two isomers in a ratio of about 1:1 and other related chiral nitrile oxide produced the similar results.

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(9) 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone is reduced to the corresponding 1,4-diphenol derivative which may result in acidic conditions.

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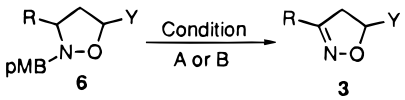
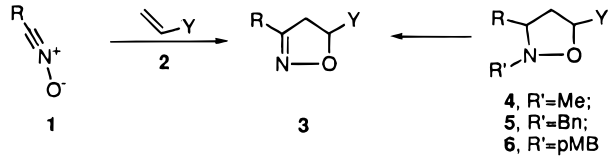
Table 1. DDQ Oxidation of Isoxazolidines to Isoxazolines



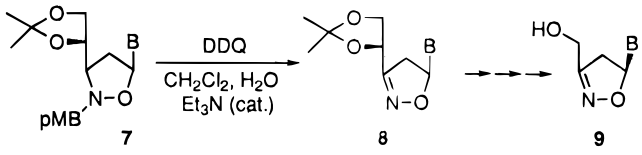
entry	substrate	Y	R	product	cond[a]	yield (%)[b]
1	**6a**	CO_2CH_3	*n*-Pr	**3a**	A	80
2	**6a**	CO_2CH_3	*n*-Pr	**3a**	B	90
3	**6b**	CO_2CH_3	*i*-Pr	**3b**	A	79
4	**6b**	CO_2CH_3	*i*-Pr	**3b**	B	92
5	**6c**	CO_2CH_3	Ph	**3c**	A	83
6	**6c**	CO_2CH_3	Ph	**3c**	B	94
7	**6d**	*p*-MeC_6H_4	Ph	**3d**	A	81
8	**6d**	*p*-MeC_6H_4	Ph	**3d**	B	91
9	**6e**	CN	*n*-Pr	**3e**	A	75
10	**6e**	CN	*n*-Pr	**3e**	B	81
11	**6f**	CN	THPO$(CH_2)_3$	**3f**	A	68
12	**6f**	CN	THPO$(CH_2)_3$	**3f**	B	75
13	**6g**	OAc	*n*-Pr	**3g**	A	60
14	**6g**	OAc	*n*-Pr	**3g**	B	82
15	**6h**	OAc	*i*-Pr	**3h**	A	72
16	**6h**	OAc	*i*-Pr	**3h**	B	87

[a] A: DDQ (2.5 equiv), CH_2Cl_2/H_2O (10:1), rt, 3 h. B: DDQ (2.5 equiv), Et_3N (0.1 equiv) CH_2Cl_2/H_2O (10:1), rt, 1−2 h. [b] Isolated yield.

Scheme 1



Scheme 2



carbonate inhibits the DDQ oxidation".[8f] We found that this was the case if a stoichiometric amount of base is used, but inclusion of a catalytic amount of triethylamine in the reaction mixture actually accelerated the DDQ oxidation of **6** with improved yield (entries 12, 14, and 16). We found a general trend of increased yields for all substrates when catalytic Et_3N was used. Although the role of triethylamine in the DDQ oxidation remains unclear, reaction condition B (0.1 equiv of Et_3N) is superior to condition A (without Et_3N) for the oxidation of *isoxazolidine* substrates (Table 1). As a corollary to these findings, we discovered that the conversion of *p-methoxybenzyl ethers* to the corresponding *alcohols* could also be improved by adding catalytic amounts of Et_3N.[10]

We have successfully extended this method to the conversion of isoxazolidine nucleoside analogues such as **7** to the corresponding isoxazolines **8** (Scheme 2). The requisite isoxazolidine nucleosides **7** were readily prepared via a hydroxylamine−Michael-addition route in both racemic[11a] and optically active D-[11b] or L-forms.[11c] Two substrates were used to evaluate the DDQ oxidation of the enantiomerically pure isoxazolidines. The purine compound **7a** (B = 6-chloropurine) reacted with DDQ/CH_2Cl_2/H_2O in the presence of a catalytic amount of triethylamine to afford the desired product **8a** (72% yield) which was transformed to the desired adenine analogue **9a**, using the reported procedure.[11b] This method is also suitable for the corresponding pyrimidine analogues since the problematic cytosine derivative **8b** (B = N^4-BOC-cytosine) is obtained in 68% yield, and compound **8b** was similarly converted to isoxazoline analogue **9b** in 34% overall yield. Thus, we have demonstrated a unique case for the selective cleavage of the N−R (R = *p*-methoxybenzyl) bond via DDQ oxidation. As an extension, we have found that catalytic amounts of Et_3N not only improve the yield of the aformentioned coversion but also significantly increase yields in the cleavage of the widely used *p*-methoxybenzyl ether protecting group. This method may be efficaciously exploited to allow access to optically active isoxazolines which are otherwise difficult to obtain.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded on 200 and 50 MHz, respectively. Unless specified, reagents and solvents were purchased from Aldrich and Acros and were used without further purification.

Synthesis of Isoxazolidines (6a−h).[1] To a stirred solution of *N*-(*p*-methoxybenzyl)hydroxylamine hrdrochloride[12] (10 mmol) in ethanol (50 mL) was added NaOMe (9 mmol) at rt. After stirring at 10 °C for 10 min, the corresponding aldehyde RCHO (10 mmol) was added. The reaction mixture was stirred at rt for 5 h. Ethyl acetate (20 mL) was added to precipitate the sodium chloride. After removal of the precipate by gravity filtration, the solvents were evaporated under reduced pressure to provide the intermediate nitrone, which was further purified by flush chromotography on silica gel eluting with 5−10% MeOH/EtOAc. To a solution of this nitrone (5 mmol) in dry benzene (10 mL) was added the corresponding olefin **2** (CH_2=CHY, 15 mmol), and the reaction mixture was refluxed for 6 h after which the solvent was removed under reduced pressure. The residue was purified by column chromotography on silica gel (20−30% EtOAc/petroleum ether) to give **6** as a mixture of two diastereoisomers. Since both isomers gave the same isoxazoline product, the mixture was used as the starting material for the subsequent oxidation reaction without further separation.

3-*n*-Propyl-5-(methoxycarbonyl)-2-*N*-(*p*-methoxybenzyl)isoxazolidine (6a): oil. ^1H NMR of the mixture ($CDCl_3$) δ 7.31 (d, 2H, J = 8.7 Hz), 6.85 (d, 2H, J = 8.6 Hz), 4.59 (dd, 0.5H, J = 5.7, 9.4 Hz), 4.54 (dd, 0.5H, J = 6.1, 8.9 Hz), 3.83−4.09 (m, 2H), (3.80, 3.79) (s, 3H), (3.76, 3.75) (s, 3H), (3.06, 2.89) (m, 1H), 2.70 (m, 1H), 2.28 (m, 1H), 1.45 (m, 4H), 0.87 (t, 3H, J = 6.8 Hz); ^{13}C NMR of the mixture ($CDCl_3$) δ 173.4, 159.3, (130.8, 130.4), (130.2, 129.6), (114.2, 114.1), (76.2, 74.9), (65.0, 64.9), (61.8, 60.1), 55.8, 52.8, (39.2, 39.1), 35.8, 20.5, 14.6. Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.49; H, 7.92, N, 4.78. Found: C, 65.62; H, 7.91; N, 4.76.

3-Isopropyl-5-(methoxycarbonyl)-2-*N*-(*p*-methoxybenzyl)isoxazolidine (6b): oil. ^1H NMR of the mixture ($CDCl_3$) δ 7.30 (d, 2H, J = 8.6 Hz), 6.83 (d, 2H, J = 8.6 Hz), 4.61 (dd, 0.5H, J = 5.9, 9.0 Hz), 4.48 (dd, 0.5H, J = 7.0, 8.1 Hz), 4.07 (d, 1H, J = 12.4 Hz), 3.85 (d, 1H, J = 9.4 Hz), 3.76 (s, 3H), (3.74, 3.73) (s, 3H), 2.87 (q, 0.5H, J = 6.6 Hz), 2.74 (q, 0.5H, J = 7.2 Hz), 2.46 (m, 2H), 1.68 (m, 1H), 0.87 (m, 6H); ^{13}C NMR of the

(10) Unpublished results.

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mixture ($CDCl_3$) δ (173.5, 172.6), 159.2, (130.7, 130.4), 129.9, 114.1, (76.7, 75.4), 70.8, (62.3, 60.7), 55.7, 52.7, (35.4, 35.1), (30.8, 30.7), (21.0, 20.9), (18.8, 18.4). Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.49; H, 7.92, N, 4.78. Found: C, 65.39; H, 7.87; N, 4.73.

3-Phenyl-5-(methoxycarbonyl)-2-*N*-(*p*-methoxybenzyl)isoxazolidine (6c): oil. ^{1}H NMR of the mixture ($CDCl_3$) δ 37 (m, 7H), 6.84 (d, 2H, J = 8.7 Hz), 4.70 (dd, 1H, J = 5.2, 8.8 Hz), 3.85−4.20 (m, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 2.75 (m, 2H); ^{13}C NMR of the mixture ($CDCl_3$) δ 172.7, 159.3, (139.1, 133.9), (130.7, 130.2), 129.2, (128.9, 128.7) 128.4, 128.1, (114.2, 114.0), 75.8, 69.4, 60.5, 55.8, 52.9, 43.4. Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.48, N, 4.28. Found: C, 69.73; H, 6.50; N, 4.22.

3-Phenyl-5-(*p*-methylphenyl)-2-*N*-(*p*-methoxybenzyl)-isoxazolidine (6d): oil. ^{1}H NMR of the mixture ($CDCl_3$) δ 7.11−7.50 (m, 11H), 6.84 (d, 2H, J = 8.7 Hz), 5.22 (t, 1H, J = 7.7 Hz), 3.85−4.12 (m, 3H), (3.80, 3.79) (s, 3H), 3.10 (td, 0.7H, J = 7.3, 12.3 Hz), 2.63 (m, 0.3H), 2.34 (m, 1H), (2.36, 2.34) (s, 3H); ^{13}C NMR of the mixture ($CDCl_3$) δ 159.2, 140.5, 140.1, 137.5, 137.3, (130.9, 130.7), (129.6, 129.5), 128.3, (128.1, 128.0), 127.0, 126.6, 114.0, (79.1, 78.9), (71.1, 70.5), 60.2, 55.8, (49.0, 48.7), 21.7; HRMS calcd for $C_{24}H_{25}NO_2$: 359.1885. Found: 359.1896.

3-*n*-Propyl-5-cyano-2-*N*-(*p*-methoxybenzyl)isoxazolidine (6e): oil. ^{1}H NMR of the mixture ($CDCl_3$) δ 7.30 (d, 2H, J = 8.8 Hz), 6.88 (d, 2H, J = 8.7 Hz), 4.70 (m, 1H), 4.12 (d, 1H, J = 12.8 Hz), 4.00 (d, 1H, J = 12.8 Hz), 3.80 (3H, s), 2.81 (m, 2H), 2.34 (m, 1H), 1.45 (m, 4H), 0.92 (m, 3H); ^{13}C NMR of the mixture ($CDCl_3$) δ 159.4, (130.8, 130.2), (129.2, 129.1), 119.8, (114.4, 114.3), (65.3, 65.0), (64.5, 64.0), (61.7, 59.7), 55.8, (41.1, 40.6), (36.1, 35.1), (20.4, 20.2), (14.7, 14.5). Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.19; H, 7.76, N, 10.76. Found: C, 69.02; H, 7.73; N, 10.79.

3-[3-[(Tetrahydro-2*H*-pyran-2-yl)oxy]propyl]-5-cyano-2-*N*-(*p*-methoxybenzyl)isoxazolidine (6f): oil. ^{1}H NMR of the mixture ($CDCl_3$) δ (7.28, 7.27) (d, 2H, J = 8.6 Hz), 6.85 (d, 2H, J = 8.7 Hz), 4.71 (dd, 0.5 H, J = 4.1, 9.2 Hz), 4.67 (dd, 0.5 H, J = 5.3, 8.8 Hz), 4.52 (m, 1H), 3.65−4.15 (m, 4H), 3.77 (3H, s), 3.40 (m, 2H), 2.83 (m, 2H), 2.35 (m, 1H), 1.65 (m, 10H); ^{13}C NMR of the mixture ($CDCl_3$) δ (159.6, 159.4), (131.3, 130.8, 130.2), (129.3, 129.1, 129.0), (120.1, 119.7), (114.3, 114.2, 114.1), (99.5, 99.4), 67.6, (65.3, 65.2, 65.0), (64.5, 64.0), 63.0, (61.7, 69.7), 55.8, (41.0, 40.5), 31.3, (31.0, 30.9, 29.8), (27.3, 27.1), 26.1, 20.3. Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.63; H, 7.84, N, 7.77. Found: C, 66.62; H, 7.77; N, 7.87.

3-*n*-Propyl-5-acetoxy-2-*N*-(*p*-methoxybenzyl)isoxazolidine (6g): oil. ^{1}H NMR of the mixture ($CDCl_3$) δ (7.28, 7.27) (d, 2H, J = 8.7 Hz), (6.86, 6.85) (d, 2H, J = 8.7 Hz), 6.29 (overlap, 1H), 3.75−4.15 (two overlap dd, 2H), 3.79 (3H, s), (3.19, 2.81) (m, 1H), 2.69 (dd, 0.5H, J = 8.4, 6.4 Hz), 2.50 (ddd, 0.5H, J = 1.1, 6.4, 13.2 Hz), 1.97−2.19 (m, 1H), (2.06, 2.05) (s, 3H), 1.42 (m, 4H), 0.90 (two overlap t, 3H); ^{13}C NMR of the mixture ($CDCl_3$) δ (171.0, 170.4), (159.4, 159.3), 131.0, (129.7, 129.0), (114.2, 114.1), (98.0, 96.0), (64.7, 63.8), (63.3, 60.7), 55.8, (42.9, 42.5), (36.5, 35.1), (22.1, 22.0), 20.6, (14.8, 14.6). Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.49; H, 7.92, N, 4.78. Found: C, 65.65; H, 7.95; N, 4.84.

3-Isopropyl-5-acetoxy-2-*N*-(*p*-methoxybenzyl)isoxazolidine (6h): oil. ^{1}H NMR of the mixture ($CDCl_3$) δ 7.27 (d, 2H, J = 8.7 Hz), (6.84, 6.83) (d, 2H, J = 8.7 Hz), 6.30 (overlap, 1H), 3.80−4.17 (two overlap dd, 2H), 3.78 (3H, s), 3.01 (td, 0.3H, J = 7.1, 8.1 Hz), 2.72 (td, 0.7H, J = 6.5, 8.5 Hz), 2.45 (m, 1H), 2.17 (m, 1H), (2.08, 2.04) (s, 3H), 1.60−1.92 (m, 1H), 0.89 (overlap, 6H); ^{13}C NMR of the mixture ($CDCl_3$) δ (170.9, 170.3), 159.3, (130.9, 130.8), (130.2, 129.3), (114.2, 114.1), (98.8, 96.4), (69.6, 69.3), (65.0, 61.4), 55.8, (39.6, 37.9), (32.1, 29.6), (22.1, 22.0), (21.3, 20.8), (19.0, 17.8). Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.49; H, 7.92, N, 4.78. Found: C, 65.37; H, 7.89; N, 4.74.

Oxidation of Isoxazolidines. General Condition A. To a mixture of *N*-pMB-isoxazolidine **6** (0.7 mmol), methylene chloride (7 mL), and H_2O (0.7 mL) was added DDQ (1.8 mmol) at rt. After stirring at this temperature for about 3 h (monitored by TLC), 15 mL of aqueous $NaHCO_3$ solution was added and extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were dried ($MgSO_4$), and the solvents removed in vacuo to give a crude product. This material was then chromotographed on silica gel eluting with 20−60% EtOAc/petroleum ether (5−10% MeOH/EtOAc for **8a** and **8b**) to give the pure product.

Oxidation of Isoxazolidines. General Condition B. To a mixture of *N*-pMB-isoxazolidine (0.7 mmol), methylene chloride (7 mL), H_2O (0.7 mL), and triethylamine (0.07 mmol) was added DDQ (1.8 mmol) at rt. After stirring at this temperature for about 2 h (monitored by TLC), 15 mL of aqueous $NaHCO_3$ solution was added and extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were dried ($MgSO_4$), and the solvents were removed in vacuo to give a crude product. This material was then chromotographed on silica gel eluting with 20−60% EtOAc/petroleum ether to give the pure product.

3-*n*-Propyl-5-(methoxycarbonyl)-2-isoxazoline (3a): oil. ^{1}H NMR ($CDCl_3$) δ 4.97 (t, 1H, J = 9.0 Hz), 3.77 (s, 3H), 3.19 (d, 2H, J = 9.0 Hz), 2.34 (t, 2H, J = 7.7 Hz), 1.60 (m, 2H), 0.95 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 171.4, 158.7, 77.3, 53.2, 41.5, 29.7, 20.3, 14.3; HRMS calcd for $C_8H_{13}NO_3$: 171.0895. Found: 171.0896.

3-Isopropyl-5-(methoxycarbonyl)-2-isoxazoline (3b): oil. ^{1}H NMR ($CDCl_3$) δ 4.96 (t, 1H, J = 8.9 Hz), 3.77 (s, 3H), 3.21 (d, 2H, J = 8.9 Hz), 2.73 (septet, 1H, J = 6.8 Hz), 1.18 (d, 6H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 171.4, 163.3, 77.4, 53.2, 39.6, 28.2, 20.7, 20.6; HRMS calcd for $C_8H_{13}NO_3$: 171.0895. Found: 171.0893. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65, N, 8.18. Found: C, 56.22; H, 7.65; N, 8.14.

3-Phenyl-5-(methoxycarbonyl)-2-isoxazoline (3c): white solid. mp 72−73 °C; ^{1}H NMR ($CDCl_3$) δ 7.68 (m, 2H), 7.41 (m, 3H), 5.19 (dd, 1H, J = 8.06, 10.18 Hz), 3.82 (s, 3H), 3.65 (dd, 2H, J = 8.06, 10.18 Hz); ^{13}C NMR ($CDCl_3$) δ 171.1, 156.4, 130.9, 129.2, 127.4, 78.5, 53.3, 39.5; HRMS calcd for $C_{11}H_{11}NO_3$: 205.0739. Found: 205.0745. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40, N, 6.83. Found: C, 64.39; H, 5.45; N, 6.81.

3-Phenyl-5-(4-methylphenyl)-2-isoxazoline (3d): white solid. mp 94−95 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (m, 2H), 7.43 (m, 3H), 7.31 (d, 2H, J = 8.14 Hz), 7.20 (d, 2H, J = 8.14 Hz), 5.72 (dd, 1H, J = 10.95, 8.50 Hz), 3.76 (dd, 1H, J = 10.95, 16.66 Hz), 3.34 (dd, 1H, J = 8.50, 16.66 Hz), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.6, 138.5, 138.4, 130.5, 129.8, 129.2, 127.2, 126.4, 83.1, 43.6, 21.8; HRMS calcd for $C_{16}H_{15}NO$: 237.1154. Found: 237.1149. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37, N, 5.90. Found: C, 81.08; H, 6.45; N, 5.87.

3-*n*-Propyl-5-cyano-2-isoxazoline (3e): oil. ^{1}H NMR ($CDCl_3$) δ 5.17 (dd, 1H, J = 10.3, 6.1 Hz), 3.30 (m, 2H), 2.40 (t, 2H, J = 7.7 Hz), 1.64 (m, 2H), 0.99 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 159.0, 117.8, 66.1, 43.7, 29.5, 20.2, 14.3; HRMS calcd for $C_7H_{10}N_2O$: 138.0793. Found: 138.0801.

3-[3-[(Tetrahydro-2*H*-pyran-2-yl)oxy]propyl]-5-cyano-2-isoxazoline (3f): oil. ^{1}H NMR ($CDCl_3$) δ 5.17 (dd, 1H, J = 10.52, 6.46 Hz), 4.56 (t, 1H, J = 1.84 Hz), 3.82 (m, 2H), 3.40 (m, 4H), 2.55 (t, 2H, J = 7.70 Hz), 1.91 (m, 2H), 1.60 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 159.0, 117.8, 99.6, 66.9, 66.1, 63.1, 43.9, 31.2, 26.9, 25.9, 25.0, 20.3; HRMS calcd for $C_{12}H_{18}N_2O_3$: 238.1317. Found: 238.1299.

3-*n*-Propyl-5-acetoxy-2-isoxazoline (3g): oil. ^{1}H NMR ($CDCl_3$) δ 6.66 (dd, 1H, J = 6.7, 1.4 Hz), 3.21 (dd, 1H, J = 18.0, 6.7 Hz), 2.87 (dd, 1H, J = 18.0, 1.4 Hz), 2.43 (t, 2H, J = 7.6 Hz), 2.06 (s, 3H), 1.64 (m, 2H), 0.99 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 170.2, 159.7, 95.8, 43.9, 29.7, 21.7, 20.4, 14.2; HRMS calcd for $C_8H_{13}NO_3$: 171.0895. Found: 171.0894. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65, N, 8.18. Found: C, 56.68; H, 7.50; N, 7.67.

3-Isopropyl-5-acetoxy-2-isoxazoline (3h): oil. ^{1}H NMR ($CDCl_3$) δ 6.65 (dd, 1H, J = 6.7, 1.4 Hz), 3.21 (dd, 1H, J = 18.5, 6.7 Hz), 2.89 (dd, 1H, J = 18.5, 1.4 Hz), 2.81 (septet, 1H, J = 6.9 Hz), 1.22 (d, 6H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 170.2, 156.2, 95.9, 42.2, 28.3, 21.7, 20.8, 20.5; HRMS calcd for $C_8H_{13}NO_3$: 171.0895. Found: 171.0886.

(5′*S*)-6-Chloro-9-[3-(2,2-dimethyl-1,3-dioxolan-4-yl)-4,5-dihydro-1,2-isoxazol-5-yl]purine (8a): oil.[11c] ^{1}H NMR ($CDCl_3$) δ 8.71 (s, 1H), 8.18 (s, 1H), 6.77 (t, 1H, J = 5.6 Hz), 5.11 (t, 1H, J = 6.1 Hz), 4.36 (dd, 2H, J = 1.1, 6.0 Hz), 3.75 (d, 2H, J = 5.9 Hz), 1.46 (s, 3H), 1.41 (s, 3H).

(5′*S*)-N^4-(*tert*-Butyloxycarbonyl)-1-[3-(2,2-dimethyl-1,3-dioxolan-4-yl)-4,5-dihydro-1,2-isoxazol-5-yl]cytosine (8b): oil.[11c] ^{1}H NMR ($CDCl_3$) 7.62 (d, 1H, J = 7.5 Hz), 7.21 (d, 1H, 7.3 Hz), 6.53 (dd, 1H, J = 2.5, 8.6 Hz), 4.96 (t, 1H, J = 5.5 Hz), 3.94 (m, 1H), 3.72 (dd, 1H, 8.4, 19.0 Hz), 3.17 (dd, 1H, J = 2.6, 19.1 Hz), 1.51 (s, 9H), 1.39 (s, 3H), 1.37 (s, 3H).

(5′*S*) 9-[3-{Hydroxymethyl)-4,5-dihydro-1,2-isoxazol-5-yl]adenine (9a): white crystal. mp 76−78 °C; ^{1}H NMR (CD_3OD) δ 8.20 (s, 1H), 8.14 (s, 1H), 6.85 (dd, 1H, J = 4.2, 8.1 Hz), 4.53 (s, 2H), 3.73 (dd, 1H, J = 6.2, 8.0 Hz), 3.33 (dd, 1H, J = 4.3, 8.0 Hz). Anal. Calcd for $C_9H_{10}N_6O_2$ $2H_2O$: C, 39.94; H, 5.22, N, 31.08. Found: C, 40.40; H, 5.57; N, 29.61.

(5′*S*)-1-[3-(Hydroxymethyl)-4,5-dihydro-1,2-isoxazol-5-yl]-cytosine (9b): mp 168 °C dec; $[\alpha]^{25}_D$ = +270.1 (*c* 0.11, MeOH). ^{1}H NMR (CD_3OD) δ 7.74 (d, 1H, J = 7.8 Hz), 6.57 (dd, 1H, J = 2.6, 9.2 Hz), 6.11 (d, 1H, J = 7.8 Hz), 4.40 (s, 2H), 3.71 (dd, 1H, J = 9.2, 17.8 Hz), 3.37 (dd, 1H, J = 2.4, 17.0 Hz). Anal. Calcd for $C_8H_9N_3O_4 \cdot 0.5H_2O$: C, 43.64; H, 4.51, N, 19.08. Found: C, 43.45; H, 4.38; N, 18.64.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of the intermediates and final products (36 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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