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Synthesis of 2′-*O*,3′-*O* bicyclic adenosine analogues using ring closing metathesis

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Abstract—The synthesis of 2′-*O*,3′-*O* bicyclic adenosine derivatives is presented as the first examples of a new family of 13-membered ring bicyclic nucleoside analogues. Cyclisation was achieved through ring closing metathesis (RCM) on a diene intermediate using Grubbs' catalyst. The *Z* and *E* isomers were purified and characterised.

Overuse and misuse of antibiotics has led to the emergence of bacterial resistance to classical antibiotics, which is a serious threat to the health care system. This observation has generated an urgent need for discovery of novel antibacterial agents, preferably with new modes of action. Recently, two ligases purified from *enterococcus faecalis*, namely BppA1 and BppA2, were shown to play a crucial role in the biosynthesis of bacterial cell-walls.[1] Indeed, these enzymes specifically and successively transfer L-alanine residues from alanyl-tRNA to a UDP-MurNAc pentapeptide, a key precursor of the bacterial peptidoglycan structure. Owing to their unusual tRNA dependent mode of action which has no equivalent in the other steps of cell-wall synthesis, these enzymes can be considered as promising unexploited targets for the development of new antibiotics, actually, inhibition of the ligation reactions will result in the synthesis of incomplete peptidoglycan precursors lacking the N-terminal amino acid required for transpeptidation.

Recently, macrocycles containing an L-alanyl group were designed and evaluated as inhibitors of the D-glutamate ligase[2] which catalyses the addition of D-glutamate to UDP-MurNAc-LAla. By analogy, and in an effort to search for potential inhibitors of the BppA1 and BppA2 enzymes, we decided to synthesise a modified 3′-L-alanyl-adenosine with a cyclised peptidic framework. This derivative was designed to be not only a mimic of the terminal part of alanyl-tRNA but also to act as a chain terminator.

To the best of our knowledge the 2′-*O*,3′-*O* bicyclic adenosine derivatives reported herein are the first examples of 13-membered ring bicyclic nucleoside analogues. The use of catalytic olefin metathesis as a carbon–carbon bond construction method has exhibited considerable growth in recent years.[3] In particular, the ring closing metathesis (RCM) has become an efficient tool for the synthesis of a great variety of macrocyclic systems.[4] However, in the field of nucleoside chemistry, very few examples of RCM have been published,[5] and none of them have dealt with the construction of a 13-membered ring in a nucleoside derivative.

Synthesis of the diene intermediates **6** and **7** started with the introduction of an allyl group to position 2′ (Scheme 1). Starting from adenosine, protection of the 6-amino group with benzoyl chloride was performed using a known procedure.[6] The 3′- and 5′-hydroxyl groups were protected under standard conditions with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane ($TIPSCl_2$), affording compound **1** in 66% overall yield. The subsequent allylation step proceeded through palladium-catalyzed chemistry.[7] Allyl ethyl carbonate, the allyl donor, was prepared from ethanol and allyl chloroformate, as described in the literature.[8b] A coupling reaction between the latter and adenosine derivative **1**, in the presence of catalytic amounts of tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) and 1,4-bis(diphenylphosphino)butane[8] (dppb) yielded the allyl derivative **2** (90%). Attempts to carry out this reaction from the *N*-monobenzoyl derivative (instead of *N*,*N*-

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Keywords: ligases; nucleosides; ring closure metathesis.

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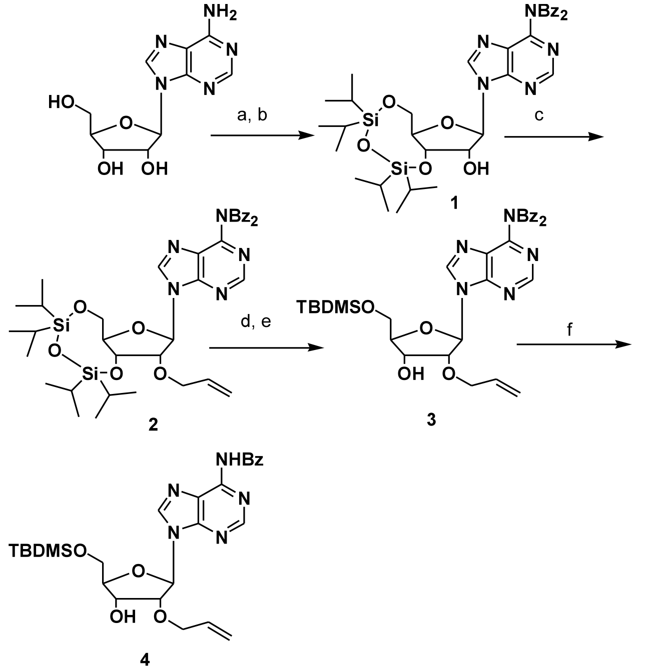
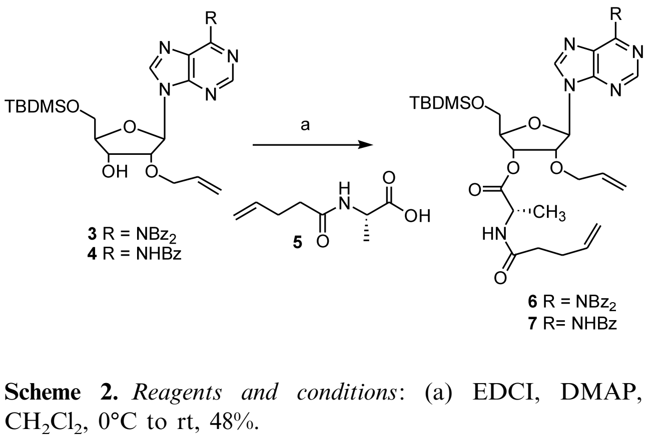


Scheme 1. *Reagents and conditions*: (a) (i) TMSCl, Pyr. (ii) BzCl, Pyr. (iii) H_2O, 80% overall; (b) $TIPSCl_2$, Pyr., 82%; (c) $AllOCO_2Et$, $Pd_2(dba)_3$, dppb, 90%;[8] (d) TBAF, AcOH, THF, 63%; (e) TBDMSCl, Pyr., 99%; (f) NH_4OH, Pyr., 88%.

dibenzoyl compound **1**) afforded a complex mixture among which simultaneous *N*- and *O*-allylation products were observed.

The TIPDS protecting group was removed using tetrabutyl ammonium fluoride in the presence of acetic acid to avoid any base-mediated side-reactions.[9] Position 5′ was silylated with *tert*-butyldimethylsilyl chloride (TBDMSCl) under standard conditions, providing adenosine derivative **3**. Monodeprotection of the 6-amino group with ammonium hydroxide afforded compound **4** in good yield (88%).

The diene intermediates **6** and **7** (Scheme 2) were prepared from the alcohol derivatives **3** and **4** by reaction with *N*-pentenoyl-L-alanine **5**.[10] The coupling step was optimised using different activating agents (Table 1) and the first attempt with compound **3** resulted in partial debenzoylation, thus lowering the yields. The best result was obtained from compound **4** using EDCI in presence of DMAP within 2 h giving the desired product in 48% yield. Since the unreacted starting material was easily recovered after chromatography, the corrected yield is satisfactory.



Scheme 2. *Reagents and conditions*: (a) EDCI, DMAP, CH_2Cl_2, 0°C to rt, 48%.

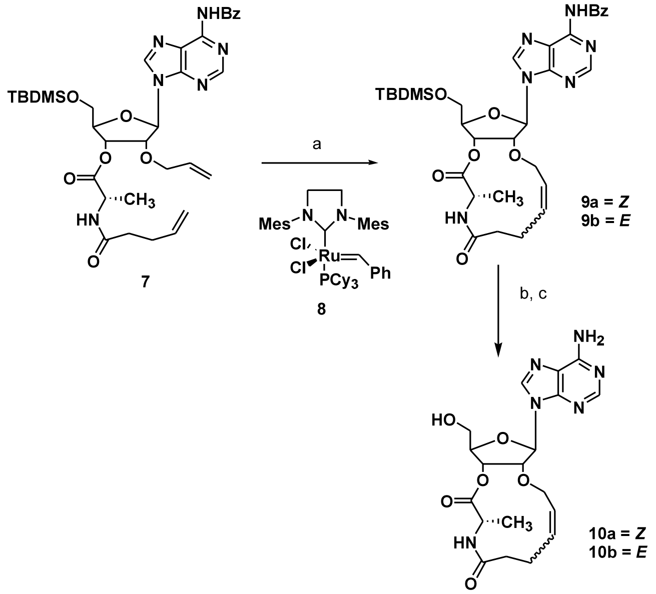
The key diene **7**[11] was subjected to an RCM reaction with Grubbs' second generation catalyst **8**[12] (Scheme 3). Under standard conditions (CH_2Cl_2, at 40°C, during 24 h) **9** was obtained in 25% yield. Based on previous reported studies on large ring synthesis,[13] the yield was improved by conducting the metathesis reaction at a higher temperature and dilution. Indeed, at 110°C in toluene over 15 min at a concentration of 0.5 mM, we obtained the cyclised intermediate **9** in 62% yield.

Compound **9**[14] was obtained as a mixture of *Z* and *E* stereoisomers in the ratio 49/51, which were separated by chromatography. For derivative **9b**, assignment by ^1H NMR spectroscopy showed a coupling constant between the two olefinic protons of 15 Hz, which is characteristic of *trans* coupling (Fig. 1).

Table 1. Optimization of the acylation

Reagent	From **3**		From **4**	
	% **6**	% **7**	% **7**	% **4**
BOP[a]	16	23	43	55
$ClCO_2iBu$[b]			38	
EDCI[c]	22	11	48	45
DEPC[d]			17	57

[a] **5**, Bop reagent, 4-pyrrolidine, Hünig's base, Pyr., rt.
[b] **5**, $ClCO_2iBu$, NEt_3, CH_2Cl_2, DMAP, −10°C to rt.
[c] **5**, EDCI, CH_2Cl_2, DMAP, 0°C to rt.
[d] **5**, DEPC, DMF, NEt_3, 0°C to rt.



Scheme 3. *Reagents and conditions*: (a) Toluene, 110°C, **8** 20 mol%, 15 min, 62% (b) phenol, DCE, 76% (c) TBAF, AcOH, 85%.

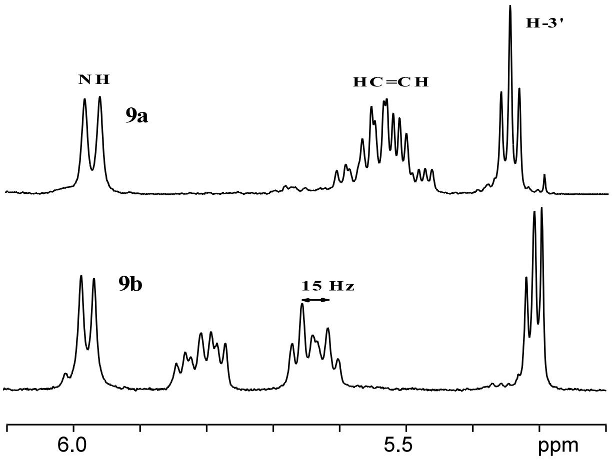


Figure 1. ^{1}H NMR zoom of the 6.1–5.2 ppm region for **9a** and **9b** (400 MHz, CDCl$_3$).

Each stereoisomer was fully deprotected. Despite the presence of an ester moiety in the macrocyclic ring, selective *N*-debenzoylation was achieved in 76% yield using phenol in refluxing dichloroethane.[15] Removal of the TBDMS group using tetrabutylammonium fluoride in the presence of acetic acid[9] afforded nucleoside analogues **10**[16] in 85% yield.

In conclusion, we have shown that ring closing metathesis can be used to access adenosine analogues **10**. This is a new family of bicyclic nucleosides containing an olefinic moiety with a high potential for further functionalisation. Moreover, our synthetic pathway allows for a wide range of amino acid residues to be introduced as well as a large variety of ring size. Efforts to develop this family of compounds are in progress and biological experiments on their inhibitory activity towards tRNA dependent ligases are currently underway.

Acknowledgements

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11. Selected spectral data for compound **7**: ^{1}H NMR (250 MHz, CDCl$_3$) δ: 0.15 (s, 6H, 2×CH$_3$-Si), 0.90 (s, 9H, *t*Bu), 1.45 and 1.42 (2d, 3H, CH$_3$, *J* 4.8), 2.34 (m, 4H, 2×CH$_2$), 3.92 (m, 4H, 2H-5′, CH$_2$), δ 4.31 (dd, 1H, H-4′, *J* 14), 4.62 (m, 2H, H-2′, CH), 5.05 (m, 4H, Hγ, =CH$_2$), 5.44 (m, 1H, H-3′), 5.5–5.9 (2×m, 2H, Hβ, CH=), 6.23 (m, 2H, H-1′, NH), 7.4–7.5 (m, 3H, HBz), δ 8.01 (d, 2H, HBz, *J* 7), 8.32 (s, 1H, H-2 or H-8), 8.79 (s, 1H, H-2 or H-8), 9.12 (s, 1H, NH); ^{13}C NMR (63 MHz, CDCl$_3$) δ: −4.5 (SiCH$_3$), 17.15 (Cq/*t*Bu, CH$_3$), 24.97 (CH$_3$/*t*Bu), 28.37 (CH$_2$), 34.40 (CH$_2$), 47.17 (CH), 61.86 (C-5′), 70.95 (Cα, C-3′), 78.71 (C-2′), 82.60 (C-4′), 85.10 (C-1′), 114.65 (CH$_2$=), 117.65 (Cγ), 122 (Cq), 126.85, 127.85, 132.23, 132.34 (CBz, C-2 or C-8), 135.84, 140.40 (Cβ, CH=), 148.38, 150.90 (Cq), 140.25, 151.84 (C-2 or C-8), 148.51, 150.35 (Cq), 164.20, 171.11 (CO); optical rotation: $[\alpha]^{20}_{\mathrm{D}} = -42$ (*c* 1, DCM); MS (IC NH$_3^+$): 679 [M+H]$^+$.
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14. Selected spectral data for compound **9**. **9a (*Z*)**: ^{1}H NMR (400 MHz, CDCl$_3$) δ: 0.10 (s, 6H, 2×CH$_3$-Si), 0.85 (s, 9H, *t*Bu), 1.36 (d, 3H, CH$_3$, *J* 7.0), 2.14–2.41 (m, 4H, 2×CH$_2$), 3.67 (dd, 1H, OCH, *J* 8, *J* 10.3), 3.9 (dd, 2H, H-5′, *J* 3.3, *J* 11.6), 4.20 (dd, 1H, CHO, *J* 4.0, *J* 10.3), 4.36 (dt, 1H,

H-4′, *J* 3, *J* 5.4), 4.65 (t, 1H, H-2′, *J* 5), 4.69 (m, 1H, CH), 5.33 (t, 1H, H-3′, *J* 5.3), 5.51 (m, 2H, CH=), 5.98 (d, 1H, NH, *J* 9), 6.10 (d, 1H, H-1′, *J* 4.6), 7.53 (m, 3H, HBz), δ 8.01 (d, 2H, HBz, *J* 7.5), 8.31 (s, 1H, H-2 or H-8), 8.79 (s, 1H, H-2 or H-8), 9.1 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.66 ($SiCH_3$), 0.84 (Cq), 18.26 (Cq/*t*Bu), 18.43 (CH_3), 25.77 (CH_3/*t*Bu), 29.52 (CH_2), 36.44 (CH_2), 47.04 (CH), 61.95 (C-5′), 71.78 (C-3′), 72.60 (CH_2O), 80.67 (C-2′), 82.19 (C-4′), 87.79 (C-1′), 127.71, 127.85, 128.70 (CBz), 132.30 (CH=), 132.63 (CH=), 141.31 (C-2 or C-8), 149.32, 151.35 (Cq), 152.61 (C-2 or C-8), 172.00 (CO), 173.63 (CO); optical rotation: $[\alpha]_D^{20} = -31$ (*c* 1, DCM); MS (FAB+): 651.3 $[M+H]^+$. **9b (*E*)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.10 (s, 6H, 2×CH_3-Si), 0.90 (s, 9H, *t*Bu), 1.42 (d, 3H, CH_3, *J* 7.3), 2.14–2.47 (m, 4H, 2×CH_2), 3.88 (m, 3H, 2H-5′, OCH), 4.27 (m, 2H, H-4′, OCH), 4.49 (t, 1H, H-2′, *J* 5.0), 4.62 (q, 1H, CH, *J* 7.5), 5.29 (m, 1H, H-3′), 5.61 (dt, 1H, CH=, *J* 15, *J* 6), 5.81 (m, 1H, CH=), 5.97 (d, 1H, NH, *J* 7.5), 6.27 (d, 1H, H-1′, *J* 4.8), 7.53 (m, 3H, HBz), δ 8.03 (d, 2H, HBz, *J* 7.6), 8.45 (s, 1H, H-2 or H-8), 8.82 (s, 1H, H-2 or H-8), 9.2 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.44 ($SiCH_3$), 17.50 (Cq/*t*Bu), 18.48 (CH_3), 26.02 (CH_3/*t*Bu), 27.78 (CH_2), 35.90 (CH_2), 49.09 (CH), 62.43 (C-5′), 70.99 (C-3′), 71.42 (CH_2O), 82.16 (C-2′), 83.73 (C-4′), 86.96 (C-1′), 127.42, 127.91, 128.87, (CBz), 132.81 (CH=), 133.64 (CH=), 140.81 (C-2 or C-8), 149.50, 151.71 (Cq), 152.73 (C-2 or C-8), 170.96 (CO), 172.16 (CO); optical rotation: $[\alpha]_D^{20} = -8$ (*c* 1.0, DCM); MS (FAB+): 651.3.

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16. Selected spectral data for compound **10**. **10a (*Z*)**: ^{1}H NMR (500 MHz CD_3OD) δ: 1.39 (d, 3H, CH_3, *J* 7.2), 2.26–2.42 (m, 4H, 2×CH_2), 3.71 (m, 3H, 2H-5′, OCH), 4.7 (m, 1H, H-2′), 4.10 (m, 2H, H-4′, OCH), 4.37 (q, 1H, CH), 5.42 (m, 3H, H-3′, 2×CH=), 6.02 (d, 1H, H-1′, *J* 6), 8.21 (s, 1H, H-2 or H-8), 8.35 (s, 1H, H-2 or H-8). **10b (*E*)**: ^{1}H NMR (500 MHz CD_3OD) δ: 1.46 (d, 3H, CH_3, *J* 7.5), 2.27–2.41 (m, 4H, 2×CH_2), 3.85 (m, 3H, 2H-5′, OCH), 4.22 (m, 2H, H-4′, OCH), 4.41 (q, 1H, CH, *J* 7.2), 4.67 (t, 1H, H-2′, *J* 5.4), 5.32 (dd, 1H, H-3′, *J* 3.9, *J* 5.4), 5.61 (dt, 1H, CH=, *J* 15.3, *J* 5.4), 5.79 (m, 1H, CH=), 6.10 (d, 1H, H-1′, *J* 5.7), 8.20 (s, 1H, H-2 or H-8), 8.39 (s, 1H, H-2 or H-8); ^{13}C NMR (125 MHz, CD_3OD) δ: 15.94 (CH_3), 27.82 (CH_2), 34.50 (CH_2), 49.74 (CH), 61.22 (C-5′), 71.07 (CH_2O), 72.48 (C-3′), 82.16 (C-2′), 85.05 (C-4′), 88.50 (C-1′), 127.54 (CH=), 132.15 (CH=), 149.18, 156.55 (Cq), 152.81 (C-2 or C-8), 172.39 (CO), 174.53 (CO); MS (DCI+): 433 $[M+H]^+$.