Supporting Information for Organic Letters

Synthesis Using Olefin Metathesis and Affinity at the Adenosine Uptake Site of a (N)-Methanocarba *S*-(4-Nitrobenzyl)thioinosine Derivative

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Proton NMR was performed on a Varian GEMINI-300 spectrometer. Chemical shifts (δ) relative to tetramethylsilane are given. FAB mass was performed with a JEOL SX102 spectrometer using 6 kV Xe atoms.

(2*S*,3*R*)-5-Benzyl-2,3-*O*-isopropylidene-4-*C*-methylene-D-erythro-pentitol (2). A solution of DMSO (1.4 ml, 21.3 mmol) in CH_2Cl_2 (10 mL) was gradually added to a solution of oxalyl chloride (1 ml, 10.7 mmol) in CH_2Cl_2 (5 mL) at –78 °C. After stirring of the resulting solution for 15 min, a solution of the alcohol **1** (2.79 g, 5.36 mmol) in CH_2Cl_2 (10 mL) was added and the reaction mixture was stirred at –78 °C for 1 h. Et_3N (4.4 ml, 32 mmol) was added to the reaction mixture, which was then gradually warmed up to room temperature, at which point water was added. The solution was washed successively with water and brine, dried and concentrated to dryness.

To a suspension of methyltriphenylphosphonium bromide (9.6 g, 26.8 mmol) in anhydrous THF (40 mL) under argon atmosphere at 0 °C was added n-butyl lithium (14 mL, 22.4 mmol) dropwise and the mixture was stirred for 30 min. To the mixture was added a solution of the ketone (1.52 g, 72.5 % from compound **1**) in THF (30 mL) at 0 °C. The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (petroleum ether : EtOAc = 30 : 1), to give the olefinic compound (1.96 g, 93.4 %) as a colorless oil. ^{1}H NMR δ ($CDCl_3$): 7.61-7.66 (m, 5H, Ph), 7.30-7.40 (m, 5H, Ph), 5.36 (s, 1H), 5.24 (s, 1H), 4.81 (d, 1H, J = 6.6 Hz), 4.50 (d, 1H, J = 12 Hz), 4.39 (d, 1H, J = 11.7 Hz), 4.32 (d, 1H, J = 6 Hz), 4.07 (d, 1H, J = 12.3 Hz), 4.00 (d, 1H, J = 12.3 Hz), 3.62 (dd, 1H, J = 10.5, 6.6 Hz), 3.47 (dd, 1H, J = 10.5, 6.6 Hz), 1.40, 1.36 (2s, 3H, 2 x CH_3).

To a stirring solution of the olefinic compound in CH_3CN (40 mL) was added Bu_4NF (1M in THF, 10 mL, 10 mmol) and the resulting mixture was stirred for 2 h at room temperature. After concentration of the reaction mixture, the residue was purified on silica gel (petroleum ether : EtOAc = 7 : 3) to give the alcohol **2** (1.18 g, 84.7 %). ^{1}H NMR δ ($CDCl_3$): 7.29-7.39 (m, 5H, Ph), 5.45 (s, 1H), 5.32 (s, 1H), 4.73 (d, 1H, J = 6.3 Hz), 4.54 (s, 2H, C*H*$_2$Ph), 4.27 (dd, 1H, J = 12, 12.3 Hz), 4.01 (m, 2H), 3.47 (m, 2H), 2.37 (t, 1H, J = 5.7 Hz, O*H*), 1.58, 1.50 36 (2s, 3H, 2 x CH_3).

(2*S*,3*R*)-5-Benzyl-2,3-*O*-isopropylidene-4-*C*-methylene-2-*C*-vinyl-D-erythro-pentitol (3). A solution of DMSO (1.36 ml, 19.15 mmol) in CH_2Cl_2 (10 mL) was gradually added to a solution of oxalyl chloride (0.84 ml, 9.57 mmol) in CH_2Cl_2 (5 mL) at –78 °C. After stirring of the resulting solution for 15 min, a solution of the alcohol **2** (1.16 g, 4.16 mmol) in CH_2Cl_2 (10 mL) was added and the reaction mixture was stirred at –78 °C for 1 h. Et_3N (3.54 ml, 25 mmol) was added to the reaction mixture, which was then gradually warmed up to room temperature, at which point water was added. The solution was washed successively with water and brine, dried and concentrated to dryness.

To a solution of the aldehyde in THF (15 mL) at –78 °C was added 4.4 mL 0f 1M solution of vinylmagnesium bromide in THF dropwise and the resulting solution was stirred for 1 h at –78 °C. Saturated NH_4Cl solution was added and the resulting solution was extracted with EtOAc. The combined organic layer was dried ($MgSO_4$) and concentrated to dryness, which was purified on silica gel (petroleum ether : EtOAc = 4 : 1) to give the diene **3** (827.7 mg, 72 % from **2**) as a diastereomeric mixture. ^{1}H NMR δ ($CDCl_3$): 7.29-7.38 (m, 5H, Ph), 6.00, 5.76 (m, 1H), 4.80 (d, 1H, J = 6.0 Hz), 4.73 (d, 1H, J = 5.4 Hz), 3.22 (d, 1H, J = 2.4 Hz, O*H*), *2*.37 (d, 1H, J = 3.9 Hz, O*H*), 1.57, 1.41 (2s, 3H, 2 x CH_3), 1.50, 1.37 (2s, 3H, 2 x CH_3). MS (FAB): *m/z* 305 (M^+ + 1).

(4*R*, 5*S*)-(-)-3-[Benzyloxy)methyl]-4,5-*O*-isopropylidene-2-cyclopenten-1-ol (5). All reagents and solvents were dried and degassed. A round-bottomed flask charged with the catalyst **4** (418 mg, 0.508 mmol) was evacuated and filled with Ar three times before the addition of the diene **3** (774.2 mg, 2.54 mmol) in degassed CH_2Cl_2 (30 mL). The resulting solution was stirred under Ar for 2 h and then stirred overnight exposed to the air. Removal of the solvent *in vacuo* gave a black oily residue that was purified by column chromatography on silica gel (petroleum ether : EtOAc = 7 : 3) to afford the product **5** (7.3 : 1, 1*R* as major isomer, 596.6 mg, 85 %). ^{1}H NMR δ ($CDCl_3$): 7.29-7.36 (m, 5H, Ph), 6.00, 5.76 (m, 1H), 4.80 (d, 1H, J = 6.0 Hz), 4.73 (d, 1H, J = 5.4 Hz), 3.22 (d, 1H, J = 2.4 Hz, O*H*), *2*.37 (d, 1H, J = 3.9 Hz, O*H*), 1.57, 1.41 (2s, 3H, 2 x CH_3), 1.50, 1.37 (2s, 3H, 2 x CH_3). MS (FAB): *m/z* 277 (M^+ + 1).

(4*R*, 5*R*)-(-)-3-[(Benzyloxy)methyl]-4,5-*O*-isopropylidene-2-cyclopentenone (6). A mixture of **5** (60 mg, 0.217 mmol) and activated MnO_2 (405 mg, 4.66 mmol) in $CHCl_3$ (4 mL) was shaken for 20 h. The resultant mixture was filtered and the solid residues washed with $CHCl_3$. The solvent was evaporated *in vacuo* to dryness, which was purified on silica gel (petroleum ether : EtOAc = 7 : 3) to give the cyclopentenone **6** (47.6 mg, 80 %) as colorless oil. $[\alpha]_D^{20}$ = -7.2 (c 1.08, CH_3Cl); ^{1}H NMR δ ($CDCl_3$):

7.28-7.30 (m, 5H, Ph), 6.13 (s, 1H, H-2), 5.01 (d, 1H, J = 5.4 Hz, H-5), 4.56 (d, 2H, CH_2), 4.44 (d, 1H, H-4), 4.39 (d, 1H, CH_2), 4.30 (d, 1H, CH_2), 1.32 (s, 6H, CH_3).

(1'*R*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-Chloropurin-9-yl)-1-[(phenylmethoxy)methyl]-bicyclo[3.1.0]hexane-2,3-(*O*-isopropylidene) (8). To a solution of PPh_3 (653 mg, 2.49 mmol) in anhydrous THF (12 mL) was added DEAD (diethyl azadicarboxylate, 0.4 ml, 2.49 mmol) dropwise at 0 °C. To this solution was added a solution of 6-chloropurine in THF (6 mL) followed by the addition of **7** (314 mg, 1.08 mmol) in THF (6 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed *in vacuo,* and the residue was purified by column chromatography on silica gel (petroleum ether : EtOAc = 7 : 3) to provide the product **8** (400 mg, 86.7 %) as a form. ^{1}H NMR δ ($CDCl_3$): 8.74 (s, 1H, H-2), 8.70 (s, 1H, H-8), 7.32-7.37 (m, 5H, Ph), 5.32 (d, 1H, J = 7.8 Hz, H-2'), 5.22 (s, 1H, H-1'), 4.62 (m, 2H, CH_2), 4.62 (d, 1H, J = 6.0 Hz, H-3'), 3.99 (d, 1H, J = 10.2 Hz, CH_2), 3.29 (d, 1H, J = 10.2 Hz, CH_2), 1.68 (m, 1H), 1.60 (s, 3H, CH_3), 1.56 (s, 1H, CH_3), 1.3 (m, 1H), 0.99 (m, 1H).

(1'*R*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-Chloropurine-9-yl)-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-(*O*-isopropylidene) (9). A stirred solution of **8** (166.9 mg, 0.391 mmol) in anhydrous CH_2Cl_2 (5 mL) was cooled to –78 °C and treated with BCl_3 (1M/CH_2Cl_2, 1.2 ml, 1.2 mmol) and stirred at room temperature for 15 min. To this mixture was added MeOH and the resulting mixture was concentrated to dryness, which was used as such in the next reaction.

To a mixture of the crude triol and pTsOH (10 mg) in acetone (20 mL) was added 2,2-dimethoxypropane (2 mL) and the resulting solution was stirred overnight. The reaction mixture was concentrated to dryness, which was purified by column chromatography ($CHCl_3$: MeOH = 15 : 1) to give the alcohol **9** (46.3 mg, 35.2 % from compound **8**). ^{1}H NMR δ ($CDCl_3$): 8.77 (s, 1H, H-2), 8.28 (s, 1H, H-8), 5.55 (d, 1H, J = 6.9 Hz, H-2'), 4.96 (s, 1H, H-1'), 4.65 (d, 1H, J = 6.6 Hz, H-3'), 4.28 (m, 1H, CH_2), 3.76 (d, 1H, J = 6.6 Hz, O*H*), 3.39 (m, 1H, CH_2), 1.77 (m, 1H), 1.56 (s, 3H, CH_3), 1.21-1.28 (m, 4H, CH_3, CH), 1.04 (m, 1H). MS (FAB): *m/z* 337 (M^+ + 1).

(1'*R*,2'*R*,3'*S*,4'*R*,5'*S*)-4-[6-(4-Nitrobenzyl)mercaptopurine-9-yl]-1-(hydroxymethyl)bicyclo[3.1.0] hexane-2,3-diol (11). To a suspension of the 6-chloropurine derivative **9** (17.5 mg, 0.052 mmol) in MeOH (1 mL) was added sodium 4-nitrobenzylmercaptide (prepared by adding 19.4 mg of 4-nitrobenzylmercaptan to 0.2 mL of 0.5 N sodium methoxide/MeOH at room temperature) in MeOH (2 mL). The mixture was heated under reflux for 2 h; solution occurred after the first few minutes of heating. After cooling to 0 °C, it was neutralized with 1N HCl and evaporated *in vacuo*. The residue was purified on preparative TLC plate (CH_3Cl : MeOH = 15 : 1) to furnish compound **9** (10.3 mg, 42.3

%). ^{1}H NMR δ ($CDCl_3$): 8.71 (s, 1H, H-2), 8.17, 8.14 (2 s, 1H), 8.04 (s, 1H, H-8), 7.67, 7.64 (2 s, 1H), 5.58 (d, 1H, J = 7.2 Hz, H-2'), 4.87 (s, 1H, H-1'), 4.72 (s, 2H, C*H*$_2$Ph), 4.63 (d, 1H, J = 7.2 Hz, H-3'), 4.51 (br s, 1H, O*H*), 4.29 (m, 1H, C*H*$_2$), 3.31 (m, 1H, C*H*$_2$), 1.74 (m, 1H), 1.55 (s, 3H, CH_3), 1.21-1.17 (m, 4H, CH_3, CH), 1.01 (m, 1H). HRMS (FAB): calcd 470.1498, found 470.1484.

A mixture of **9** (9.9 mg, 0.021 mmol), 10 % CF_3CO_2H/MeOH (2 mL), and H_2O (0.2 mL) was heated at 60 °C for 4 h. The solvent was removed, and the resulting residue was coevaporated with toluene. The residue was purified on silica gel (CH_3Cl : MeOH = 15 : 1) to give the final product **11** (6.8 mg, 75.4 %). ^{1}H NMR δ (CD_3OD): 8.79 (s, 1H, H-2), 8.74 (s, 1H, H-8), 8.18, 8.15 (2 s, 2H), 7.76, 7.64 (2 s, 2H), 4.69-4.99 (m, 3H, H-2', H-1', H-3'), 4.87 (s, 1H, H-1'), 4.72 (s, 2H, C*H*$_2$Ph), 4.24 (m, 1H, C*H*$_2$), 3.89 (m, 1H, C*H*$_2$), 1.64 (m, 1H), 1.56 (m, 1H), 0.93 (m, 1H). HRMS (FAB): calcd 430.1185, found 430.1171.