# Application of Wittig Reaction to Adenosine Derivatives

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2′,3′-*O*-Ethoxymethyleneadenosine 5′-aldehyde (**3**) was reacted with Wittig reagents **4** and **5** to give the corresponding $\alpha,\beta$-unsaturated adenosine esters **6** and **7**. The dehydrated compounds **9** and **10** were separated from this reaction and inversion of configuration at C-3′ in ribofuranoside was observed.

It was reported that 5′-deoxy-5′-adenosineacetic acid (AAA) can replace adenosine 5′-monophosphate (AMP) in oligonucleotides and act as a substrate for enzymes such as AMP aminohydrolase.[1–3] Several derivatives of AAA have been reported.[4–9] We were interested in synthesizing some nucleotide analogues, in which the phosphate group of the natural nucleotide is replaced by a carboxyalkyl group. In order to introduce the carboxyalkyl group at the 5′-position of adenosine, the application of Wittig reaction to adenosine derivatives was investigated.

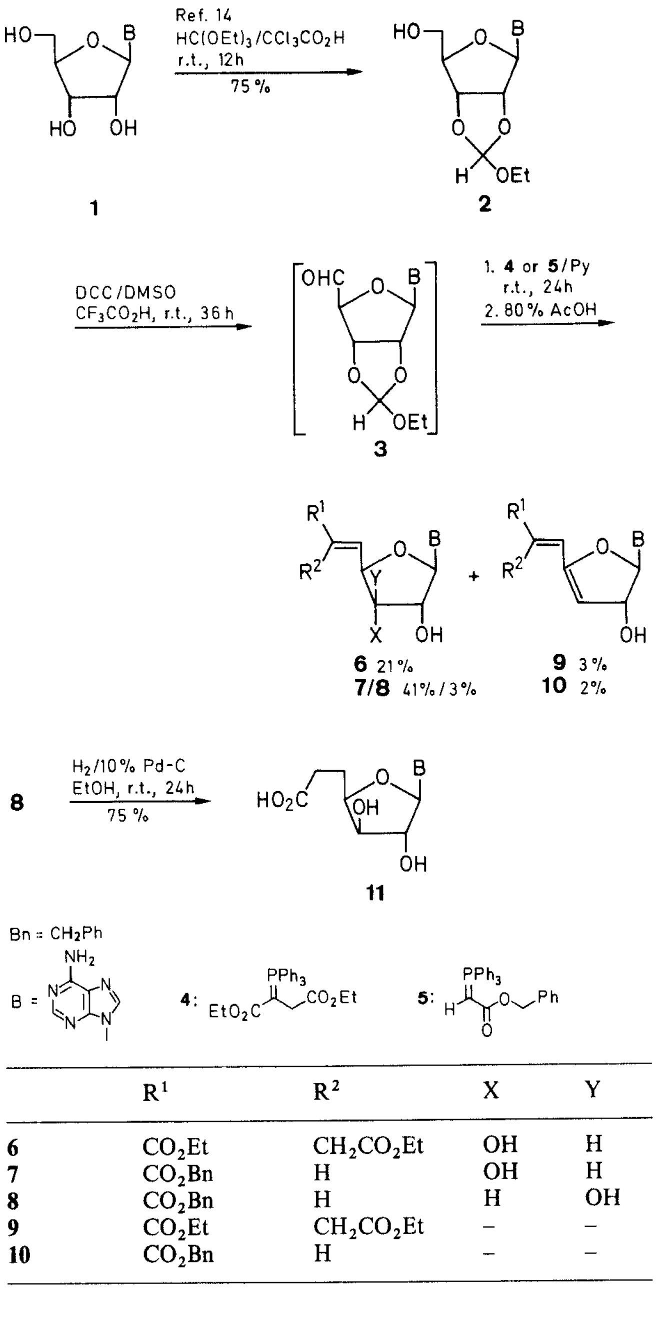
2′,3′-*O*-Ethoxymethyleneadenosine (**2**) prepared from adenosine (**1**) was oxidized by Moffatt reagent (1,3-dicyclohexylcarbodiimide/dimethyl sulfoxide) in the presence of pyridine and trifluoroacetic acid at room temperature to give compound **3**, which was condensed directly, without separation, with Wittig reagent **4** followed by hydrolysis with 80% acetic acid to give compounds **6** and **9** in 21 and 3% yields, respectively. Similarly, compounds **7**, **8** and **10** were obtained in 41,3 and 2% yields, respectively, from reaction of **3** with Wittig reagent **5** (Table).

Spectroscopic data indicated that in **7**, **8** and **10**, the 5′,6′-C=C bonds resulting from Wittig reaction are in *E* form ($J_{5'6'}$ = 15.6–15.9 Hz). 2-Dimensional $^1$H-NMR measurements (NOESY) showed that in **6** and **9**, the methylene protons of $CH_2CO_2Et$ interacted with H-4′ but not with H-5′, it also indicated that the 5′,6′-C=C bonds in **6** and **9** also have *E*-stereochemistry. Compounds **7** and **8** are found to be structural isomers, the hydroxyl groups at C-2′,3′ being *cis* in **7** and *trans* in **8**. Accordingly from $^1$H- and $^{13}$C-data **8** is found to be (*E*)-9(benzyl-5′,6′-dideoxy-5′-eno-$\beta$-D-xyloheptfuranosyluronate)adenine.

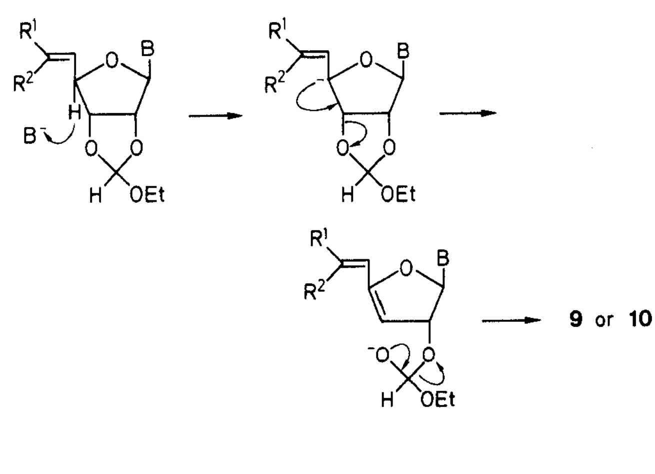
Compound **8** was hydrogenated to **11** in 75% yield. $^1$H-NMR data of **11** showed that H-3′ is *cis* to H-4′ ($J_{3'-4'}$ = 2.4 Hz) and H-1′ is *trans* to H-2′ ($J_{1'-2'}$ = 7.0 Hz). All this data supports compound **11** to be 9-(5′,6′-dideoxy-$\beta$-D-xyloheptfuranosyluronic acid)adenine.

The formation of dehydrated compounds **9** and **10** resulted from initial abstraction of the 4′-proton followed by elimination of ethyl formate. Considerable literature precedent exists for this pathway.[10,11] It is also reasonable that in the presence of acetic acid, compound **8** could be obtained from diene **10** by the attack of water on the $\beta$ direction of sugar ring, but corresponding inversion of configuration at C-3′ in **6** has not been observed.

The column chromatography was performed on silica gel (100–200 mech, purchased from Qing-Dao Chemical Company, China). $^1$H- and $^{13}$C-NMR spectra were recorded with Fx-90Q and VXR-300




| | R¹ | R² | X | Y |
|---|---|---|---|---|
| 6 | $CO_2Et$ | $CH_2CO_2Et$ | OH | H |
| 7 | $CO_2Bn$ | H | OH | H |
| 8 | $CO_2Bn$ | H | H | OH |
| 9 | $CO_2Et$ | $CH_2CO_2Et$ | – | – |
| 10 | $CO_2Bn$ | H | – | – |



spectrometers with TMS as internal standard. UV spectra were recorded with DU-7 spectrophotometer. A ZAB-HS was used for mass spectra (glcerol matrix). Evaporations were carried out under reduced pressure with the bath temperature below 40°C.

Ethoxycarbonyl(β-ethoxycarbonyl)ethylenetriphenylphosphorane (**4**)[12] and benzyloxycarbonylmethylenetriphenylphosphorane (**5**)[13] were prepared according to literature.

**(*E*)-9-[Ethyl 5′,6′-dideoxy-6′-(ethoxycarbonyl)methyl-β-D-ribohept-5′-enofuranosyluronate]adenine (6) and (5′-*E*)-9-[Ethyl 3′,5′,6′-trideoxy-6′-(ethoxycarbonyl)methyl-β-D-glycero-hept-3′,5′-dienofuranosyluronate]adenine (9):**
2′,3′-Ethoxymethyleneadenosine (**2**;[14] 0.6 g, 1.8 mmol) is stirred with 1,3-dicyclohexylcarbodiimide (1.5 g, 7.3 mmol) in a mixture of DMSO (7 mL), benzene (7 mL), pyridine (1.3 mL), and $CF_3CO_2H$ (0.8 mL) for 36 h at r.t. To the mixture is added the Wittig reagent **4** (1.2 g, 2.8 mmol) and the mixture is stirred for 24 h at 40°C. The mixture is diluted with EtOAc (20 mL) and stirred with oxalic acid (1.5 g). After filtration, the EtOAc layer is washed with water (2 × 10 mL) and evaporated to dryness. The residue is stirred with 80% AcOH (20 mL) for 24 h at 37°C and evaporated under reduced pressure. The crude product is purified by column chromatography on silica gel using $CHCl_3$/MeOH (20:1) as eluent to give **6**; yield: 0.27 g (21%), and **9**; yield: 24 mg (3%) as white powders.

**(*E*)-9-[Benzyl 5′,6′-dideoxy-β-D-ribohept-5′-enofuranosyluronate]-adenine (7), (*E*)-9-[Benzyl 5′,6′-dideoxy-β-D-xylohept-5′-enofuranosyluronate]adenine (8) and (5′*E*)-9-[Benzyl-3′,5′,6′-trideoxy-β-D-glycero-hept-3′,5′-dienofuranosyluronate]adenine (10):**
2′,3′-*O*-Ethoxymethyleneadenosine (**2**;[14] 3.23 g, 10 mmol) is stirred with dicyclohexylcarbodiimide (6.72 g, 30 mmol) in a mixture of DMSO (30 mL), benzene (30 mL), pyridine (0.8 mL) and

**Table.** Compounds **6** to **11** Prepared

| Product | Yield (%) | Molecular Formula[a] | UV (EtOH) $\lambda_{max}$ (nm) | $^1$H-NMR $\delta$, $J$(Hz) | $^{13}$C-NMR $\delta$ |
|---|---|---|---|---|---|
| **6** | 21 | $C_{18}H_{23}N_5O_7$ (421.4) | 259 | 1.16 (t, 3H, $CH_2CO_2CH_2C\underline{H}_3$, $J$ = 7.2), 1.22 (t, 3H, $CO_2CH_2C\underline{H}_3$, $J$ = 7.2), 3.35 (s, 2H, $CH_2CO_2$), 4.05 (q, 2H, $CH_2CO_2C\underline{H}_2CH_3$, $J$ = 7.2), 4.13 (q, 2H, $CO_2C\underline{H}_2CH_3$, $J$ = 7.2), 4.26 (m, 1H, H-3′), 4.72 (m, 1H, H-4′), 4.84 (m, 1H, H-2′), 5.57 (d, 1H, OH-3′, $J$ = 5.7), 5.64 (d, 1H, OH-2′, $J$ = 6.0), 5.94 (d, 1H, H-1′, $J_{1',2'}$ = 5.8), 7.11 (d, 1H, H-5$^1$, $J_{4',5'}$ = 7.8), 7.35 (s, 2H, $NH_2$), 8.28 (s, 1H, H-2), 8.39 (s, 1H, H-8) | 14.31 (2 × $CH_2\underline{C}H_3$), 32.85 ($CH_2CO_2$), 60.49 ($CH_2CO_2\underline{C}H_2CH_3$), 60.86 ($CO_2\underline{C}H_2CH_3$), 72.75 (C-2′), 74.76 (C-3′), 80.77 (C-4′), 88.66 (C-1′), 119.40 (C-5′), 127.47 (C-6′), 140.60 (C-5), 141.88 (C-8), 149.22 (C-4), 152.60 (C-2), 156.18 (C-6), 165.93 ($CH_2\underline{C}O_2$), 169.97 ($\underline{C}O_2CH_2CH_3$) |
| **7** | 41 | $C_{19}H_{19}N_5O_5$ (397.4) | 259 | 4.30 (m, 1H, H-3′), 4.57 (m, 1H, H-4′), 4.77 (m, 1H, H-2′), 5.19 (s, 2H, $C\underline{H}_2Ph$), 5.60 (d, 1H, OH-3′, $J$ = 5.4), 5.65 (d, 1H, OH-2′, $J$ = 5.7), 5.98 (d, 1H, H-1′, $J_{1',2'}$ = 4.8), 6.13 (d, 1H, H-6′, $J_{5',6'}$ = 15.6), 7.15 (dd, 1H, H-5′, $J_{5',6'}$ = 15.6, $J_{4',5'}$ = 5.7), 7.40 (m, 5H, $C_6H_5$), 8.12 (s, 1H, H-2), 8.39 (s, 1H, H-8) | 65.84 ($\underline{C}H_2Ph$), 72.68 (C-2′), 73.81 (C-3′), 82.66 (C-4′), 88.25 (C-1′), 121.36 (C-5′), 128.55 ($C_6H_5$), 136.15 (C-6′), 140.26 (C-5), 145.94 (C-8), 149.37 (C-4), 152.66 (C-2), 156.18 (C-6), 165.19 (C=O) |
| **8** | 2 | $C_{19}H_{19}N_5O_5$ (397.4) | 258.5 | 3.38 (dd, 1H, H-3′, $J$ = 2.7), 5.12 (m, 2H, H-2′, 4′), 5.19 (s, 1H, $C\underline{H}_2Ph$), 5.43 (d, 1H, OH-3′, $J$ = 4.5), 5.58 (d, 1H, OH-2′, $J$ = 6.6), 5.98 (d, 1H, H-1′, $J_{1',2'}$ = 7.2), 6.10 (d, 1H, H-6′, $J_{5',6'}$ = 15.9), 6.97 (dd, 1H, H-5′, $J_{5',6'}$ = 15.9, $J_{4',5'}$ = 4.2), 7.39 (m, 5H, $C_6H_5$), 8.17 (s, 1H, H-2), 8.41 (s, 1H, H-8) | 65.50 ($\underline{C}H_2Ph$), 72.61 (C-2′), 74.30 (C-3′), 80.67 (C-4′), 87.67 (C-1′), 21.20 (C-5′), 129.90 ($C_6H_5$), 135.94 (C-6′), 140.30 (C-5), 145.04 (C-8), 149.26 (C-4), 152.39 (C-2), 155.86 (C-6), 164.95 (C=O) |
| **9** | 3 | $C_{18}H_{21}N_5O_6$ (403.4) | 258.5 | 0.94 (t, 3H, $CH_2CO_2CH_2C\underline{H}_3$, $J$ = 7.2), 1.19 (t, 3H, $CO_2CH_2C\underline{H}_3$, $J$ = 7.2), 3.55 (s, 2H, $CH_2CO_2$), 3.77 (m, 2H, $CH_2CO_2C\underline{H}_2CH_3$), 4.14 (q, 2H, $CO_2C\underline{H}_2CH_3$), 5.36 (m, 1H, H-2′), 6.00 (m, 2H, H-3′ + OH-2′), 6.34 (d, 1H, H-1′, $J_{1',2'}$ = 0.5), 7.18 (s, 1H, H-5′), 7.34 (s, 2H, $NH_2$), 8.15 (s, 1H, H-2), 8.18 (s, 1H, H-8) | 14.03 ($CH_2CO_2CH_2\underline{C}H_3$), 14.11 ($CO_2CH_2\underline{C}H_3$), 33.14 ($\underline{C}H_2CO_2CH_2CH_3$), 60.05 ($CH_2CO_2\underline{C}H_2CH_3$), 60.98 ($CO_2\underline{C}H_2CH_3$), 76.23 (C-2′), 91.54 (C-1′), 113.63 (C-3′), 118.57 (C-5′), 127.24 (C-4′), 127.62 (C-6′), 138.74 (C-5), 148.89 (C-8), 152.84 (C-4), 154.16 (C-2), 155.03 (C-6), 166.04 ($CH_2\underline{C}O_2$), 169.69 ($\underline{C}O_2CH_2CH_3$) |
| **10** | 3 | $C_{19}H_{17}N_5O_4$ (379.4) | 259 | 5.17 (s, 2H, $C\underline{H}_2Ph$), 5.44 (m, 1H, H-2′), 6.02 (d, 1H, H-2′, $J_{1',2'}$ = 3.6), 6.07 (d, 1H, H-6′, $J_{5',6'}$ = 15.9), 6.36 (d, 1H, H-1′, $J_{1',2'}$ = 3.6), 7.27 (d, 1H, H-5′, $J_{5',6'}$ = 15.9), 7.35 (m, 5H, $C_6H_5$), 8.15 (s, 1H, H-2), 8.25 (s, 1H, H-8) | 66.02 ($\underline{C}H_2Ph$), 77.25 (C-2′), 91.66 (C-1′), 112.89 (C-3′), 120.76 (C-5′), 128.37 ($C_6H_5$), 132.26 (C-4′), 136.05 (C-6′), 139.31 (C-5), 149.30 (C-8), 153.06 (C-4), 153.76 (C-2), 156.16 (C-6), 165.24 (C=O) |
| **11** | 75 | $C_{12}H_{15}N_5O_5$[b] (309.3) | 259 | 1.84 (m, 2H, H-5′), 2.26 (t, 2H, H-6′, $J_{5',6'}$ = 7), 4.20 (dd, 1H, H-3′, $J_{2',3'}$ = 4.1, $J_{3',4'}$ = 2.4), 4.49 (m, 1H, H-4′, $J_{4',5'}$ = 5.9), 4.88 (dd, 1H, H-2′, $J_{1',2'}$ = 7, $J_{2',3'}$ = 4.1), 5.86 (d, 1H, H-1′, $J_{1',2'}$ = 7), 8.08 (s, 1H, H-2), 8.19 (s, 1H, H-8) | – |

[a] Satisfactory HRMS (FAB) obtained for $M^+ + H$: ±0.0061.
[b] HRMS not determined.

$CF_3CO_2H$ (0.38 mL) for 24 h at r.t. To this mixture is added the Wittig reagent **5** (5.0 g, 15 mmol) and the solution is stirred for 24 h at 40 °C. The reaction solution is diluted by EtOAc (100 mL) and stirred with oxalic acid (3.6 g). After filtration, the EtOAc layer is washed by water (2 × 50 mL) and evaporated to dryness. The residue is stirred with 80% AcOH (80 mL) for 24 h at r.t. and evaporated under reduced pressure. The crude product is purified by column chromatography on silica gel using $CHCl_3$/MeOH (20:1) as eluent to give **7**; yield: 1.64 g (41%), **10**; yield: 0.12 g (3%), and **8**; yield: 83 mg (2%) as white powders.

**9-[5′,6′-Dideoxy-β-D-xyloheptfuranosyluronic acid]adenine (11):** Compound **8** (24 mg) is hydrogenated in 95% EtOH (20 mL) in the presence of 10% Pd/C (100 mg) at 1 bar for 24 h. The crude product is purified by column chromatography on silica gel using $CHCl_3$/MeOH as eluent to give **11** as white powder; yield: 14 mg (75%).

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(1) Walker, T.E.; Follman, H.; Hogenkamp, H.P.C. *Carbohydr. Res.* **1973**, *27*, 225.
(2) Follman, H. *Angew. Chem.* **1974**, *86*, 41; *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 77.
(3) Meyer, W.; Follman, H. *Z. Naturforsch.* **1980**, *35C*, 273.
(4) Montgomery, J.A.; Laseter, A.G.; Hewson, K.J. *J. Heterocycl. Chem.* **1974**, *11*, 211.
(5) Baker, D.C.; Crew, R.P.; Haskell, T.H.; Putt, S.R.; Arnett, G.; Shannon, W.M.; Reinke, C.M.; Katlama, N.B.; Drach, J.C. *J. Med. Chem.* **1983**, *26*, 1530.
(6) Montgomery, J.A.; Thomas, H.J. *J. Org. Chem.* **1981**, *46*, 594.
(7) Montgomery, J.A.; Thomas, H.J.; Brockman, R.W.; Elliott, R.D. *J. Med. Chem.* **1984**, *27*, 680.
(8) Kurihara, T.; Ota, A.; Hayashi, H.; Urata, H.; Inoue, M.; Ishida, T. *Chem. Pharm. Bull.* **1983**, *31*, 2126.
(9) Kurihara, T.; Ota, A.; Hayashi, H.; Inoue, M.; Ishida, T. *J. Heterocycl. Chem.* **1984**, *21*, 259.
(10) Howgate, P.; Jones, A.S.; Tittenson, J.R. *Carbohydr. Res.* **1970**, *12*, 403.
(11) Lyga, J.W.; Secrit III, J.A. *J. Org. Chem.* **1983**, *48*, 1982.
(12) Hoffmann, H. *Chem. Ber.* **1961**, *94*, 1331.
(13) Chopard, P.A. *Helv. Chim. Acta* **1967**, *50*, 1016.
(14) Eckstein, F.; Cramer, F. *Chem. Ber.* **1965**, *98*, 995.