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Synthesis and Antiviral Evaluation of Some 3'-Carboxymethyl-3'-deoxyadenosine Derivatives

Houguang Shi
Brigham Young University - Provo

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SYNTHESIS AND ANTIVIRAL EVALUATION OF SOME 3'-CARBOXY-METHYL-3'-DEOXYADENOSINE DERIVATIVES

by

Houguang Shi

A thesis submitted to the faculty of

Brigham Young University

in partial fulfillment of the requirements for the degree of

Master of Science

Department of Chemistry and Biochemistry

Brigham Young University

August 2007
This thesis has been read by each member of the following graduate committee and by majority vote has been found to be satisfactory.

Date                                                                 Matt A. Peterson, Chair

Date                                                                 Merritt B. Andrus

Date                                                                 Heidi R. Vollmer-Snarr

Date                                                                 Greg F. Burton
As chair of the candidate’s graduate committee, I have read the thesis of Houguang Shi in its final form and have found that (1) its format, citations, and bibliographical style are consistent and acceptable and fulfill university and department style requirements; (2) its illustrative materials including figures, tables, and charts are in place; and (3) the final manuscript is satisfactory to the graduate committee and is ready for submission to the university library.

Date

Matt A. Peterson
Chair, Graduate Committee

Accepted for the Department

David V. Dearden
Graduate Coordinator

Accepted for the College

Thomas W. Sederberg, Associate Dean
College of Physical and Mathematical Sciences
SYNTHESIS AND ANTIVIRAL EVALUATION OF SOME 3'-CARBOXY-
METHYL-3'-DEOXYADENOSINE DERIVATIVES

Houguang Shi
Department of Chemistry and Biochemistry
Master of Science

3'-Carboxymethyl-3'-deoxyadenosine derivatives were prepared from 2'-O-TBDMS-3'-
deoxy-3'-[(ethoxycarbonyl)methyl]adenosine (1) via simple and efficient procedures. Conversion of 1 to 5'-azido-2'-O-TBDMS-3', 5'-dideoxy -3'-[(ethoxycarbonyl) methyl]adenosine (4) was accomplished via a novel one-pot method employing 5'-activation (TosCl) followed by efficient nucleophilic displacement with tetramethylguanidinium azide. Compound 4 was converted to a 5'-[\(N\)-methylcarbamoyl]amino] derivative (5) via one-pot reduction/acylation employing \(H_2/Pd-C\) followed by treatment with \(p\)-nitrophenyl \(N\)-methylcarbamate. The latter step of this two-step process required an efficient source of \(p\)-nitrophenyl \(N\)-methylcarbamate, thus a highly efficient new method for preparing \(p\)-nitrophenyl \(N\)-alkylcarbamate was developed. \(N^6\)-phenylcarbamoyl groups were introduced by treatment with phenylisocyanate, and an efficient new method
for lactonization of 2'-O-TBDMS-3'-deoxy-3'-'[(ethoxycarbonyl)methyl]adenosines to give corresponding 2', 3'-lactones was also developed. Target compounds were evaluated for anti-HIV and anti-HIV integrase activities, but were not active at the concentrations tested.
ACKNOWLEDGMENTS

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Introduction

2' and 3'-C-Branched nucleosides have been attractive synthetic targets for quite some time due to their potential biological activities. For example, hepatitis C virus (HCV) RNA replication has been potently inhibited by 2'-C-β-methyladenosine and the corresponding 7-deazaadenosine analogue in vivo\textsuperscript{1,2} (Figure 1).

![Figure 1. 2'-C-β-Methyladenosine and its 7-deaza analogue.](image)

2'-C-β-Methyladenosine exhibited resistance against adenosine deaminase and was shown to inhibit KB cells.\textsuperscript{3} 2'-C-β-Difluoromethyl derivatives were also synthesized as potential mediators of RNA function in vitro (Figure 2).\textsuperscript{4} Additional 2' C-branched ribonucleosides include 2'-C-vinyl or 2'-C-ethynylribonucleosides which have been synthesized as bioorganic tools and potential antiviral agents (Figure 3).\textsuperscript{5} Like 2'-C-branched nucleosides, 3'-C-methylribonucleosides and 3'-C-methyl-2'-deoxyribonucleosides have demonstrated interesting properties.\textsuperscript{6}
The 3'-C-branched deoxynucleosides can be incorporated into single stranded viral DNA\(^7\) and 3'-C-methyladenosine (3'-Me-Ado) showed significant activity against human myelogenous leukemia K562, multidrug resistant human leukemia k562IU, human promyelocytic leukemia HL-60, human breast carcinoma MCF-7 and human colon carcinoma HT-29 cell lines in vitro (Table 1).\(^8\)
Table 1. In vitro activities of 3'-Me-Ado (IC$_{50}$ in µM)$^a$ against K562, K562IU, HT-29, and MCF-7 Cell Lines.\(^8\)

<table>
<thead>
<tr>
<th>Compound</th>
<th>K562</th>
<th>K562IU</th>
<th>HT-29</th>
<th>MCF-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>3'-Me-Ado</td>
<td>18.2</td>
<td>38.3</td>
<td>23.2</td>
<td>17.5</td>
</tr>
</tbody>
</table>

$^a$IC$_{50}$ values show the drug concentration required to inhibit cancer cell replication by 50%.

Intramolecular Reformatsky reaction has been used to synthesize 3'-β-branched uridine derivatives. This represents the first time SmI$_2$-mediated carbon-carbon bond formation was employed for the synthesis of nucleoside derivatives$^9$ (Scheme 1).

![Scheme 1. Synthesis of 3'-β-branched uridine derivative by intramolecular Reformatsky reaction.](image)

Nucleoside [3.3.0]-γ-butyrolactones have increased reactivity relative to monocyclic lactones and can couple with 5'-amino-5'-deoxynucleosides to give amide-linked nucleotide-analouges directly. Since protection/deprotection and purification steps could be avoided, this coupling reaction offers advantages not provided conventional DCC-promoted coupling reactions (Scheme 2).\(^{10}\)
Compounds 9-[2', 3'-dideoxy-3'-C-(hydroxymethyl)-β-D-erythro-pentofuranosyl]adenine and 6-hexyloxy-9-[2', 3'-dideoxy-3'-C-(hydroxymethyl)-β-D-erythro-pentofuranosyl] purine were tested for HIV inhibition\textsuperscript{11} and 9-[2', 3'-dideoxy-3'-C-(hydroxymethyl)-β-D-erythro-pentofuranosyl] adenine had very similar effects on HIV replication when compared to standard anti-HIV agents AZT and ddI. The synthesis of these compounds is illustrated in scheme 3 and involved photochemical ring expansion of (2S)-trans-2, 3-bis [(benzoyloxy)methyl]cyclobutanone and a 6-substituted purine.

**Scheme 2.** Amide-linked nucleotide-analogues.

**Scheme 3.** Photochemical synthesis of 2', 3'-dideoxy-3'-C-hydroxymethyl nucleosides.
1-(3'-C-Ethynyl-β-D-erythro-pentofuranosyl)uracil (EUrd) was designed as a potential antitumor agent. A series of 3'-C-ethynyl nucleoside analogues of EUrd was prepared (Figure 4) and tested against mouse leukemia L1210 and human nasopharyngeal KB cells (Table 2).

Among these 3'-C-ethynyl-β-D-erythro-pentofuranosyl nucleosides, ECyd was the most effective against KB and L1210 cells. EUrd had almost the same effect against KB cells as ECyd but much less against L1210 than ECyd. EFCyd and EFUrd both showed reduced activity.

**Figure 4.** 3’-C-Ethynyl nucleoside analogues of EUrd
Table 2. In vitro activities of various 3'-C-ethynyl-β-D-erythro-pentofuranosyl nucleosides (IC\textsubscript{50} in µM) against L1210 and KB cells.\textsuperscript{12}

<table>
<thead>
<tr>
<th>Compounds</th>
<th>KB</th>
<th>L1210</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECyd</td>
<td>0.028</td>
<td>0.016</td>
</tr>
<tr>
<td>EFCyd</td>
<td>0.46</td>
<td>0.53</td>
</tr>
<tr>
<td>EUrd</td>
<td>0.029</td>
<td>0.13</td>
</tr>
<tr>
<td>EFUrd</td>
<td>1.4</td>
<td>2.5</td>
</tr>
</tbody>
</table>

The interesting biological activities of the above discussed 2'- or 3'-branched nucleosides prompted us to consider 3'-carboxymethyl-3'-deoxyadenosine derivatives as potential inhibitors of HIV integrase (Figure 5).

**Figure 5.** Nucleosides as inhibitors of HIV IN.

HIV Integrase (IN) plays an important role in integrating viral DNA into the host genome. IN is part of a superfamily of polynucleotidyl transferases.\textsuperscript{13} In the active site of IN, a metal dication is required for catalysis. The metal dication is essential for 3'-end processing of viral DNA and strand transfer (Figure 6).
By magnesium-mediated phosphodiester hydrolysis, IN catalyzes cleavage of a GT dinucleotide from each 3'-end of the viral DNA. In the strand transfer process, each free 3'-OH on the 3'-processed viral cDNA undergoes transesterification to produce totally integrated provirus. We proposed that appropriately functionalized 3'-carboxymethyl-3'-deoxyadenosine derivatives might be inhibitors of IN by binding to the active site Mg\(^{2+}\) and active site amino acid residues (Figure 5). Ligand-docking calculations and photo-crosslinking experiments both supported binding interactions of IN and the 3'-terminal deoxyadenosine of its natural DNA substrate.\(^{14}\) These observations supported the notion that 3'-carboxymethyl-3'-deoxyadenosine derivatives might bind to HIV IN and thus potentially inhibit its normal function. Accordingly, we performed docking studies (FlexX, Tripos, Inc.) where R\(^1\) and R\(^2\) were varied (compound I, Figure 5) and various metal binding moieties were also examined. Using the FlexX software, a virtual library consisting of approximately 49,000 compounds was docked against the active site of HIV IN crystal structure 1BIU. The library compounds were generated by varying R\(^1\) and R\(^2\) with 222 different functional group at these position (222 \(\times\) 222 \(\approx\) 49,000). The metal
binding moiety was CH$_2$CO$_2$H. The top binding compounds from the library were identified, and a majority of the top 30 hits (lowest binding scores determined by FlexX) had R$^1 = \text{CH}_3\text{NHCONH}$. The most common R$^2$ group in this set was R$^2 = \text{PhNHCONH}$. Binding interactions for the top hit from the library are shown in Figure 7.

**Figure 7.** Binding interactions for the top hit.
Synthesis of 3'-Carboxymethyl-3'-deoxyadenosine Derivatives

Based on the foregoing discussion, we prepared a series of 3'-carboxymethyl-3'-deoxyadenosine derivatives which could potentially inhibit HIV. Our synthesis began with compound 1 which was easily prepared in five steps from adenosine (Scheme 4).

![Scheme 4](image)

Scheme 4. Preparation of compound 1 from adenosine.

In order to synthesize 5'-chloro-5'-deoxyadenosine derivative 2, we treated compound 1 with standard chlorination conditions (SOCl₂/Pyr/CH₂Cl₂) and obtained desired product in low yields (30%) (Scheme 5). There were large amounts of an unisolated polar byproduct observed on the baseline by TLC. We reasoned this byproduct might be the N³, 5'-cyclonucleoside salt.
Compound 3 was formed in excellent yield (77%) by treatment of compound 1 with TsCl/DMAP in cold CH₂Cl₂ (Scheme 6).¹⁷

We attempted to convert compounds 2 and 3 into 5'-azido-5'-deoxyadenosine derivative 4 using standard conditions (NaN₃/DMF).¹⁸ Unfortunately yields for compound 4 were unacceptably low (20–40%). Large amounts of a very polar byproduct (TLC) suggested that the main reason for these low yields is that intramolecular alkylation of N3 competes with intermolecular nucleophilic substitution of 5'-activated adenosine derivatives to form cyclonucleosides¹⁹ and derived rearrangement products.²⁰
With this as our assumption, we proposed that the yields for compound 4 might be improved if concentrations of the soluble azide nucleophile could be increased. Solutions to the problem of adenosine cyclonucleoside formation have been previously suggested. These reports show that protecting either N6 or N1 with electron withdrawing groups decreases electron-density of the adenine base. While such approaches successfully suppress cyclonucleoside formation, they do increase the length of the synthesis which can lead to decreased yields of the target compounds. Since we did not wish to unnecessarily extend the length of our synthesis by introducing additional protection and deprotection steps which could decrease the overall yields of compound 4, we investigated optimal conditions for preparing this target (Table 3). Ultimately we found that compound 4 can be prepared in excellent yield (83%) by using 7 equiv. of tetramethylguanidinium azide (TMGA; [(Me₂N)₂CNH₂]N₃) in DMF (65 °C) (Table 3).

Table 3. Investigation of azido-nucleophilic substitution of compounds 2 and 3.

\[
\begin{align*}
\text{2} & \quad R = \text{Cl} \\
\text{3} & \quad R = \text{OTs}
\end{align*}
\]
<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Azido reagent</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time(h)</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>NaN₃(10 equiv)</td>
<td>DMSO</td>
<td>40</td>
<td>96</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>NaN₃(10 equiv)</td>
<td>DMF</td>
<td>40</td>
<td>84</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>NaN₃(10 equiv)</td>
<td>DMF</td>
<td>65</td>
<td>72</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>NaN₃(10 equiv)</td>
<td>DMF</td>
<td>100</td>
<td>9</td>
<td>39</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>NaN₃(10 equiv)</td>
<td>EtOAc</td>
<td>40</td>
<td>96</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>NaN₃(10 equiv)</td>
<td>EtOAc/H₂O</td>
<td>40</td>
<td>96</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>NaN₃(10 equiv)</td>
<td>THF</td>
<td>40</td>
<td>96</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>NaN₃(10 equiv)</td>
<td>Acetone</td>
<td>40</td>
<td>96</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>NaN₃(10 equiv)</td>
<td>DMF</td>
<td>40</td>
<td>96</td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>NaN₃(10 equiv)</td>
<td>DMF</td>
<td>25</td>
<td>66</td>
<td>20</td>
</tr>
<tr>
<td>11</td>
<td>3</td>
<td>NaN₃(10 equiv)</td>
<td>EtOAc</td>
<td>60</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td>12</td>
<td>3</td>
<td>NaN₃(10 equiv)</td>
<td>THF</td>
<td>60</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td>13</td>
<td>3</td>
<td>TMGA (7 equiv)</td>
<td>DMF</td>
<td>25</td>
<td>68</td>
<td>70</td>
</tr>
<tr>
<td>14</td>
<td>3</td>
<td>TMGA (7 equiv)</td>
<td>DMF</td>
<td>65</td>
<td>7</td>
<td>83</td>
</tr>
<tr>
<td>15</td>
<td>3</td>
<td>TMGA (7 equiv)</td>
<td>DMF</td>
<td>100</td>
<td>1</td>
<td>81</td>
</tr>
<tr>
<td>16</td>
<td>3</td>
<td>TMGA (7 equiv)</td>
<td>DMF</td>
<td>100</td>
<td>10</td>
<td>79</td>
</tr>
</tbody>
</table>

To the best of our knowledge, this represents the first time TMGA has been used to solve the problem of cyclonucleoside formation.
In order to introduce the 5’-N-methylurea group indicated by docking studies, compound 4 was hydrogenated and the resulting 5’-amino-5’-deoxyadenosine intermediate was treated with 4-nitrophényl-N-methylcarbamate to provide compound 5 (Scheme 7).

![Chemical structure 4 to 5](attachment:image.png)

**Scheme 7.** Synthesis of compound 5.
Reagents: i. H₂/Pd-C/EtOAc, ii. 4-NO₂-C₆H₄OCONHCH₃/Na₂CO₃.

Since published methods for preparing 4-nitrophényl-N-methylcarbamate suffer from several limitations including low yields, labor intensive procedures, and use of toxic reagents,²³⁻²⁷ we developed a simple and effective method for preparing this compound in high yields.²⁸ Treatment of 4-nitrophényl chloroformate with alkylammonium hydrochloride salts and solid anhydrous Na₂CO₃ provided 4-nitrophényl N-methylcarbamate in excellent yield (Scheme 8).

![Chemical structure 6](attachment:image.png)

**Scheme 8.** Preparation of 4-nitrophényl N-methylcarbamate.
We extended this method to other substrates by using different primary ammonium salts in either CH$_2$Cl$_2$ or CH$_3$CN and obtained the corresponding $N$-alkylcarbamates in excellent yields (Table 4).

**Table 4.** Preparation of 4-Nitrophenyl $N$-Alkylcarbamates.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Solvent</th>
<th>Time (h or d)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>CH$_3$-</td>
<td>CH$_2$Cl$_2$</td>
<td>48 h</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td>PhCH$_2$-</td>
<td>CH$_2$Cl$_2$</td>
<td>24 h</td>
<td>62</td>
</tr>
<tr>
<td>8</td>
<td>CH$_3$CH$_2$CH$_2$-</td>
<td>CH$_2$Cl$_2$</td>
<td>7 d</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>PhCH$_2$O-</td>
<td>CH$_2$Cl$_2$</td>
<td>22 h</td>
<td>81</td>
</tr>
<tr>
<td>10</td>
<td>CH$_3$O$_2$CCH(CH$_2$Ph)-</td>
<td>CH$_3$CN</td>
<td>24 h</td>
<td>80</td>
</tr>
<tr>
<td>11</td>
<td>CH$_3$O$_2$CCH$_2$-</td>
<td>CH$_2$Cl$_2$</td>
<td>8 h</td>
<td>82</td>
</tr>
<tr>
<td>12</td>
<td>CH$_3$O$_2$CCH(Ph)-</td>
<td>CH$_2$Cl$_2$</td>
<td>67 h</td>
<td>70</td>
</tr>
<tr>
<td>13</td>
<td>(CH$_3$)$_3$C-</td>
<td>CH$_3$CN</td>
<td>9 d</td>
<td>55</td>
</tr>
</tbody>
</table>

There was a pronounced solvent effect for the synthesis of 4-nitrophenyl $N$-methylcarbamate. Yields for the reaction in CH$_3$CN were much lower than in CH$_2$Cl$_2$ (Table 5).
Table 5. Optimization of synthesis of 4-nitrophenyl N-methylcarbamate.

<table>
<thead>
<tr>
<th>Product</th>
<th>Solvent</th>
<th>Concentration</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-nitrophenyl N-methylcarbamate</td>
<td>CH₂Cl₂</td>
<td>0.2 M</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>CH₃CN</td>
<td>0.2 M</td>
<td>25</td>
</tr>
<tr>
<td>4-nitrophenyl N-methylcarbamate</td>
<td>CH₂Cl₂</td>
<td>0.1 M</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>CH₃CN</td>
<td>0.1 M</td>
<td>50</td>
</tr>
<tr>
<td>4-nitrophenyl N-methylcarbamate</td>
<td>CH₂Cl₂</td>
<td>0.04 M</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>CH₃CN</td>
<td>0.04 M</td>
<td>60</td>
</tr>
</tbody>
</table>

The major byproduct for these reactions was the bis-substitution product 1, 3-dimethyl urea. The concentrations of this byproduct were higher in CH₃CN than in CH₂Cl₂ and in the higher concentration reactions in either solvent.

Treatment of Compound 4 with NaOH/H₂O/MeOH/THF gave compound 14 in good yield (85%) (Scheme 9).

\[ \text{Scheme 9. Synthesis of compound 14.} \]
\[ \text{Reagents: NaOH/H₂O/MeOH/THF.} \]

Treatment of compound 14 with carbonyldiimidazole and N-methoxymethylamine gave compound 15 (Scheme 10).
Scheme 10. Synthesis of compound 15.
Reagents: Carbonyldiimidazole/CH₃NHOCH₂HCl/Et₃N.

Compounds 16 and 17 were prepared by treatment of 4 and 15 with phenylisocyanate in CH₂Cl₂ (Scheme 11).

Scheme 11. Synthesis of compounds 16 and 17.
Reagent: PhNCO/CH₂Cl₂.

Two of our target compounds (18 and 19) can be achieved via one-pot reduction/acylation of 16 (17) using the same conditions employed for transformation of compound 4 into compound 5 (Scheme 12).
Scheme 12. Synthesis of compounds 18 and 19.
Reagents: i. H₂/Pd-C/EtOAc, ii. 4-NO₂-C₆H₄OCONHCH₃/Na₂CO₃.

Attempted synthesis of the 2', 3'-lactone derived from compound 1 by employing conditions previously reported for the synthesis of a related uridine-derived 2', 3'-lactone (TBAF/THF)¹⁵ was complicated by purification problems stemming from co-elution of tetrabutylammonium salts with the derived product. We reasoned that the problem of co-elution of tetrabutylammonium salts could be avoided by employing alternative desilylating agents. Toward this end, we screened a variety of known conditions for desilylating the tert-butyldimethylsilyl group (TBDMS). The TBDMS group has been regarded as one of most useful protective groups for the hydroxyl group since it is easily introduced and can be cleaved readily without affecting other sensitive moieties. While there have been numerous reagents used to deprotect TBDMS groups up to the present, none of the alternatives we examined were successful. Eventually, we investigated a biphasic system consisting of KF/PhCH₂N(Et)₃Cl/CH₃CN/H₂O. We were delighted to find that these conditions worked well and that phase transfer salts caused no problems with the purifications (Scheme 13).
Since we were unable to find any literature precedent for this reaction (CAS and Beilstein Crossfire searches), we decided to test its scope and generality. Accordingly, compounds 21–27 were prepared (Figure 8) and subjected to our biphasic KF-promoted desilylation conditions (Table 6).

**Scheme 13.** Desilylation reaction of compound 1. Reagents: KF/PhCH₂N(Et)₃Cl/CH₃CN/H₂O.

**Figure 8.** Compounds 21–27.
Table 6. Deprotection of TBDMS groups of compounds 21–27.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Biphasic conditions</th>
<th>Time(h)</th>
<th>Yield(%)</th>
<th>Product</th>
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<td>PhCH$_2$N(Et)$_3$Cl (2.5 equiv)</td>
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<td>H$_2$O/CH$_3$CN</td>
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From the results we obtained, it is evident that this biphasic method is effective for deprotection of tert-butyldimethylsilyl ethers from a range of substrates.

Application of the same conditions to compounds 4, 5, 16 and 18 gave compounds 28, 29, 30 and 31 in good yields (79–92%) (Scheme 14).
Compounds 20, 28, 30 and 31 were saponified to provide compounds 32–35 (Scheme 15).

After our target compounds 18, 19, 30, 31, 33–35 were all synthesized, we focused on evaluating the potential anti-HIV and IN inhibitory activities of these 3’-carboxy methyl-3’-deoxyadenosine derivatives. Unfortunately the compounds tested did not show...
promising anti-HIV or IN inhibitory activities (Table 7). The lack of promising activity may be due to possible binding to sites remote from the active site, or may also reflect weaknesses in the algorithm employed for the docking calculations.\textsuperscript{29, 30} Entropic and enthalpic contributions of dissociating water ligands from the active-site Mg\textsuperscript{2+} are not accounted for by FlexX, and the FlexX scoring function is known to give occasional “false positives”.\textsuperscript{31} Since no full-length HIV IN structure has been reported, our lack of success in binding potent lead inhibitors may be due to incomplete structural information.

**Table 7.** Activities of test compounds in biochemical assays.

<table>
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<tr>
<th>Compd</th>
<th>ED\textsubscript{50}\textsuperscript{a} (µM)</th>
<th>CT\textsubscript{50}\textsuperscript{b} (µM)</th>
<th>CT\textsubscript{5}\textsuperscript{c} (µM)</th>
<th>IC\textsubscript{50}\textsuperscript{d} (µM)</th>
<th>EP\textsuperscript{e}</th>
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<td>143</td>
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<td>&gt;10</td>
<td>&gt;10</td>
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</tbody>
</table>

\textsuperscript{a}Inhibitory concentration required to protect MT-2 cells from 50% viral induced cell death.  
\textsuperscript{b}Cytotoxic concentration required to inhibit cell growth by 50%.  
\textsuperscript{c}Cytotoxic concentration required to inhibit cell growth by 5%.  
\textsuperscript{d}Inhibitory concentration required to inhibit IN 3'-end processing (EP) or strand transfer (ST) by 50%.  
\textsuperscript{e}3'-End processing.  
\textsuperscript{f}Strand transfer.
Conclusion
A series of 3'-carboxymethyl-3'-deoxyadenosine derivatives was prepared and their anti-HIV and IN inhibitory activities were tested. Although the tested derivatives did not exhibit the anticipated biological activities, significant results from the synthetic procedures were obtained: (1) TMGA-promoted nucleophilic substitution of compound 3 gave excellent yields of 5'-azido-5'-deoxyadenosine derivative 4, thus demonstrating a potentially general alternative to reported strategies for suppressing cyclonucleoside formation from 5'-activated adenosine precursors; (2) the biphasic reagent/solvent KF/PhCH$_2$N(Et)$_3$Cl/CH$_3$CN/H$_2$O gave enhanced yields of 2', 3'-lactone nucleosides from 2'-O-TBDMS-3'-deoxy-3'-'[(ethoxycarbonyl)methyl] precursors and appears to be a generally applicable reagent system for cleavage of TBDMS groups from a broad array of substrates; (3) an effective biphasic method for preparation of 4-nitrophenyl $N$-methylcarbamate and related $N$-alkyl derivatives was developed; and (4) conversion of 5'-azido-5'-deoxyadenosine analogues to $N$-methylurea derivatives was achieved via an efficient one-pot acylation/reduction procedure.
**Experimental Section**

**General Experimental**

Flash chromatography was carried out using 230–400 mesh silica gel. Preparative TLC was performed using Merck Kieselgel 60 F$_{254}$ sheets. UV spectra were obtained in MeOH and water. $^1$H NMR spectra were obtained on either a Varian 300 MHz or a Varian 500 MHz spectrometer using internal references at $\delta$ 7.27 (CDCl$_3$) and $\delta$ 2.50 (DMSO-$d_6$). $^{13}$C NMR spectra were obtained using internal references at $\delta$ 77.3 (CDCl$_3$) and $\delta$ 39.5 (DMSO-$d_6$). High resolution mass spectra were obtained by using FAB and ESI techniques. Commercially available reagents were used as supplied, and tetramethylguanidinium azide$^{32}$ and compound 1$^{15}$ were prepared as previously reported. All water sensitive reactions were performed in flame-dried flasks under Nitrogen or Argon. Solvents used in the reactions were dried by passing through columns of activated alumina under Argon.
Experimental Procedures

\[
\begin{align*}
\text{Thionyl chloride (2 M in CH}_2\text{Cl}_2, \ 1.0 \ \text{mL}, \ 2.0 \ \text{mmol}) & \text{ was added to a stirred solution of 1 (200 mg, 0.443 mmol) and pyridine (100 mg, 1.27 mmol) in CH}_2\text{Cl}_2 (3.0 \ \text{mL}) \text{ at 0°C. After the mixture was stirred for 30 min, it was stirred at room temperature overnight. Volatiles were removed under reduced pressure and the residue was partitioned (EtOAc//NaHCO}_3\text{(aq)). The organic layer was dried by anhydrous sodium sulfate (Na}_2\text{SO}_4), filtered, and volatiles were removed under reduced pressure. The residue was flash chromatographed (5% MeOH/CH}_2\text{Cl}_2) \text{ to give 2 (62 mg, 30%): UV (MeOH) } & \\
\lambda_{\text{max}}\ 260 \text{ nm, } \lambda_{\text{min}}\ 230 \text{ nm; } & \\
^1\text{H NMR (CDCl}_3, \ 500 \ \text{MHz}) \ & \\
\delta\ 8.35 \ (s, \ 1\text{H}), \ 8.18 \ (s, \ 1\text{H}), \ 5.97 \ (s, \ 1\text{H}), \ 5.59 \ (\text{br s, 2H}), \ 4.94 \ (d, \ J = 4.5 \ \text{Hz, 1H}), \ 4.37–4.34 \ (m, \ 1\text{H}), \ 4.12 \ (q, \ J & \\
= 7.4 \ \text{Hz, 2H}), \ 4.01 \ (dd, \ J = 3.0, \ 12.5 \ \text{Hz, 1H}), \ 3.78 \ (dd, \ J = 4.3, \ 12.8 \ \text{Hz, 1H}), \ 2.85–2.82 & \\
(m, \ 1\text{H}), \ 2.70 \ (dd, \ J = 9.0, \ 17.0 \ \text{Hz, 1H}), \ 2.42 \ (dd, \ J = 5.8, \ 16.8 \ \text{Hz, 1H}), & \\
1.26 \ (t, \ J = 7.3 & \\
\text{Hz, 3H}), \ 0.90 \ (s, \ 9\text{H}), \ 0.15 \ (s, \ 3\text{H}), \ 0.07 \ (s, \ 3\text{H}); \ ^{13}\text{C NMR (CDCl}_3, \ 50 \ \text{MHz} \ ) & \\
\delta\ 171.9, \ 155.8, \ 153.2, \ 138.2, \ 120.4, \ 91.3, \ 82.9, \ 77.5, \ 61.1, \ 45.2, \ 40.7, \ 30.1, \ 25.9, \ 18.1, \ 14.3, & \\
-4.4, \ -5.4; \ MS \ (FAB) \ m/z \ 492.1805 \ (\text{MNa}^+) \ [C_{20}H_{32}^{35}\text{ClN}_3O_4\text{SiNa}] = 492.1810). & 
\end{align*}
\]
$2'O$-(tert-Butyldimethylsilyl)-3'-deoxy-3'-$[($ethoxycarbonyl)methyl]$-5'$-O$-($p$-toluenesulfonyl)adenosine (3).

$p$-Toluenesulfonylchloride (278 mg, 1.46 mmol) and DMAP (218 mg, 1.78 mmol) were added to a solution of 1 (378 mg, 0.837 mmol; azeotropically dried by evaporation of benzene, 5 X 20 mL) in dry CH$_2$Cl$_2$ (4.0 mL) at 0 °C. The mixture was stirred for 24 h at 0°C, then poured directly on to a chromatography column and eluted (80% EtOAc/hexanes$\uparrow$EtOAc). Appropriate fractions were pooled and volatiles were removed under reduced pressure ($\leq$ 20 °C) to give 3 (390 mg, 77%): UV (MeOH) $\lambda_{\text{max}}$ 263 nm, $\lambda_{\text{min}}$ 240 nm; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.30 (s, 1H), 7.95 (s, 1H), 7.77–7.75 (m, 2H), 7.29–7.28 (m, 2H), 5.91 (d, $J = 1.0$ Hz, 1H), 5.56 (br s, 2H), 4.85 (d, $J = 4.0$ Hz, 1H), 4.37 (dd, $J = 2.0$, 8.5 Hz, 1H), 4.27–4.20 (m, 2H), 4.11 (q, $J = 7.2$ Hz, 2H), 2.82–2.76 (m, 1H), 2.64 (dd, $J = 8.8$, 16.8 Hz, 1H), 2.42 (s, 3H), 2.32 (dd, $J = 5.5$, 17.0 Hz, 1H), 1.19 (t, $J = 7.2$ Hz, 3H), 0.89 (s, 9H), 0.14 (s, 3H), 0.03 (s, 3H); MS (FAB) $m/z$ 606.2417 (MH$^+$ [C$_{27}$H$_{46}$N$_3$O$_7$SSi] = 606.2418).
5'-Azido-2'-O-(tert-butyldimethylsilyl)-3',5'-dideoxy-3'-[(ethoxycarbonyl)methyl]-adenosine (4).

*p*-Toluenesulfonyl chloride (208 mg, 1.10 mmol), and DMAP (208 mg, 1.70 mmol) were added to a solution of 1 (360 mg, 0.797 mmol; azeotropically dried via evaporation of benzene, 5 X 20 mL) in ice-cold CH$_2$Cl$_2$ (16 mL) at 0°C. Volatiles were removed under reduced pressure (≤ 20°C) after the mixture was stirred for 24 h at 0°C. Tetramethylguanidinium azide (880 mg, 5.56 mmol) and DMF (4 mL) were added and the resulting mixture was heated at 65 °C for 7 h. The solution was cooled to room temperature and then vigorously stirred while anhydrous Et$_2$O (100 mL) was added slowly. Precipitated TMGA was filtered through celite. The white solid mass and the filter cake were washed with anhydrous Et$_2$O to ensure complete transfer of product. Volatiles were evaporated under reduced pressure (40 °C) and the residue was flash chromatographed (90% EtOAc/hexanes⇑EtOAc) to give 4 (315 mg, 83%): UV (MeOH) λ$_{\text{max}}$ 262 nm, λ$_{\text{min}}$ 233 nm; $^1$H NMR (CDCl$_3$, 500 MHz) δ 8.36 (s, 1H), 8.16 (s, 1H), 5.98 (s, 1H), 5.54 (br s, 2H), 4.86 (d, $J$ = 5.0 Hz, 1H), 4.22–4.20 (m, 1H), 4.14 (q, $J$ = 7.0 Hz, 2H), 3.78 (dd, $J$ = 3.3, 13.8 Hz, 1H), 3.61 (dd, $J$ = 4.8, 13.8 Hz, 1H), 2.85–2.77 (m, 1H), 2.69 (dd, $J$ = 8.3, 16.8 Hz, 1H), 2.37 (dd, $J$ = 5.8, 16.8 Hz, 1H), 1.26 (t, $J$ = 7.3 Hz,
3H), 0.91 (s, 9H), 0.17 (s, 3H), 0.07 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 171.6, 155.4, 153.0, 149.4, 138.7, 120.2, 91.1, 82.2, 77.3, 60.9, 52.2, 40.0, 29.9, 25.7, 17.9, 14.1, -4.5, -5.5; MS (FAB) $m/z$ 499.2214 (MNa$^+$ [C$_{20}$H$_{32}$N$_8$O$_4$SiNa] = 499.2214).
2'-O-(tert-Butyldimethylsilyl)-3',5'-dideoxy-3'-(ethoxycarbonyl)methyl]-5'-[(N-methylcarbamoyl)amino]adenosine (5).

A solution of 4 (613 mg, 1.29 mmol) and 10% Pd–C (220 mg) in EtOAc (11 mL) was vigorously stirred overnight under an atmosphere of H₂ (balloon pressures). p-Nitrophenyl N-methyl carbamate (440 mg, 2.24 mmol) and anhydrous Na₂CO₃ (440 mg, 4.15 mmol) were added and the resulting mixture was stirred for 5 h under N₂. Solids were filtered through celite, and the filter cake was washed with EtOAc. Volatiles were removed under reduced pressure. The residue was flash chromatographed (10% MeOH/CH₂Cl₂) to give 5 (600 mg, 92%): UV (MeOH) λ max 260 nm, λ min 229 nm; ¹H NMR (CDCl₃, 500 MHz) δ 8.37 (s, 1H), 7.88 (s, 1H), 6.02 (br s, 1H), 5.78 (d, J= 4.0 Hz, 1H), 5.57 (br s, 2H), 4.95–4.93 (m, 1H), 4.51–4.38 (m, 1H), 4.24–4.22 (m, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.71–3.66 (m, 1H), 3.49 (dd, J = 4.0, 15.0 Hz, 1H), 2.84–2.80 (m, 1H), 2.80 (d, J = 5.0 Hz, 3H), 2.69 (dd, J = 6.8, 17.3 Hz, 1H), 2.49 (dd, J = 6.8, 17.3 Hz, 1H), 1.28 (t, J = 7.0 Hz, 3H), 0.84 (s, 9H), -0.07 (s, 3H), -0.14 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 172.1, 159.5, 155.8, 152.8, 149.2, 139.4, 120.4, 91.4, 83.7, 76.2, 60.7, 41.9, 39.7, 30.4, 27.1, 25.6, 17.8, 14.1, -4.80, -5.40; MS (ES) m/z 508.2699 (MH⁺ [C₂₂H₃₈N₇O₅Si] = 508.2698).
5'-Azido-2'-O-(tert-butyldimethylsilyl)-3'-(carboxymethyl)-3',5'-dideoxyadenosine (14).

NaOH (200 µL, 5.0 M, 1.0 mmol), and MeOH (400 µL) were added to a stirred solution of 4 (150 mg, 0.315 mmol) in THF (2 mL). The solution was stirred at ambient temperature until starting material had been converted to baseline product (6 h, TLC). Volatiles were removed under reduced pressure (≤ 20 °C) and the crude material was partitioned (CH₂Cl₂//H₂O). Ice was added and the pH was carefully adjusted to ≈ 3 via dropwise addition of 1% HCl (aq). The aqueous layer was washed (CH₂Cl₂) until the organic layer was UV transparent (TLC). The combined organic layers were dried by anhydrous sodium sulfate (Na₂SO₄), and then filtered. Volatiles were evaporated under reduced pressure (≤ 20 °C) to give 14 (120 mg, 85%): UV (MeOH) λ max 260 nm, λ min 233 nm; ¹H NMR (CDCl₃, 500 MHz) δ 8.32 (s, 1H), 8.25 (s, 1H), 7.27 (br s, 2H), 6.02 (s, 1H), 4.76 (d, J = 4.0 Hz, 1H), 4.25 (dd, J = 6.5, 10.5 Hz, 1H), 3.86 (d, J = 13.0 Hz, 1H), 3.63 (dd, J = 3.5, 13.5 Hz, 1H), 2.83–2.80 (m, 1H), 2.71 (dd, J = 8.5, 17.0 Hz, 1H), 2.42 (dd, J = 4.8, 17.3 Hz, 1H), 0.93 (s, 9H), 0.21 (s, 3H), 0.10 (s, 3H); ¹³C NMR (CDCl₃, 125
MHz) δ 176.1, 155.4, 151.8, 148.9, 138.8, 118.9, 91.1, 82.5, 77.9, 51.9, 39.8, 30.2, 29.7, 25.7, 18.0, -4.5, -5.5; MS (FAB) m/z 471.1902 (MNa\(^+\) \[C_{18}H_{28}N_{8}O_{4}SiNa\] = 471.1901).
5′-Azido-2′-O-(tert-butyldimethylsilyl)-3′,5′-dideoxy-3′-[(N-methoxy-N-methylcarboxamido)methyl]adenosine (15).

To a stirred solution of 14 (50 mg, 0.112 mmol) in CH₂Cl₂ (1.0 mL) at 0 °C was added carbonyl diimidazole (500 µL of 0.36 M solution in CH₂Cl₂, 29 mg, 0.18 mol). The ice-bath was removed and the reaction was allowed to warm to ambient temperature for 1 h. N, O-Dimethylhydroxylamine hydrochloride (18 mg, 0.19 mmol), and Et₃N (82 mg, 0.82 mmol) were added and the reaction was followed by TLC (24 h). The solvent was removed under reduced pressure and the residue was flash chromatographed (5%MeOH/EtOAc) to give 15 (46 mg, 84%): UV (MeOH) λ max 260 nm, λ min 230 nm; ¹H NMR (CDCl₃, 500 MHz) δ 8.35 (s, 1H), 8.16 (s, 1H), 5.99 (d, J = 2.0 Hz, 1H), 5.67 (br s, 2H), 4.87–4.86 (m, 1H), 4.25–4.22 (m, 1H), 3.77 (dd, J = 2.8, 13.3 Hz, 1H), 3.70 (s, 3H), 3.65 (dd, J = 4.5, 13.5 Hz, 1H), 3.16 (s, 3H), 2.85–2.83 (m, 2H), 2.60–2.52 (m, 1H), 0.90 (s, 9H), 0.11 (s, 3H), 0.02 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 172.6, 155.7, 153.2, 149.8, 138.8, 120.3, 91.0, 82.9, 77.8, 61.5, 53.0, 39.9, 32.5, 28.4, 26.0, 18.2, -4.40, -5.10; MS (FAB) m/z 514.2327 (MNa⁺ [C₂₀H₃₃N₉O₄SiNa] = 514.2323).
5'-Azido-2'-O-(tert-butyldimethylsilyl)-3',5'-dideoxy-3'-[(ethoxycarbonyl)methyl]-N⁶- (N-phenylcarbamoyl)adenosine (16).

To a stirred solution of 4 (633 mg, 1.33 mmol) in CH₂Cl₂ (16 mL) was added phenylisocyanate (190 mg, 1.60 mmol). The resulting mixture was stirred at room temperature until TLC showed complete conversion of 4 to desired product (5 d). The mixture was added to a chromatography column directly and eluted (10–40% EtOAc/hexanes) to give 16 (755 mg, 95%): UV (MeOH) λ_max 279 nm, λ_min 243 nm; 

\[ \text{^1H NMR (CDCl}_3, 500 MHz) \delta 11.74 (s, 1H), 8.62 (s, 1H), 8.39 (s, 1H), 8.11 (s, 1H), 7.65 (d, J = 8.5 Hz, 2H), 7.39–7.36 (m, 2H), 7.14–7.12 (m, 1H), 6.04 (s, 1H), 4.86 (d, J = 5.0 Hz, 1H), 4.24–4.22 (m, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.81 (dd, J = 2.8, 13.3 Hz, 1H), 3.63 (dd, J = 4.3, 13.3 Hz, 1H), 2.81–2.79 (m, 1H), 2.69 (dd, J = 8.5, 17.0 Hz, 1H), 2.39 (dd, J = 5.3, 17.3 Hz, 1H), 1.26 (t, J = 7.3 Hz, 3H), 0.93 (s, 9H), 0.19 (s, 3H), 0.07 (s, 3H); \]

\[ \text{^13C NMR (CDCl}_3, 125 MHz) \delta 171.5, 151.4, 150.8, 150.0, 149.9, 141.5, 138.1, 129.0, 123.8, 120.2, 91.3, 82.5, 77.5, 60.9, 52.2, 40.1, 29.7, 25.7, 18.0, 14.1, -4.5, -5.5; \]

MS (FAB) m/z 596.2772 (MH⁺ [C₂₇H₃₆N₉O₅Si] = 596.2765).
5'-Azido-2'-O-(tert-butyldimethylsilyl)-3',5'-dideoxy-3'-[(N-methoxy-N-methyl-carboxamido)methyl]-N6-(N-phenylcarbamoyl)adenosine (17).

To a solution of 15 (46 mg, 0.094 mmol) in CH2Cl2 (1.0 mL) was added phenylisocyanate (12 mg, 0.10 mmol). The resulting mixture was stirred at room temperature until TLC showed complete conversion of 15 to desired product (7 d). The mixture was added to a chromatography column directly and eluted (80% EtOAc/hexanes⇑EtOAc) to give 17 (54 mg, 94%): UV (MeOH) λ\textsubscript{max} 279 nm, λ\textsubscript{min} 242 nm; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz) δ 11.77 (s, 1H), 8.63 (s, 1H), 8.40 (s, 1H), 8.13 (s, 1H), 7.66 (d, \textit{J} = 8.0 Hz, 2H), 7.40–7.37 (m, 2H), 7.15–7.11 (m, 1H), 6.05 (s, 1H), 4.88 (m, 1H), 4.28–4.26 (m, 1H), 3.82 (d, \textit{J} = 10.5 Hz, 1H), 3.71–3.66 (m, 1H), 3.70 (s, 3H), 3.17 (s, 3H), 2.86–2.53 (m, 2H), 2.56–2.53 (m, 1H), 0.90 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz) δ 172.1, 151.2, 150.8, 149.9, 141.1, 138.0, 129.0, 123.8, 120.8, 120.3, 91.0, 82.8, 77.7, 61.2, 52.5, 39.6, 32.2, 29.7, 25.7, 17.9, -4.6, -5.4; MS (ES) \textit{m/z} 633.2695 (MNa\textsuperscript{+} [C\textsubscript{27}H\textsubscript{38}N\textsubscript{10}O\textsubscript{5}SiNa] = 633.2694).
2'-O-(tert-Butyldimethylsilyl)-3',5'-dideoxy-3'-(ethoxycarbonylmethyl)-5'-
[(N-methylcarbamoyl)amino]-N⁶-(N-phenylcarbamoyl)adenosine (18).

A solution of 16 (100 mg, 0.168 mmol) and 10% Pd–C (50 mg) in EtOAc (2 mL)
was vigorously stirred for 15 h under H₂ (balloon pressures). p-Nitrophenyl N-methyl
carbamate (45 mg, 0.23 mmol) and anhydrous Na₂CO₃ (45 mg, 0.42 mmol) were added
and the resulting mixture was stirred for 4 h under N₂. Solids were removed via filtration
(celite/EtOAc), and volatiles were evaporated under reduced pressure. The crude residue
was chromatographed (5%10% MeOH/CH₂Cl₂) to give 18 (101 mg, 96%): UV (MeOH)
λ max 279 nm, λ min 242 nm; ¹H NMR (CDCl₃, 500 MHz) δ 12.31 (s, 1H), 10.13 (br s,
1H), 8.86 (s, 1H), 8.64 (s, 1H), 7.57 (d, J = 7.5 Hz, 2H), 7.42–7.39 (m, 2H), 7.21–7.18 (m,
1H), 5.94 (s, 1H), 5.78 (t, J = 6.3 Hz, 1H), 5.06–5.03 (m, 2H), 4.20 (d, J = 10.5 Hz, 1H),
4.11–4.07 (m, 2H), 3.85–3.83 (m, 1H), 3.49 (d, J = 13.0 Hz, 1H), 2.79 (dd, J = 4.5, 17.0
Hz, 1H), 2.62 (d, J = 5.0 Hz, 3H), 2.62–2.50 (m, 1H), 2.49–2.48 (m, 1H), 1.24 (t, J = 7.0
Hz, 3H), 0.94 (s, 9H), 0.27 (s, 3H), 0.11 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 172.0,
159.4, 153.3, 149.9, 149.8, 142.8, 137.3, 129.1, 124.6, 121.2, 92.0, 84.7, 77.2, 60.3, 39.7,
38.5, 28.8, 26.7, 25.7, 17.9, 14.0, -4.3, -5.8; MS (FAB) \[m/z \text{ 649.2899 (MNa}^+\text{)}\] 
\[\text{[C}_{29}\text{H}_{42}\text{N}_{8}\text{O}_{6}\text{SiNa}] = 649.2894\).
(s, 3H), 0.10 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 172.7, 159.3, 153.2, 150.04, 150.01, 149.9, 142.8, 137.5, 129.1, 124.5, 121.2, 92.1, 84.8, 77.6, 61.1, 40.3, 38.4, 32.1, 29.7, 26.8, 25.8, 18.0, -4.4, -5.5; MS (ES) $m/z$ 642.3182 ($\text{MH}^+ [C_{29}H_{44}N_9O_6\text{Si}] = 642.3184$).

3'-{(Carboxymethyl)-3'-deoxyadenosine-2',3'-lactone (20).}

To a stirred solution of 1 (50 mg, 0.11 mmol) in CH$_3$CN (1.0 mL) were added PhCH$_2$N(Et)$_3$Cl (5 mg, 0.022 mmol), KF (15 mg, 0.26 mmol), and H$_2$O (40 µL). The mixture was vigorously stirred at ambient temperature until TLC indicated that 1 had been consumed (42 h). Silica gel was added and volatiles were evaporated under reduced pressure ($\leq 20 \, ^\circ\text{C}$). The dried silica gel was poured onto the top of a chromatography column packed with CH$_2$Cl$_2$ and eluted (5% $\sim$ 10% MeOH/CH$_2$Cl$_2$). Evaporation of pooled fractions gave 20 (26 mg, 80%). $^1$H and $^{13}$C NMR and UV data agreed with reported values.$^{15}$
5'-Azido-3'-(carboxymethyl)-3',5'-dideoxyadenosine-2',3'-lactone (28).

To a stirred solution of 4 (50 mg, 0.105 mmol) in CH$_3$CN (1.0 mL) were added PhCH$_2$N(Et)$_3$Cl (5.0 mg, 0.022 mmol), KF (15 mg, 0.26 mmol), and H$_2$O (80 µL). The mixture was vigorously stirred at room temperature until TLC indicated that 4 had been consumed (72 h). Silica gel was added and volatiles were evaporated under reduced pressure ($\leq$ 20 °C). The dried silica gel was poured onto the top of a chromatography column packed with CH$_2$Cl$_2$ and eluted (2.5 $\rightarrow$ 10% MeOH/CH$_2$Cl$_2$). Evaporation of pooled fractions gave 28 (27 mg, 81%): UV (MeOH) $\lambda_{\text{max}}$ 259 nm, $\lambda_{\text{min}}$ 236 nm; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.35 (s, 1H), 7.91 (s, 1H), 6.17 (s, 1H), 5.61 (dd, $J$ = 1.0, 6.5 Hz, 1H), 5.54 (br s, 2H), 4.14–4.10 (m, 1H), 3.82–3.79 (m, 1H), 3.61 (dd, $J$ = 4.8, 12.8 Hz, 1H), 3.55 (dd, $J$ = 5.5, 13.0 Hz, 1H), 2.96 (dd, $J$ = 8.8, 18.3 Hz, 1H), 2.55 (dd, $J$ = 1.0, 18.0 Hz, 1H); $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta$ 175.6, 156.2, 152.9, 148.8, 139.9, 119.1, 88.0, 86.6, 84.1, 51.8, 40.8, 61.6; MS (ES) $m/z$ 317.1110 (MH$^+$ [C$_{12}$H$_{13}$N$_8$O$_3$] = 317.1111).

To a stirred solution of 5 (26 mg, 0.051 mmol) in CH₃CN (1.0 mL) were added PhCH₂N(Et)₃Cl (30 mg, 0.13 mmol), KF (15 mg, 0.26 mmol), and H₂O (80 µL). The mixture was vigorously stirred at room temperature until TLC showed that 5 had been consumed (9 h). The reaction mixture was added directly to a column and chromatographed (EtOAc:H₂O:CH₃CHOHCH₃ = 4:2:1) to give 29 (14 mg, 79%): UV (MeOH) λ max 260 nm, λ min 239 nm; ¹H NMR (DMSO-d₆, 500 MHz) δ 8.32 (s, 1H), 8.17 (s, 1H), 7.34 (br s, 2H), 6.24 (d, J = 1.5 Hz, 1H), 6.07 (t, J = 5.8 Hz, 1H), 5.78 (q, J = 4.7 Hz, 1 H), 5.51 (dd, J = 2.3, 7.3 Hz, 1H), 3.97–3.93 (m, 1H), 3.28–3.24 (m, 1H), 2.94 (dd, J = 8.5, 18.0 Hz, 1H), 2.53 (d, J = 5.0 Hz, 3 H), 2.51–2.46 (m, 2H); ¹³C NMR (DMSO-d₆, 125 MHz) δ 175.7, 158.6, 156.1, 152.8, 148.8, 139.6, 119.1, 87.8, 86.8, 84.5, 41.8, 40.9, 31.8, 26.3; MS (ES) m/z 348.1416 (MH⁺ [C₁₄H₁₈N₇O₄] = 348.1420).
5'-Azido-3'-(carboxymethyl)-3',5'-dideoxy-N^6-(N-phenylcarbamoyl)adenosine-2',3'-lactone (30).

To a stirred solution of 16 (73 mg, 0.123 mmol) in CH$_3$CN (2.0 mL) were added PhCH$_2$N(Et)$_3$Cl (5 mg, 0.022 mmol), KF (15 mg, 0.26 mmol), and H$_2$O (40 µL). The mixture was vigorously stirred at ambient temperature until TLC showed that 8 had been consumed (4 d). Silica gel was added and volatiles were evaporated under reduced pressure (≤ 20 °C). The dried silica gel was poured onto the top of a column packed with 75% EtOAc/hexanes and product was eluted (75% EtOAc/hexanes$\uparrow$EtOAc). Evaporation of pooled fractions gave 30 (46 mg, 86%): UV (MeOH) $\lambda_{\text{max}}$ 279, $\lambda_{\text{min}}$ 240; $^1$H NMR (DMSO-$d_6$, 500 MHz,) δ 11.70 (s, 1H), 10.21 (s, 1H), 8.72 (s, 1H), 8.66 (s, 1H), 7.63 (d, $J$ = 7.5 Hz, 2H), 7.38–7.35 (m, 2H), 7.08 (t, $J$ = 7.5 Hz, 1H), 6.43 (d, $J$ = 2.0 Hz, 1 H), 5.65 (dd, $J$ = 1.8, 6.8 Hz, 1H), 4.28–4.24 (m, 1H), 3.73 (dd, $J$ = 3.0, 13.5 Hz, 1H), 3.55–3.49 (m, 2H), 2.98 (dd, $J$ = 8.5, 18.0 Hz, 1H), 2.69 (dd, $J$ = 1.5, 18.0 Hz, 1H); $^{13}$C NMR (DMSO-$d_6$, 125 MHz) δ 175.3, 151.0, 150.7, 150.0, 142.6, 138.4, 128.9, 123.2, 120.5, 119.4, 88.2, 86.4, 84.3, 51.7, 40.6, 31.5; MS (ES) $m/z$ 436.1483 (MH$^+$ [C$_{19}$H$_{18}$N$_9$O$_4$] = 436.1482).
3’-(Carboxymethyl)-3’,5’-dideoxy-5’-[(N-methylcarbamoyl)amino]-N6-(N-phenyl-carbamoyl)adenosine-2’,3’-lactone (31).

To a stirred solution of 18 (82 mg, 0.131 mmol) in CH3CN (3.0 mL) were added PhCH2N(Et)3Cl (50 mg, 0.22 mmol), KF (22 mg, 0.38 mmol), and H2O (80 µL). The mixture was vigorously stirred at room temperature until TLC showed that 18 had been consumed (60 h). Silica gel was added and volatiles were evaporated under reduced pressure (≤ 20 °C). The dried silica gel was poured onto the top of a column packed with 5% MeOH/CH2Cl2 and eluted (5↑10% MeOH/CH2Cl2). Evaporation of pooled fractions gave 31 (56 mg, 92%): UV (MeOH) λ max 279 nm, λ min 240 nm; 1H NMR (DMSO- d6, 500 MHz) δ 11.74 (s, 1H), 10.18 (br s, 1H), 8.71 (s, 1H), 8.66 (s, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.38–7.35 (m, 2H), 7.09 (t, J = 7.5 Hz, 1H), 6.37 (d, J = 2.0 Hz, 1H), 6.05 (t, J = 6.0 Hz, 1H), 5.77 (dd, J = 4.5, 8.5 Hz, 1H), 5.57 (dd, J = 1.8, 7.3 Hz, 1H), 4.03–3.99 (m, 1H), 3.41–3.36 (m, 2H), 2.98 (dd, J = 8.5, 18.0 Hz, 1H), 2.55 (d, J = 5.0 Hz, 3H); 13C NMR (DMSO- d6, 125 MHz) δ 76.3, 159.3, 151.8, 151.6, 150.8, 143.3, 139.2, 129.7, 123.9,
121.4, 120.1, 88.8, 87.5, 85.7, 42.4, 41.5, 40.7, 32.5, 27.1; MS (ES) m/z 467.1795 (MH$^+$ [C$_{21}$H$_{23}$N$_8$O$_5$] = 467.1791).

To a solution of 20 (21 mg, 0.072 mmol) in THF:MeOH [0.6 mL, (5:1)] was added NaOH (80 µL of 1.0 M, 0.080 mmol). The resulting mixture was stirred at 65 °C until TLC showed conversion of 20 to baseline product. Volatiles were removed under reduced pressure to give 32 (24 mg, quant). The crude residue was dissolved in H$_2$O (100 µL). Silica gel and solvent A were added, and volatiles were evaporated under reduced pressure ($\leq$ 20 °C). The dried silica gel was added to a column and chromatographed (EtOAc:H$_2$O:CH$_3$CHOHCH$_3$ = 4:2:1) to give 32 (18 mg, 81%): UV (MeOH) $\lambda_{max}$ 261 nm, $\lambda_{min}$ 229 nm; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 8.57 (br s, 1H), 8.42 (s, 1H), 8.12 (s, 1H), 7.22 (br s, 2H), 5.84 (d, $J = 2.5$ Hz, 1H), 5.52 (br s, 1H), 4.32 (d, $J = 4.5$ Hz, 1H), 4.01–3.98 (m, 1H), 3.69 (d, $J = 12.0$ Hz, 1H), 3.62–3.59 (m, 1H), 3.59–3.55 (m, 1H)

3'-(Carboxymethyl)-3',5'-dideoxyadenosine (32).
3.50 (d, J = 12.0 Hz, 1H), 2.24 (dd, J = 7.5, 14.5 Hz, 1H), 2.17 (dd, J = 5.3, 14.8 Hz, 1H), 1.77–1.75 (m, 1H); \textsuperscript{13}C NMR (DMSO-\textit{d}_6, 125 MHz) δ 173.4, 156.0, 152.4, 148.6, 138.6, 119.1, 90.4, 84.3, 75.4, 60.7, 37.5, 29.6; MS (ES) \textit{m}/\textit{z} 310.1144 (MH\textsuperscript{+} [C\textsubscript{12}H\textsubscript{16}N\textsubscript{5}O\textsubscript{5}] = 310.1151).
5'-Azido-3'- (carboxymethyl) -3', 5'-dideoxyadenosine (33).

To a solution of 28 (22 mg, 0.070 mmol) in THF:MeOH [0.6 mL, (5:1)] was added NaOH (80 µL of 1.0 M, 0.080 mmol). The resulting mixture was stirred at 65 °C until TLC showed conversion of 28 to baseline product. The mixture was added directly to a chromatography column and chromatographed (5%–10% MeOH/CH₂Cl₂). Pooled fractions were evaporated under reduced pressure (≤ 20°C) to give 33 (20 mg, 85%): UV (MeOH) ʎ_max 260 nm, ʎ_min 228 nm; ¹H NMR (DMSO-­d₆, 500 MHz) δ 8.27 (s, 1H), 8.17 (s, 1H), 7.30 (br s, 2H), 5.96 (d, 𝐽 = 2.0 Hz, 1H), 4.64 (dd, 𝐽 = 2.0, 5.5 Hz, 1H), 4.10–4.07 (m, 1H), 3.70–3.66 (m, 2H), 3.33 (br s, 1H), 2.77–2.71 (m, 1H), 2.57 (dd, 𝐽 = 8.8, 17.3 Hz, 1H), 2.43 (dd, 𝐽 = 5.3, 17.3 Hz, 1H); ¹³C NMR (DMSO-­d₆, 125 MHz) δ 173.3, 156.1, 152.6, 149.0, 138.7, 119.1, 90.4, 82.2, 74.8, 52.2, 39.8, 29.6; MS (ES) m/z 335.1230 (MH⁺ [C₁₂H₁₅N₈O₄] = 335.1216).
5'-Azido-3'-(carboxymethyl)-3',5'-dideoxy-\(N^\delta\)-(N-phenylcarbamoyl)adenosine sodium salt (34).

To a solution of 30 (29 mg, 0.067 mmol) in DMSO (0.5 mL) was added NaOH (0.10 mL of 1.0 M, 0.10 mmol). The resulting mixture was stirred at room temperature until TLC showed conversion of 30 to baseline product. Volatiles were removed under reduced pressure to give 34 (32 mg, quant). This material was >98% pure as determined by reverse phase HPLC and \(^1\)H NMR: UV (MeOH) \(\lambda_{max} 279\) nm, \(\lambda_{min} 241\) nm; \(^1\)H NMR (D\(_2\)O:DMSO-d\(_6\) (1:9), 500 MHz) \(\delta 8.24\) (s, 1H), \(8.13\) (s, 1H), \(7.49\) (dd, \(J = 1.8, 7.3\) Hz, 2H), \(7.26-7.16\) (m, 2H), \(6.87-6.83\) (m, 1H), \(5.86\) (d, \(J = 2.5\) Hz, 1H), \(4.54\) (dd, \(J = 2.0, 6.0\) Hz, 1H), \(4.03-4.00\) (m, overlaps with solvent), \(3.54\) (dd, \(J = 2.3, 13.8\) Hz, 1H), \(3.42\) (dd, \(J = 5.8, 13.8\) Hz, 1H), \(2.45-2.44\) (m, 1H), \(2.26\) (dd, \(J = 7.8, 15.3\) Hz, 1H), \(2.08\) (dd, \(J = 5.5, 15.0\) Hz, 1H); \(^{13}\)C NMR (D\(_2\)O:DMSO-d\(_6\) (1:9), 125 MHz) \(\delta 177.3, 160.7, 158.3, 152.4, 148.9, 141.2, 138.7, 138.6, 129.4, 124.2, 122.2, 119.5, 90.3, 83.3, 76.5, 53.1, 41.8, 34.4; MS (ES) \(m/z 476.1404\) (MH\(^+\) [C\(_{19}\)H\(_{19}\)N\(_{9}\)O\(_{5}\)Na] = 476.1407).
3'-[Carboxymethyl]-3',5'-dideoxy-5'-(N-methylcarbamoyl)amino]-N^6-(N-phenylcarbamoyl)adenosine sodium salt (35).

To a solution of 31 (54 mg, 0.12 mmol) in DMSO (0.5 mL) was added NaOH (0.20 mL of 1.0 M, 0.20 mmol). The mixture was stirred at ambient temperature until TLC showed conversion of 31 to baseline product. Volatiles were removed under reduced pressure to give 35 (64 mg, quant). This material was >98% pure as determined by reverse phase HPLC and ^1H NMR: UV (MeOH) \( \lambda_{\text{max}} \) 279 nm, \( \lambda_{\text{min}} \) 243 nm; \(^1H\) NMR (D\(_2\)O:DMSO-\(d_6\) (1:9), 500 MHz) \( \delta \) 8.25 (s, 1H), 8.11 (s, 1H), 7.55 (d, \( J = 8.0 \) Hz, 2H), 7.22 (t, \( J = 7.8 \) Hz, 2H), 6.90–6.87 (m, 1H), 5.83 (d, \( J = 3.0 \) Hz, 1H), 4.50 (dd, \( J = 2.0, 6.0 \) Hz, 1H), 3.90–3.87 (m, overlaps with solvent), 3.41 (dd, \( J = 3.0, 14.5 \) Hz, 1H), 3.16 (dd, \( J = 6.5, 14.0 \) Hz, 1H), 2.52 (s, 3H), 2.42–2.38 (m, 1H), 2.31 (dd, \( J = 8.0, 14.8 \) Hz, 1H), 2.15 (dd, \( J = 5.3, 14.8 \) Hz, 1H); \(^{13}C\) NMR (D\(_2\)O:DMSO-\(d_6\) (1:9), 125 MHz) \( \delta \) 177.5, 161.6, 159.8, 159.1, 152.3, 148.5, 141.5, 138.2, 129.3, 124.7, 121.8, 119.2, 90.3, 83.8, 76.8, 42.8, 42.0, 35.0, 26.9; MS (ES) \( m/z \) 507.1711 (MH\(^+\) [C\(_{21}\)H\(_{24}\)N\(_8\)O\(_6\)Na] = 507.1717).
4-nitrophenyl N-methylcarbamate (6).

To a flame-dried 500 mL Kjeldahl flask containing dried CH₂Cl₂ (240 mL) were added 4-nitrophenyl chloroformate (2.0 g, 9.9 mmol), anhydrous Na₂CO₃ (2.4 g, 23 mmol), and methylvammonium chloride (0.680 g, 10.2 mmol). The resulting suspension was stirred protected from moisture (N₂ atmosphere or simple capping of flask worked equally well) until 4-nitrophenyl chloroformate was consumed (48–72 h). The reaction rate depended on the rate of stirring, as is generally the case for biphasic reactions, and maximum stir-plate speeds were required to achieve optimal results. Solids were removed via filtration (celite or Whatman GF/A glass microfibre filter paper) and volatiles were removed under reduced pressure to give 4-nitrophenyl N-methylcarbamate as a light yellow solid in quantitative yield. This material was ≥ 95% pure (determined by ¹H NMR) and could be used for carbamoylation reactions without further purification. The crude material was flash chromatographed (40% EtOAc/hexanes) to give compound 6 as a white solid (1.8 g, 93%). ¹H NMR (CDCl₃, 500 MHz) δ 8.25 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 5.08 (br s, 1H), 2.94 (d, J = 5.0 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 155.9, 153.7, 125.1, 121.9, 27.8; mp = 150–152 °C; MS 197.0561 (ES) m/z ([M+H]⁺ [C₈H₉N₂O₄] = 197.0557), Anal. Calcd. for C₈H₈N₂O₄: C, 48.98; H, 4.11; N, 14.28. Found: C, 49.04; H, 4.30; N, 14.27.
4-nitrophenyl N-benzylcarbamate (7).

To a flame-dried 30 mL Kjeldahl flask containing dried CH$_2$Cl$_2$ (12 mL) were added 4-nitrophenyl chloroformate (0.1 g, 0.5 mmol), anhydrous Na$_2$CO$_3$ (0.10 g, 0.94 mmol), and benzylammonium chloride (0.072 g, 0.50 mmol). The resulting suspension was stirred vigorously until 4-nitrophenyl chloroformate was consumed (7 d). Solids were removed via filtration (celite) and volatiles were removed under reduced pressure. The residue was flash chromatographed to give 7 (0.124 g, 92%). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.26–8.24 (m, 2H), 7.40–7.32 (m, 7H), 5.51 (br s, 1H), 4.48 (d, $J = 6.0$ Hz, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 156.0, 153.4, 144.9, 137.5, 129.1, 128.2, 127.9, 125.3, 122.2, 115.8, 45.6; MS (ES) $m/z$ 273.0877 ([M+H]$^+$ [C$_{14}$H$_{13}$N$_2$O$_4$] = 273.0870).
**4-nitrophenyl N-propylcarbamate (8).**

To a flame-dried 30 mL Kjeldahl flask containing dried CH₂Cl₂ (12 mL) were added 4-nitrophenyl chloroformate (0.1 g, 0.5 mmol), anhydrous Na₂CO₃ (0.10 g, 0.94 mmol), and propylammonium chloride (0.048 g, 0.50 mmol). The resulting suspension was stirred vigorously until 4-nitrophenyl chloroformate was consumed (24 h). Solids were removed via filtration (celite) and volatiles were removed under reduced pressure. The residue was flash chromatographed to give 8 (0.089 g, 80%). ¹H NMR (CDCl₃, 500 MHz) δ 8.24 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H), 5.27 (br s, 1H), 3.29–3.25 (m, 2H), 1.65–1.61 (m, 2H), 0.99 (t, J = 7.5 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 156.1, 153.6, 144.9, 126.3, 125.3, 122.2, 115.8, 43.3, 23.1, 11.4; MS (ES) m/z 247.0701 ([M+Na]⁺ [C₁₀H₁₂N₂O₄Na] = 247.0689).
4-nitrophenyl N-benzyloxycarbamate (9).

To a flame-dried 30 mL Kjeldahl flask containing dried CH$_2$Cl$_2$ (12 mL) were added 4-nitrophenyl chloroformate (0.1 g, 0.5 mmol), anhydrous Na$_2$CO$_3$ (0.10 g, 0.94 mmol), and $O$-benzylhydroxylammonium chloride (0.080 g, 0.50 mmol). The resulting suspension was stirred vigorously until 4-nitrophenyl chloroformate was consumed (9 d). Solids were removed via filtration (celite) and volatiles were removed under reduced pressure. The residue was flash chromatographed to give 9 (0.128 g, 89%). Compound 9 had spectral data that agreed with published values.$^{33}$
Methyl 2-[(4-nitrophenoxy)carbonylamino]-3-phenylpropanoate (10).

To a flame-dried 30 mL Kjeldahl flask containing dried CH₂Cl₂ (12 mL) were added 4-nitrophenyl chloroformate (0.1 g, 0.5 mmol), anhydrous Na₂CO₃ (0.10 g, 0.94 mmol), and L-phenylalanine methyl ester ammonium chloride (0.108 g, 0.50 mmol). The resulting suspension was stirred vigorously until 4-nitrophenyl chloroformate was consumed (5 d). Solids were removed via filtration (celite) and volatiles were removed under reduced pressure. The residue was flash chromatographed to give 10 (0.148 g, 87%).

**¹H NMR** (CDCl₃, 300 MHz) δ 8.22 (d, J = 5.7 Hz, 2H), 7.35–7.17 (m, 7H), 5.68 (d, J = 4.8 Hz, 1H), 4.74–4.71 (m, 1H), 3.80 (s, 3H), 3.25 (dd, J = 8.3, 3.4 Hz, 1H), 3.15 (dd, J = 8.4, 3.9 Hz, 1H); **¹³C NMR** (CDCl₃, 75 MHz) δ 171.8, 155.6, 153.0, 145.1, 135.3, 129.4, 129.0, 127.7, 126.4, 125.4, 122.2, 115.8, 55.2, 53.0, 38.2; **MS (ES)** m/z 345.1071 ([M+H]+ [C₁₇H₁₇N₂O₆] = 345.1081).
Methyl 2-[(4-nitrophenoxy)carbonylamino]ethanoate (11).

To a flame-dried 30 mL Kjeldahl flask containing dried CH$_2$Cl$_2$ (12 mL) were added 4-nitrophenyl chloroformate (0.1 g, 0.5 mmol), anhydrous Na$_2$CO$_3$ (0.10 g, 0.94 mmol), and glycine methyl ester ammonium chloride (0.063 g, 0.50 mmol). The resulting suspension was stirred vigorously until 4-nitrophenyl chloroformate was consumed (7 d). Solids were removed via filtration (celite) and volatiles were removed under reduced pressure. The residue was flash chromatographed to give 11 (0.069 g, 55%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 8.25 (d, $J$ = 9.3 Hz, 2H), 7.34 (dd, $J$ = 7.2, 2.1 Hz, 2H), 5.75 (br s, 1H), 4.09 (d, $J$ = 5.4 Hz, 2H), 3.81 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 170.1, 155.9, 153.4, 145.2, 125.4, 122.3, 115.8, 52.9, 43.0; MS (ES) m/z 255.0619 ([M+H]$^+$ [C$_{10}$H$_{11}$N$_2$O$_6$] = 255.0612).
(S)-Methyl 2-[(4-nitrophenoxy)carbonylamino]-2-phenylethanoate (12).

To a flame-dried 30 mL Kjeldahl flask containing dried CH$_2$Cl$_2$ (12 mL) were added 4-nitrophenyl chloroformate (0.1 g, 0.5 mmol), anhydrous Na$_2$CO$_3$ (0.10 g, 0.94 mmol), and S-(+)-2-phenyl glycine methyl ester ammonium chloride (0.101 g, 0.50 mmol). The resulting suspension was stirred vigorously until 4-nitrophenyl chloroformate was consumed (5 d). Solids were removed via filtration (celite) and volatiles were removed under reduced pressure. The residue was flash chromatographed to give 12 (0.120 g, 73%). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.22 (d, $J = 9.5$ Hz, 2H), 7.41–7.39 (m, 5H), 7.30 (d, $J = 9.0$ Hz, 2H), 6.31 (br s, 1H), 5.42 (d, $J = 7.5$ Hz, 1H), 3.77 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 171.0, 155.7, 152.4, 145.1, 135.9, 129.4, 129.2, 127.4, 125.3, 122.1, 115.7, 58.2, 53.3; MS 331.0925 (ES) $m/z$ ([M+H]$^+$ [C$_{16}$H$_{15}$N$_2$O$_6$] = 331.0925).
Procedure for deprotection of tert-butyldimethylsilyl group of compound 21.

To a dried 10 mL flask containing CH$_3$CN (2 mL) were added compound 21 (0.042 g, 0.10 mmol), KF (0.029 g, 0.50 mmol), PhCH$_2$N(Et)$_3$Cl (0.057 g, 0.25 mmol) and two drops of H$_2$O. The resulting mixture was stirred vigorously at room temperature until TLC showed that compound 21 had been consumed (24 h). Volatiles were removed under reduced pressure. The residue was transferred to the column directly and eluted (EtOAc/i-PrOH/H$_2$O; 4:1:2) to give 21' (0.030 g, 98%). Compound 21' had spectral data that agreed with published values.\textsuperscript{34}
Procedure for deprotection of tert-butyldimethylsilyl group of compound 22.

To a dried 10 mL flask containing CH$_3$CN (2 mL) were added compound 22 (0.040 g, 0.14 mmol), KF (0.029 g, 0.50 mmol), PhCH$_2$N(Et)$_3$Cl (0.057 g, 0.25 mmol), and two drops of H$_2$O. The resulting mixture was stirred vigorously at room temperature until TLC showed that compound 22 had been consumed (24 h). Volatiles were removed under reduced pressure. The residue was transferred to the column directly and eluted (EtOAc/i-PrOH/H$_2$O; 4:1:2) to give 22' (0.027 g, 94%). Compound 22' had spectral data that agreed with published values.$^{35}$
Procedure for deprotection of *tert*-butyldimethylsilyl group of compound 23.

To a dried 10 mL flask containing CH$_3$CN (2 mL) were added compound 23 (0.040 g, 0.10 mmol), KF (0.029 g, 0.50 mmol), PhCH$_2$N(Et)$_3$Cl (0.057 g, 0.25 mmol) and two drops of H$_2$O. The resulting mixture was stirred vigorously at room temperature until TLC showed that compound 23 had been consumed (30 h). Volatiles were removed under reduced pressure. The residue was transferred to the column directly and eluted (EtOAc/i-PrOH/H$_2$O; 4:1:2) to give 23' (0.027 g, 95%). Compound 23' had spectral data that agreed with published values.$^{36}$
Procedure for deprotection of tert-butyldimethylsilyl group of compound 24.

To a dried 25 mL flask containing CH$_3$CN (10 mL) were added compound 24 (0.374 g, 0.61 mmol), KF (0.178 g, 3.06 mmol), PhCH$_2$N(Et)$_3$Cl (0.350 g, 1.26 mmol) and ten drops of H$_2$O. The resulting mixture was stirred vigorously at room temperature until TLC showed that compound 24 had been consumed (24 h). Volatiles were removed under reduced pressure. The residue was transferred to the column directly and eluted (EtOAc/i-PrOH/H$_2$O; 4:1:2) to give 24' (0.091 g, 56%). Compound 24' had spectral data that agreed with published values.$^{37,38}$
Procedure for deprotection of tert-butyldimethylsilyl group of compound 25.

To a dried 25 mL flask containing CH$_3$CN (2 mL) were added compound 25 (0.042 g, 0.13 mmol), KF (0.038 g, 0.65 mmol), PhCH$_2$N(Et)$_3$Cl (0.074 g, 0.32 mmol) and two drops of H$_2$O. The resulting mixture was stirred vigorously at room temperature until TLC showed that compound 25 had been consumed (24 h). Volatiles were removed under reduced pressure. The residue was transferred to the column directly and eluted (EtOAc/i-PrOH/H$_2$O; 4:1:2) to give 25' (0.012 g, 45%). Compound 25' had spectral data that agreed with published values.$^{39}$
Procedure for deprotection of tert-butyldimethylsilyl group of compound 26.

To a dried 25 mL flask containing CH$_3$CN (2 mL) were added compound 26 (0.068 g, 0.2 mmol), KF (0.059 g, 1.0 mmol), PhCH$_2$N(Et)$_3$Cl (0.116 g, 0.51 mmol) and two drops of H$_2$O. The resulting mixture was stirred vigorously at room temperature until TLC showed that compound 26 had been consumed (6 h). Volatiles were removed under reduced pressure. The residue was transferred to the column directly and eluted (EtOAc/i-PrOH/H$_2$O; 4:1:2) to give 26' (0.032 g, 73%). Compound 26' had spectral data that agreed with published values.\textsuperscript{40}
Procedure for deprotection of tert-butyldimethylsilyl group of compound 27.

To a dried 25 mL flask containing CH$_3$CN (2 mL) were added compound 27 (0.026 g, 0.075 mmol), KF (0.022 g, 0.38 mmol), PhCH$_2$N(Et)$_3$Cl (0.043 g, 0.19 mmol) and two drops of H$_2$O. The resulting mixture was stirred strongly at room temperature until TLC showed that compound 27 had been consumed (24 h). Volatiles were removed under reduced pressure. The residue was transferred to the column directly and eluted (EtOAc/i-PrOH/H$_2$O; 4:1:2) to give 27' (0.013 g, 74%). Compound 27' had spectral data that agreed with published values.$^{41}$
References:


