Eur. J. Org. Chem. **2006** · © WILEY-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, 2006 ·
ISSN 1434–193X

SUPPORTING INFORMATION

Title: **Synthesis and Conformational Analysis of C-4'-Modified (2-Oxabicyclo-[3.1.0]hexyl)pyrimidine Nucleosides**

Author(s): Julien Gagneron, Gilles Gosselin, and Christophe Mathé*

Ref. No.: O200600550

Experimental Details

[(1*S*,3*R*,4*R*,5*S*)-3-(2,4-Dioxo-3,4-dihydro-1(2*H*)-pyrimidinyl)-4-hydroxy-2-oxabicyclo[3.1.0]hex-1-yl]methyl benzoate 3. Benzoyl chloride (0.6 mL, 5.2 mmol) was added over a 30 min period with stirring to a cooled (ice-bath) solution of **1**[7](1 g, 4.1 mmol) in anhydrous pyridine (32 mL) and anhydrous DMF (8.8 mL). After 3h, CH_2Cl_2 (20 mL) was added and stirring was continued for 15 min. The mixture was successively washed with a saturated $NaHCO_3$ solution (100 mL), a 0.1N HCl solution (100 mL) and brine. The organic layer was dried (Na_2SO_4), evaporated under reduced pressure and coevaporated with toluene. The residue was purified by silica gel column chromatography with a stepwise gradient of MeOH (3–5%) in CH_2Cl_2 to afford compound **3** which was crystallized from absolute ethanol.

[(1*S*,3*R*,4*R*,5*S*)-4-Hydroxy-3-(5-methyl-2,4-dioxo-3,4-dihydro-1(2*H*)-pyrimidinyl)-2-oxabicyclo[3.1.0]hex-1-yl]methyl benzoate 4. Benzoyl chloride (0.36 mL, 3.11 mmol) was added dropwise over a 30 min period with stirring to a cooled (ice-bath) solution of **2**[7] (720 mg, 2.83 mmol) in anhydrous pyridine (21.6 mL) and anhydrous DMF (6 mL). After 5 h, CH_2Cl_2 (20 mL) was added and stirring was continued for 15 min. The mixture was successively washed with a saturated $NaHCO_3$ solution (100 mL), a 0.1N HCl solution (100 mL) and brine. The organic layer was dried (Na_2SO_4), evaporated under reduced pressure and coevaporated with toluene. The residue was purified by silica gel column chromatography with a stepwise gradient of MeOH (3–12%) in CH_2Cl_2 to afford compound **4** which was crystallized from absolute ethanol.

1-[(1*S*,3*R*,5*S*)-1-(Hydroxymethyl)-4-methylene-2-oxabicyclo[3.1.0]hex-3-yl]-2,4(1*H*,3*H*)-pyrimidinedione 5. Periodinane (1.29 g, 3.05 mmol) was added under argon to a cooled (ice-bath) solution of **3** (570 mg, 1.66 mmol) in anhydrous CH_2Cl_2 (22 mL). After 12h, the mixture was diluted with diethyl ether (30 mL). The resulting precipitate was filtered and the filtrate was evaporated under reduced pressure. The resulting ketonucleoside was used in the next step reaction without further purification. To a suspension of methyltriphenylphosphonium bromide (2.13 g, 5.96 mmol) in THF (20 mL) at 0°C under argon was added sodium *tert*-pentoxyde (585 mg, 5.32 mmol). The mixture was stirred at room temperature until the solution became orange. The solution was then cooled to 0°C and a solution of the ketonucleoside in THF (5 mL) was added. The reaction was controlled by TLC and an equal quantity of reagents were added after 3h to complete the reaction. The mixture was then diluted with ethyl acetate (50 mL), washed successively with brine, saturated solution of $NaHCO_3$ and water. The organic layer was dried (Na_2SO_4), evaporated under reduced pressure and the residue was purified by silica gel column chromatography (dichloromethane:methanol = 96:4). The appropriate fractions were combined, evaporated and treated with sodium methylate (305 mg, 5.65 mmol) in methanol (30 mL). The reaction mixture was stirred at room temperature overnight and neutralized with a 2N HCl solution, then evaporated to dryness. The residue was purified by silica gel column chromatography (dichloromethane:methanol = 95:5) to give compound **5** which was lyophylizated from dioxane.

1-[(1*S*,3*R*,5*S*)-1-(Hydroxymethyl)-4-methylene-2-oxabicyclo[3.1.0]hex-3-yl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione 6. Periodinane (1.07 g, 2.52 mmol) was added under argon to a cooled solution of **4** (485 mg, 1.35 mmol) in anhydrous CH_2Cl_2 (18 mL). After 12h, the mixture was diluted with diethyl ether (30 mL). The resulting precipitate was filtered and the filtrate was evaporated under reduced pressure. The resulting ketonucleoside was used in the next step without further purification. To a suspension of methyltriphenylphosphonium bromide (1.735 g, 4.86 mmol) in THF (20 mL) at 0°C under argon was added sodium *tert*-pentoxide (475 mg, 4.32 mmol). The mixture was stirred overnight at room temperature. The resulting orange solution was then cooled to 0°C and a solution of the ketonucleoside in THF (7 mL) was added. The reaction was controlled by TLC and an equal quantity of reagents were added after 3h to complete the reaction. The mixture was then diluted with ethyl acetate (50 mL), washed successively with brine, saturated solution of $NaHCO_3$ and water. The organic layer was dried (Na_2SO_4), evaporated under reduced pressure and the residue was purified by silica gel column chromatography (dichloromethane:methanol = 96:4). The appropriate fractions were combined, evaporated and treated with sodium methylate (190 mg, 3.52 mmol) in methanol (18 mL). The mixture was stirred at room temperature overnight and neutralized with a 2N HCl solution, then evaporated to dryness. The residue was purified by silica gel column chromatography (dichloromethane:methanol = 95:5) to give compound **6** which was lyophylizated from water.

4-Amino-1-[(1*S*,3*R*,5*S*)-1-(hydroxymethyl)-4-methylene-2-oxabicyclo[3.1.0]hex-3-yl]-2(1*H*)-pyrimidinone 8. To a solution of compound **7** (160 mg, 0.57 mmol) in anhydrous 1,2-dichloroethane (18.4 mL) was added Lawesson's reagent (163 mg, 0.40 mmol). After stirring for 1h30 under reflux, the solution was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (dichloromethane:methanol = 99:1) to give the corresponding 4-thio intermediate (125 mg, 74%) as a yellow foam. A solution of the 4-thio intermediate in methanolic ammonia (saturated beforehand at -10°C), (ca. 25 mL $mmoL^{-1}$) was heated in a stainless-steel bomb for 3h, and then cooled to r.t. The solution was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (dichloromethane:methanol = 85:15) to give compound **8** which was lyophylizated from water.

[(5a*R*,6a*S*,7a*S*,7b*S*)-2-Oxo-5a,7,7a,7b-tetrahydro-2*H*,6a*H*-cyclopropa[4',5'] furo[2',3':4,5][1,3]oxazolo[3,2-*a*]pyrimidin-6a-yl]methyl benzoate 9. To a solution of compound **1** (670 mg, 2.79 mmol) and triphenylphosphine (1.1 g, 4.19 mmol) in anhydrous DMF (5.5 mL) was added dropwise at room temperature a solution of DEAD (0.647 mL, 4.19 mmol) and benzoic acid (510 mg, 4.19 mmol) in anhydrous DMF (1.2 mL). After stirring for 4h, additional ammount of triphenylphosphine (1.1 g, 4.19 mmol) and DEAD (0.647 mL, 4.19 mmol) were added at room temperature. After 1h, the mixture was evaporated under reduced pressure, diluted with CH_2Cl_2 (30 mL) and washed with water. The organic layer was dried (Na_2SO_4), concentrated to dryness and the residue was purified by silica gel column chromatography (dichloromethane:methanol = 97:3) to give compound **9** as a white foam.

[(5a*R*,6a*S*,7a*S*,7b*S*)-3-Methyl-2-oxo-5a,7,7a,7b-tetrahydro-2*H*,6a*H*-cyclopropa[4',5']furo[2',3':4,5][1,3]oxazolo[3,2-*a*]pyrimidin-6a-yl]methyl benzoate 10. To a solution of compound **2** (590 mg, 2.32 mmol) and triphenylphosphine (912 mg, 3.48 mmol) in anhydrous DMF (4.5 mL) was added dropwise at room temperature a solution of DEAD (0.54 mL, 3.48 mmol) and benzoic acid (424 mg, 3.48 mmol) in anhydrous DMF (1.0 mL). After stirring for 4h, additional ammount of triphenylphosphine (912 mg, 3.48 mmol) and DEAD (0.54 mL, 3.48 mmol) were added at room temperature. After 1h, the mixture was evaporated under reduced pressure, diluted with CH_2Cl_2 (30 mL) and washed with water. The organic layer was dried (Na_2SO_4), concentrated to dryness and the residue was purified by silica gel column chromatography (dichloromethane:methanol = 97:3) to give compound **10** which was crystallized from absolute ethanol.

[(1*S*,3*R*,4*R*,5*S*)-4-Azido-3-(2,4-dioxo-3,4-dihydro-1(2*H*)-pyrimidinyl)-2-oxabicyclo[3.1.0]hex-1-yl]methyl benzoate 11. To a solution of compound **9** (100 mg, 0.30 mmol) in anhydrous DMF (5 mL) was added successively at room temperature sodium azide (200 mg, 3 mmol) and 18-crown-6 (80 mg, 0.30 mmol). After stirring at 125°C for 15h, the reaction was stopped and the mixture was evaporated under reduced pressure. The residue was then diluted with CH_2Cl_2 (30 mL)and washed with water. The organic layer was dried (Na_2SO_4), concentrated to dryness and the crude product was purified by silica gel column chromatography (dichloromethane:methanol = 96:4) to give compound **11**.

[(1*S*,3*R*,4*R*,5*S*)-4-Azido-3-(5-methyl-2,4-dioxo-3,4-dihydro-1(2*H*)-pyrimidinyl)-2-oxabicyclo[3.1.0]hex-1-yl]methyl benzoate 12. To a solution of compound **10** (250 mg, 0.73

mmol) in anhydrous DMF (10.5 mL) was added successively at room temperature sodium azide (454 mg, 7.3 mmol) and 18-crown-6 (185 mg, 0.70 mmol). After stirring under reflux for 15h, the mixture was evaporated under reduced pressure. The residue was diluted with CH_2Cl_2 (30 mL) and washed with water. The organic layer was dried (Na_2SO_4), concentrated to dryness and the residue was purified by silica gel column chromatography (dichloromethane:methanol = 96:4) to give compound **12**.

1-[(1*S*,3*R*,4*R*,5*S*)-4-Azido-1-(hydroxymethyl)-2-oxabicyclo[3.1.0]hex-3-yl]-2,4(1*H*,3*H*)-pyrimidinedione 13. To a solution of compound **11** (200 mg, 0.54 mmol) in methanol (10.2 mL) was added sodium methylate (100 mg, 1.85 mmol). The reaction mixture was stirred at room temperature overnight and neutralized with a 2N HCl solution, then evaporated to dryness. The residue was purified by silica gel column chromatography (dichloromethane:methanol = 92:8) to give compound **13** which was crystallized from absolute ethanol.

1-[(1*S*,3*R*,4*R*,5*S*)-4-Azido-1-(hydroxymethyl)-2-oxabicyclo[3.1.0]hex-3-yl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione 14. To a solution of compound **12** (120 mg, 0.30 mmol) in methanol (5.4 mL) was added sodium methylate (55 mg, 1.01 mmol). The reaction mixture was stirred at room temperature overnight and neutralized with a 2N HCl solution, then evaporated to dryness. The residue was purified by silica gel column chromatography (dichloromethane:methanol = 95:5) to give compound **14** which was lyophylizated from a water/dioxane mixture.

1-[(1*S*,3*R*,4*S*,5*S*)-4-Hydroxy-1-(hydroxymethyl)-2-oxabicyclo[3.1.0]hex-3-yl]-2,4(1*H*,3*H*)-pyrimidinedione 16. To a solution of compound **9** (200 mg, 0.61 mmol) in a mixture methanol/water (1/1:v/v, 6.0 mL) was added a 1N NaOH solution (0.6 mL). The reaction mixture was stirred at room temperature overnight and neutralized with glacial acetic acid, then evaporated to dryness. The residue was purified by silica gel column chromatography (dichloromethane:methanol = 9:1) to give compound **16** which was crystallized from acetonitrile.

1-[(1*S*,3*R*,4*S*,5*S*)-4-Hydroxy-1-(hydroxymethyl)-2-oxabicyclo[3.1.0]hex-3-yl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione 17. To a solution of compound **10** (360 mg, 1.00 mmol) in a methanol/water mixture (1/1:v/v, 10.6 mL) was added a 1N NaOH solution (1 mL). The reaction mixture was stirred at room temperature for 48h and neutralized with glacial acetic acid, then evaporated to dryness. The residue was purified by silica gel column chromatography (dichloromethane:methanol = 9:1) to give compound **17** which was crystallized from absolute ethanol.

4-Amino-1-[(1*S*,3*R*,4*S*,5*S*)-4-hydroxy-1-(hydroxymethyl)-2-oxabicyclo[3.1.0]hex-3-yl]-2(1*H*)-pyrimidinone 19. To a solution of compound **18** (115 mg, 0.35 mmol) in anhydrous 1,2-dichloroethane (11 mL) was added Lawesson's reagent (100 mg, 0.24 mmol). After stirring for 1h30 under reflux, the solution was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (dichloromethane:methanol = 98:2) to give the 4-thio intermediate (120 mg) as a yellow foam. A solution of the 4-thio intermediate in methanolic ammonia (saturated beforehand at -10°C), (ca. 25 mL mmoL^{-1}) was heated in a stainless-steel bomb for 3h, and then cooled to r.t. The solution was evaporated under reduced pressure and the residue was purified by silica gel column chromatography with a stepwise gradient of MeOH (12–25%) in CH_2Cl_2 to give compound **19**. After filtration on Millex HV-4 (0.45 µm, Millipore) compound **19** was lyophylizated from water.