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Synthesis of {[A15-^{13}C]5'-Deoxy-*N*1-methyladenosylcobalamin^{+}}Cl^{-}

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SUMMARY

The synthesis of {[A15-^{13}C]5'-deoxy-*N*1-methyladenosylcobalamin^{+}}Cl^{-}, an analog of coenzyme B_{12}, was accomplished by glycosidation of [5-^{13}C]D-ribose with 4-pentenol, followed by benzoylation, coupling to *N*^{6}-benzoylaminopurine, deprotection, chlorination at C5', methylation at *N*1, and oxidative addition to reduced cobalamin. The α and β anomers of the intermediate pent-4-enyl-*erythro*-furanosides were detected and quantified for the first time.

Keywords: Nucleoside; coenzyme B_{12}; {[A15-^{13}C]5'-deoxy-*N*1-methyladenosylcobalamin^{+}}Cl^{-}; anomer; [5'-^{13}C]pent-4-enyl 2',3',5'-tri-*O*-benzoyl-α-D-*erythro*-pentofuranoside.

INTRODUCTION

Vitamin B_{12} has been extensively studied since its structure was first determined over 40 years ago (1). However, the means by which B_{12}-dependent enzymes catalyze the homolysis of the carbon-cobalt bond of coenzyme B_{12} (5'-deoxyadenosylcobalamin, Figure 1) by some 9 to 12 orders of magnitude (2,3) are unknown. A large number of analogs of the coenzyme have been synthesized (4), many of which retain partial coenzymatic activity, at least with some enzymes. We have been interested in the analog methylated at adenosyl *N*1 ([5'-Deoxy-*N*1-methyladenosylcobalamin^{+}]Cl^{-}) (5), since it is the only analog we have studied which has no residual coenzymatic activity with the B_{12}-dependent ribonucleoside triphosphate reductase, and

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thus behaves as a linear inhibitor (6). In order to facilitate further mechanistic study of the enzymatic activation of the carbon-cobalt bond of the coenzyme by ^{13}C NMR, it was thus of interest to prepare {[A15-^{13}C]5'-deoxy-*N*1-methyladenosylcobalamin^{+}}Cl^{-}.

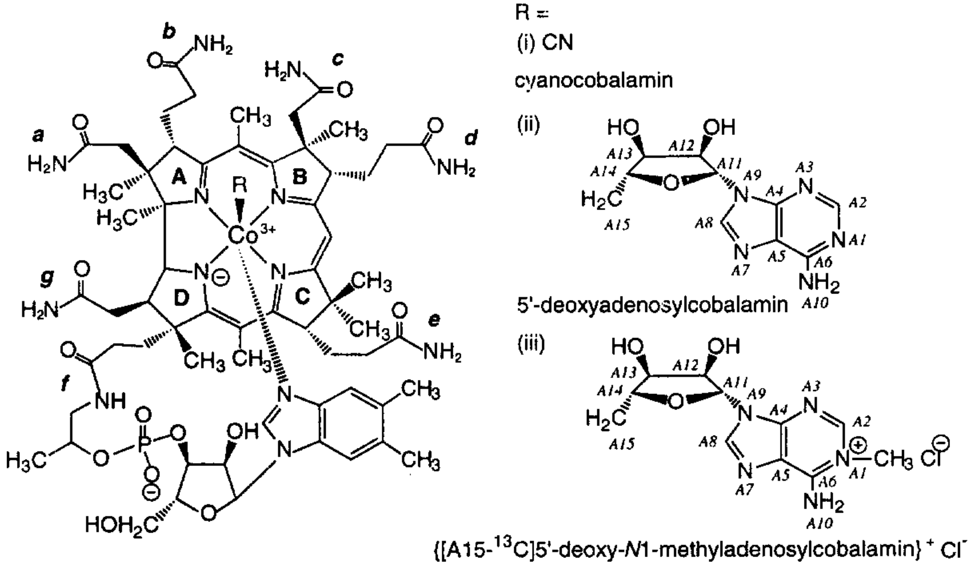
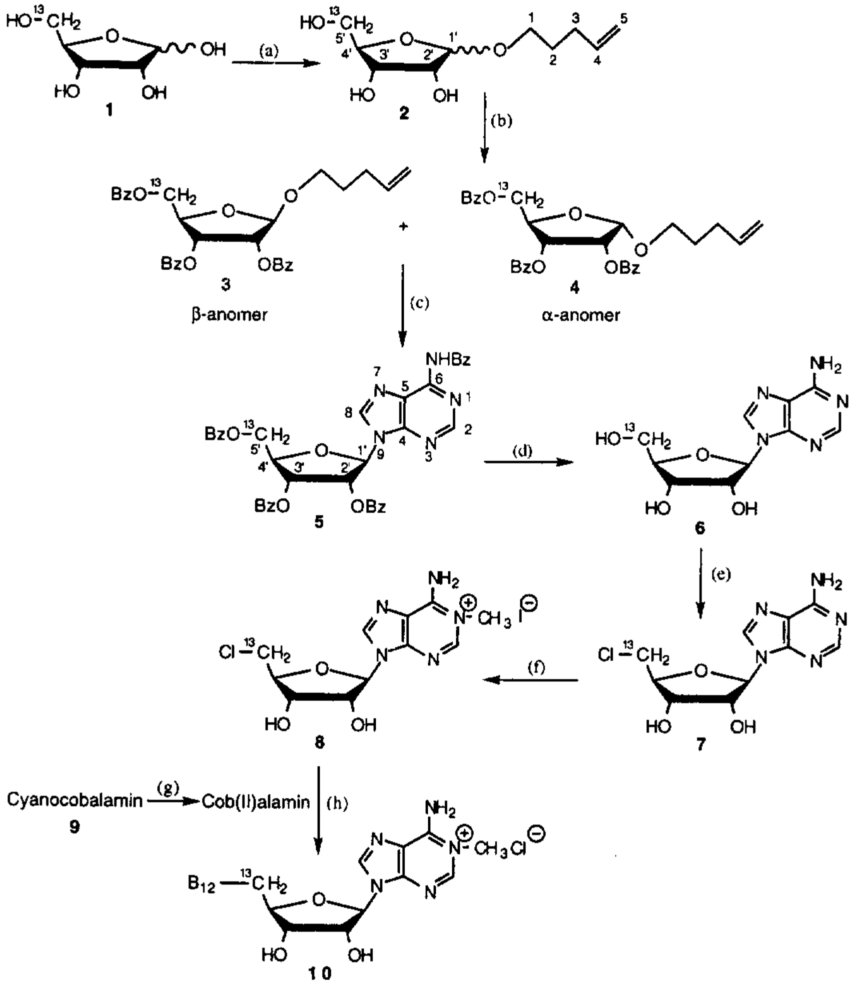


Figure 1. Structures of (i) Cyanocobalamin, (ii) Coenzyme B_{12} (5'-deoxyadenosylcobalamin), and (iii) {[A15-^{13}C]5'-Deoxy-*N*1-methyladenosylcobalamin^{+}}Cl^{-}.

RESULTS AND DISCUSSION

The synthesis was carried out as shown in Scheme 1 (5,7,8). The [5-^{13}C]-D-ribose (**1**, Cambridge Isotopes) was a mixture of α and β anomers suggesting that anomeric intermediates should be obtained during the synthesis. We did detect both anomers of [5'-^{13}C]pent-4-enyl-D-*erythro*-pentofuranoside, **2**, by ^{13}C NMR in the reaction mixture. Furthermore, we were able to separate the two stereoisomers of the protected glycoside, [5'-^{13}C]pent-4-enyl-2',3',5'-tri-*O*-β-D-*erythro*-pentofuranoside (**3**, 79%) and [5'-^{13}C]pent-4-enyl-2',3',5'-tri-*O*-α-D-*erythro*-pentofuranoside (**4**, 21%), which have not been previously reported in the literature. Based on molecular modeling (Cerius^{2} 3.0, Molecular Simulations Inc.), the dihedral angle between the 1' and 2' protons for the β anomer **3** is much larger than that for the α anomer **4**, but both are less than 90°. The Karplus relationship (9) therefore predicts that $J_{1',2'}$ will be



Scheme 1. Synthesis of {[A15-^{13}C]5′-Deoxy-*N*1-methyladenosylcobalamin^{+}}Cl^{-}. (a) 4-pentenol, 10-camphorsulfonic acid, 48 h, RT; (b) benzoyl chloride, pyridine, RT, 24 h; (c) *N*^{6}-benzoyl aminopurine, trifluoromethane sulfonic acid, CH_3CN, RT, 2 h; (d) 0.1 N CH_3ONa, reflux, 45 min; (e) thionyl chloride, hexamethylphosphoramide, RT, 15 h; (f) CH_3I, dimethylacetamide, RT, 20 h; (g) Zn, 10% NH_4Cl, Ar, RT; (h) cob(II)alamin, RT.

smaller for the β anomer than for the α anomer. We found $J_{1',2'}$ to be 0 Hz for **3** and 4.4 Hz for **4**.

Both **3** and **4** condense with *N*-benzoylaminopurine to form the β nucleoside, [5′-^{13}C]*N*^{6}-benzoyl-2′,3′,5′-tri-*O*-benzoyl-7-(β-D-ribofuranosyl)adenine **5** as the major product. The yield from condensation with the α anomer **4** (24%) was lower than that from the β anomer **3** (41%), probably due to larger steric hindrance in the formation of the acyloxonium ion.

The [5'-^{13}C]adenosine obtained by deprotection of **5** could presumably be either first chlorinated at the 5' position (10) and then methylated at N^1, or *vice versa*. The former route was chosen to prevent the possibility of a Dimroth rearrangement to N^6-methyladenosine (5,7) under the chlorination conditions. Thus, **6** was chlorinated by the method of Kikugawa and Ichino (10) and methylated at N^1 with CH_3I to afford **8**. The final product was then obtained by oxidative addition of **8** to reduced cobalamin, formed by reduction of cyanocobalamin with zinc in NH_4Cl.

EXPERIMENTAL

All reagents used were of reagent grade or better. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were acquired using a Bruker AF-250 or Varian VXR400 spectrometer. Chemical shifts were based on the internal standards tetramethylsilane (in DMSO-d_6 and $CDCl_3$) or 3-(trimethylsilyl)propionic acid (in D_2O) except in the solvent CD_3OD, for which the solvent itself was used as a chemical shift standard. The exchangeable protons (O*H*, N*H*) were confirmed by addition of D_2O. A Beckman System Gold HPLC was used to monitor the progress of the reaction [Phenomenex column (C8 100A, 5 μ, 250 × 4.6 mm); Gradient A: 5%-35% CH_3CN in pH 3 phosphate buffer; Gradient B: 45%-70% CH_3CN in water; 2 mL/min].

[5'-^{13}C]Pent-4-enyl-D-*erythro*-pentofuranoside (2)

4-Pentenol (10 mL, 97 mmol) was added to [5-^{13}C]-D-ribose (521 mg, 3.45 mmol) to form a white suspension, to which 10-camphorsulfonic acid (25 mg, 0.11 mmol) in 4-pentenol (2.5 mL) was added. The mixture was allowed to react at room temperature for 48 h after which silver carbonate (182 mg, 0.66 mmol) was added to quench the reaction. After filtering, the unreacted 4-pentenol was recovered *in vacuo* to afford the oily crude product **2** (849 mg, 3.87 mmol,112%) as a mixture of α and β anomers, immediately used in the next step.

^{1}H NMR ($CDCl_3$): δ 5.80 (m, 1 H, H-4), 4.99 (m, 2 H, H-5), 4.91 (s, 1 H, H-1'), 3.30-4.46 (overlapping m, 10 H, H-1, H-2', H-3', H-4', H-5', O*H*), 2.10 (m, 2 H, H-3), 1.65 (m, 2 H, H-2); ^{13}C NMR ($CDCl_3$): δ 138.0 (C-4, α), 137.8 (C-4, β), 114.7 (C-5, β), 114.2 (C-5, α), 107.3 (C-1', β), 101.8 (C-1', α), 84.7 (C-4', d, $J_{4',5'}$ = 42.3 Hz, α), 83.3 (C-4', d, $J_{4',5'}$ = 41.6 Hz, β), 72.0 (C-3', β), 75.2 (C-2', β), 71.6 (C-2', α), 70.2 (C-3', α), 67.9 (C-1, α), 67.5 (C-1, β), 64.1 (C-5', β), 61.9 (C-5', α), 31.5 (C-3, α), 30.1(C-3, β), 30.0 (C-2, α), 28.7 (C-2, β).

[5'-^{13}C]Pent-4-enyl 2',3',5'-tri-*O*-benzoyl-β-D-*erythro*-pentofuranoside (3) and [5'-^{13}C]Pent-4-enyl 2',3',5'-tri-*O*-benzoyl-α-D-*erythro*-pentofuranoside (4)

Benzoyl chloride (3 mL, 26 mmol) in anhydrous pyridine (8 mL) was added dropwise to a solution of **2** in anhydrous pyridine (4 mL). After 24 h at room temperature, the reaction mixture was poured into water (50 mL) and was extracted with ether (3 × 30 mL). The combined ether extracts were washed with 2.5% H_2SO_4 (50 mL × 2), 1 M K_2CO_3 (40 mL × 4), and dried with anhydrous Na_2SO_4 for several hours. After removal of the solvent *in vacuo*, the residue was purified by chromatography on silica gel with gradient elution (0-6% v/v EtOAc in hexane), which was monitored by HPLC, to afford the products, **3** (1.28 g, 2.40 mmol, 70%) and **4** (0.34 g, 0.64 mmol, 19%).

(3) ^{1}H NMR ($CDCl_3$): δ 7.29-7.33, 7.35-7.43, 7.47-7.58, 7.88-7.91 and 8.01-8.09 (five m, 15 H, benzoyl H), 5.89 (m, 1 H, H-3'), 5.76 (m, 1 H, H-4), 5.70 (d, $J_{2',3'}$ = 4.8 Hz, 1 H, H-2'), 5.26 (s, 1 H, H-1'), 4.96 and 5.01 (two m, 2 H, H-5), 4.70-4.77 (m, 1 H, H-4'), 4.73 (ddd, $J_{5',^{13}C}$ = 148 Hz, J_{gem} = 11.6 Hz, $J_{4',5'}$ = 4.2 Hz, 1 H, H-5'), 4.54 (ddd, $J_{5',^{13}C}$ = 148 Hz, J_{gem} = 11.6 Hz, $J_{4',5'}$ = 5.6 Hz, 1 H, H-5'), 3.47 and 3.80 (two d and t, J_{gem} = 9.6 Hz, $J_{1,2}$ = 6.9 Hz, 2 H, H-1), 2.09 (m, 2 H, H-3), 1.64 (m, 2 H, H-2); ^{13}C NMR ($CDCl_3$): δ 165.2, 165.4, and 166.1 (3C, benzoyl *C*=O), 137.8 (C-4), 128.3, 128.4, 128.5, 129.0, 129.3, 129.7, 129.8, 130.1, 133.1, 133.3, and 133.4 (18C, phenyl C), 115.0 (C-5), 105.5 (C-1'), 78.8 (d, $J_{4',5'}$= 44.3 Hz, C-4'), 75.6 (C-2'), 72.6 (C-3'), 67.8 (C-1), 64.9 (C-5'), 30.1 (C-3), 28.5 (C-2).

(4) ^{1}H NMR ($CDCl_3$): δ 7.23-7.27, 7.38-7.47, 7.50-7.60, 7.90-7.93, and 8.08-8.14 (five m, 15 H, benzoyl H), 5.69-5.82 (two overlapping m, 2 H, H-4, H-3'), 5.52 (d, $J_{1',2'}$ = 4.4 Hz, 1 H, H-2'), 5.36 (dd, $J_{2',3'}$ = 6.8 Hz, $J_{1',2'}$ = 4.4 Hz, 1 H, H-2'), 4.88 and 4.91 (two m, 2 H, H-5), 4.74 (ddd, $J_{5',^{13}C}$ = 149 Hz, J_{gem} = 12.0 Hz, $J_{4',5'}$ = 3.2 Hz, 1 H, H-5'), 4.69 (m, 1 H, H-4'), 4.63 (ddd, $J_{5',^{13}C}$ = 149 Hz, J_{gem} = 12.0 Hz, $J_{4',5'}$ = 4.0 Hz, 1 H, H-5'), 3.50 and 3.88 (two d and t, J_{gem} = 9.4 Hz, $J_{1,2}$ = 6.4 Hz, 2 H, H-1), 2.09 (m, 2 H, H-3), 1.68 (m, 2H, H-2); ^{13}C NMR ($CDCl_3$): δ 165.4, 165.9, and 166.1 (3C,

benzoyl *C*=O), 138.0 (C-4), 128.3, 128.4, 128.5, 129.3, 129.6, 129.7, 129.9, 130.1, 133.2, 133.3, and 133.5 (18C, phenyl C), 114.8 (C-5), 100.9 (C-1'), 79.5 (d, $J_{4',5'}$ = 43.9 Hz, C-4'), 71.9 (C-2'), 71.0 (C-3'), 67.6 (C-1), 64.2 (C-5'), 30.2 (C-3), 28.9 (C-2).

[5'-^{13}C]*N*^{6}-Benzoyl-2',3',5'-tri-*O*-benzoyladenosine (5) from 3

Anhydrous acetonitrile (36 mL), *N*-iodosuccinimide (573 mg, 2.55 mmol), *N*-benzoylaminopurine (643 mg, 2.69 mmol), and some molecular sieves (4 Å) were added to **3** (1.28 g, 2.40 mmol). After stirring for a few minutes, trifluoromethanesulfonic acid (221 μL, 2.50 mmol) was added and the reaction was allowed to proceed at room temperature for 2 h. The reaction mixture was poured into saturated Na_2HPO_4 (150 mL), extracted with ether (75 mL × 4) and the combined ether extracts were dried with anhydrous Na_2SO_4 for 12 h. After filtering and removal of the solvent *in vacuo*, the residue was applied to a silica gel column and the column was developed with gradient elution (0-2% v/v EtOAc in $CHCl_3$). The collected fractions (R_f 0.63; TLC, 3% v/v methanol in $CHCl_3$ as development solvent) were evaporated to dryness *in vacuo* to afford the product **5** (676 mg, 0.99 mmol, 41%).

^{1}H NMR ($CDCl_3$): δ 8.67 (s, 1 H, H-2), 8.23 (s, 1 H, H-8), 7.33-7.48, 7.51-7.60, and 7.91-8.11 (three overlapping m, 20 H, benzoyl H), 6.51 (d, $J_{1',2'}$ = 5.2 Hz, 1 H, H-1'), 6.44 (dd, $J_{1',2'}$ = 5.2 Hz, $J_{2',3'}$ = 5.2 Hz, 1 H, H-2'), 6.28 (m, 1 H, H-3'), 4.92 (ddd, $J_{5'',^{13}C}$ = 150 Hz, J_{gem} = 12.4 Hz, $J_{4',5'}$ = 3.2 Hz, 1 H, H-5'), 4.85 (m, 1 H, H-4'), 4.71 (ddd, $J_{5',^{13}C}$ = 150 Hz, J_{gem} = 12.4 Hz, $J_{4',5'}$ = 4.4 Hz, 1 H, H-5'); ^{13}C NMR ($CDCl_3$): δ 165.1, 165.3, and 166.1 (3C, benzoyl *C*=O), 164.8 (benzamido *C*=O), 152.8 (C-2), 151.7 (C-4), 149.8 (C-6), 141.8 (C-8), 127.9, 128.3, 128.5, 128.6, 128.7, 128.8, 129.3, 129.7, 129.8, 132.8, 133.5, and 133.8 (24C, phenyl C), 123.7 (C-5), 87.1 (C-1'), 80.9 (d, $J_{4',5'}$ = 43.5 Hz, C-4'), 73.9 (C-2'), 71.5 (C-3'), 63.5 (C-5').

[5'-^{13}C]*N*^{6}-Benzoyl-2',3',5'-tri-*O*-benzoyladenosine (5) from 4

As described above, **4** (340 mg, 0.64 mmol), was reacted with *N*-iodosuccinimide (153 mg, 0.68 mmol), *N*-benzoylaminopurine (170 mg, 0.71 mmol), some molecular sieves (4 Å), and trifluoromethanesulfonic acid (60 μL, 0.68 mmol) in anhydrous acetonitrile (12 mL) to afford the product (107 mg, 0.16 mmol, 24%). The proton NMR was exactly the same as above for **5**.

[5'-^{13}C]Adenosine (6)

NaOCH$_3$ in methanol (0.1 N, 30 mL) was added to **5** (676 mg, 0.99 mmol) and the solution was refluxed for 45 min. After removal of the solvent, the residue was dissolved in water (50 mL), the aqueous solution was neutralized with 1 N acetic acid, washed with CHCl$_3$ (25 mL × 3), and concentrated to 2-3 mL *in vacuo* for crystallization to afford the product **6** (164 mg, 0.61 mmol, 62%).

^{1}H NMR (DMSO-d$_6$): δ 8.34 (s, 1 H, H-8), 8.13 (s, 1 H, H-2), 7.33 (s, 2 H, NH_2), 5.87 (d, $J_{1',2'}$ = 6.0 Hz, 1 H, H-1'), 5.43 and 5.65 (two br s, 3 H, OH), 4.59 (dd, $J_{1',2'}$ = 6.0 Hz, $J_{2',3'}$ = 6.0 Hz, 1 H, H-3'), 4.14 (m, 1 H, H-2'), 3.96 (m, 1 H, H-4'), 3.54 and 3.66 (two ddd, $J_{5',^{13}C}$ = 141 Hz, J_{gem} = 48.8 Hz, $J_{4',5'}$ = 10.8 Hz, 2 H, H-5'), ^{13}C NMR (DMSO-d$_6$): δ 156.1 (C-6), 152.3 (C-2), 149.0 (C-4), 139.8 (C-8), 119.3 (C-5), 87.8 (C-1'), 85.8 (d, $J_{4',5'}$ = 41.9 Hz, C-4'), 73.4 (C-2'), 70.5 (C-3'), 61.6 (C-5').

[5'-^{13}C]5'-Chloro-5'-deoxyadenosine (7)

Thionyl chloride (250 µL, 3.43 mmol) in hexamethylphosphoramide (3 mL) was added dropwise to a solution of **6** (160 mg, 0.60 mmol) in hexamethylphosphoramide (5 mL). After 15 h at room temperature, the reaction mixture was poured into a beaker containing Dowex 50WX8 50-100 mesh (H$^+$ form, 25 g) and water (200 mL). The mixture was stirred for 0.5 h, loaded onto a glass column, and eluted with water (1000 mL), followed by 1 M NH$_4$OH (500 mL). The ammonia eluate was concentrated to 20 mL *in vacuo* for crystallization to afford the product 7 (131 mg, 0.46 mmol, 77%).

^{1}H NMR (DMSO-d$_6$): δ 8.34 (s, 1 H, H-8), 8.16 (s, 1 H, H-2), 7.31 (s, 2 H, NH_2), 5.93 (d, $J_{1',2'}$ = 5.6 Hz, 1 H, H-1'), 5.59 (d, 1 H, J = 6.0 Hz, 1 H, OH), 5.45 (d, J = 5.6 Hz, 1 H, OH), 4.76 (m, 1 H, H-3'), 4.22 (m, 1 H, H-2'), 4.09 (m, 1 H, H-4'), 3.95 (ddd, $J_{5',^{13}C}$ = 152 Hz, J_{gem} = 11.6 Hz, $J_{4',5'}$ = 5.2 Hz, 1 H, H-5"), 3.85 (ddd, $J_{5',^{13}C}$ = 152 Hz, J_{gem} = 11.6 Hz, $J_{4',5'}$ = 6.2 Hz, 1 H, H-5'); ^{13}C NMR (DMSO-d$_6$): δ 156.0 (C-6), 152.6 (C-2), 149.3 (C-4), 139.6 (C-8), 119.0 (C-5), 87.3 (C-1'), 83.5 (d, $J_{4',5'}$ = 41.2 Hz, C-4'), 72.5 (C-2'), 71.1 (C-3'), 44.7 (C-5').

{[5'-^{13}C]5'-Chloro-5'-deoxy-*N*1-methyladenosine$^+$}I$^-$ (8)

Methyl iodide (100 µL, 1.61 mmol) was added to a solution of **7** (105 mg, 0.37 mmol) in dimethylacetamide (1.2 mL) and allowed to react at room temperature for 20 h. Acetone (5 mL) was added, followed by ether dropwise until a white precipitate appeared. The mixture was stored at room temperature for crystallization to afford the product **8** (118 mg, 0.28 mmol, 71%).

^{1}H NMR (DMSO-d$_6$): δ 9.18 and 10.0 (two br s, 2 H, N*H*$_2$), 8.71 (s, 1 H, H-8), 8.68 (s, 1 H, H-2), 5.98 (d, $J_{1',2'}$ = 5.6 Hz, 1 H, H-1'), 5.73 (d, *J* = 6.4 Hz, O*H*), 5.59 (d, *J* = 5.2 Hz, O*H*), 4.67 (m, 1 H, H-3'), 4.21 (m, 1 H, H-2'), 4.15 (m, 1 H, H-4'), 3.96 (ddd, $J_{5'',^{13}C}$ = 152 Hz, J_{gem} = 12.4 Hz, $J_{4',5'}$ = 4.4 Hz, 1 H, H-5"), 3.86 (ddd, $J_{5',^{13}C}$ = 152 Hz, J_{gem} = 12.4 Hz, $J_{4',5'}$ = 6.0 Hz, 1 H, H-5'), 3.77 (s, 3 H, *N*1-methyl H); ^{13}C NMR (DMSO-d$_6$): δ 150.7 (C-6), 148.0 (C-2), 146.7 (C-4), 142.7 (C-8), 119.0 (C-5), 87.6 (C-1'), 84.0 (d, $J_{4',5'}$ = 40.4 Hz, C-4'), 73.2 (C-2'), 71.0 (C-3'), 44.6 (C-5'), 37.6 (*N*1-methyl C).

{[A15-^{13}C]5'-Deoxy-*N*1-methyladenosylcobalamin$^+$}Cl$^-$ (10)

A solution of cyanocobalamin **9** (160 mg, 0.118 mmol) in 10% NH$_4$Cl (60 mL) was deaerated with argon for 0.5 h, followed by addition of Zn wool (6.5 g, 100 mmol). The reduction was monitored by HPLC until **9** was exhausted. {[5'-^{13}C]5'-Chloro-5'-deoxy-*N*1-methyl-adenosine$^+$}I$^-$ (**8**, 34 mg, 0.079 mmol) was added to the solution and the reaction was monitored by HPLC until **8** was exhausted. After addition of 1 N HCl (5 mL), the reaction mixture was filtered and applied to a CG-161 C column (3 cm × 7 cm) eluted with water (500 mL) followed by 50% CH$_3$CN in water (250 mL). The collected acetonitrile solution was directly applied to a SP Sephadex C25 column (2 cm × 9 cm) and eluted with water (100 mL) and then 0.2% NaCl (250 mL). The collected fractions (monitored by HPLC) were desalted by chromatography on CG-161 C as above, to afford the product **10** (74.1 mg, 0.045 mmol, 57%). The purity of **10** was 100% as determined by HPLC.

^{1}H NMR (CD$_3$OD): δ 8.29 (s, 1 H), 8.04 (s, 1 H), 7.12 (s, 1 H), 7.07 (s, 1 H), 6.35 (s, 1 H), 6.18 (s, 1H), 5.95 (s, 1 H), 5.54 (s, 1 H), 3.76 (s, 3 H); ^{13}C NMR (CD$_3$OD): δ 177.9, 177.7, 177.4, 177.3, 177.2, 176.3, 175.9, 175.0, 174.8, 172.1, 165.7, 165.4, 154.4, 149.4, 146.3, 143.3, 142.0, 139.0, 134.1, 132.2, 132.1, 121.9, 119.8, 111.5, 106.6, 105.3, 95.7, 89.8, 87.5, 87.0, 86.7 (d, $J_{A14,A15}$ = 41.1 Hz), 83.3 (J_{pc} = 6.8 Hz), 75.6 (J_{pc} = 3.0 Hz), 75.5, 74.7, 74.5, 73.5 (J_{pc} = 6.0 Hz), 71.1, 62.7, 59.3, 57.1, 55.8, 53.9, 51.2, 47.9, 47.6, 46.4, 43.9, 43.8, 40.8, 37.5, 36.6, 35.8, 33.5, 33.4, 32.7, 32.4, 32.1, 28.8, 27.8, 27.6, 25.5 (A15), 24.7, 22.2, 22.1, 20.7, 20.3, 20 (J_{pc} = 5.3 Hz), 19.9, 18.4, 17.8, 17.0, 16.5.

ESI-MS: Calculated for $^{13}C^{12}C_{72}H_{103}N_{18}O_{17}PCo^+$: 1595.6. Found: 1595 (M$^+$).

CONCLUSION

{[A15-^{13}C]5'-Deoxy-*N*1-methyladenosylcobalamin$^+$}Cl$^-$ has been synthesized in satisfactory yield. The synthetic route may be used for the synthesis of other ^{13}C labeled nucleosides, as well as other ^{13}C labelled coenzyme B_{12} analogs.

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