SUPPLEMENTARY MATERIAL

Synthesis of loganVir, a New Carbocyclic Nucleoside Analog

Luigi Ornano^{*a,b}, Armandodoriano Bianco^{a,b}

^{a)} *Dipartimento di Chimica, Università di Roma "La Sapienza", P.le Aldo Moro, 5, 00185 Roma.*

^{b)} *Consorzio CoSMese, Dipartimento di Scienze della Vita e dell'Ambiente, Università di Cagliari, Via S.Ignazio da Laconi 11, 09123 Cagliari.*

luigi.ornano@uniroma1.it

Abstract

Starting from a natural cyclopentanoid monoterpene belonging to the class of iridoid glucosides called Loganin, we performed the synthesis of a new carbocyclic nucleoside, allowing the preparation of a new lead compound, with a potential HIV antiviral activity as a RT competitive inhibitor that we named LoganVir. The stereocontrol of the coupling reaction was completed utilizing the procedure described by Mitsunobu with a purinic base.

Key words: *Antiviral agents / Terpenoids / Rearrangements / Chiral intermediates / synthons*

Spectrometric identification

¹H and ¹³C NMR spectra were recorder on Varian Mercury 300 MHz instrument using CDCl₃, CD₃OD and D₂O as deuterated solvents, the chemical shift was expressed in ppm from TMS (the signal of HDO at 4.78 ppm is used as reference for spectra in D₂O) MS spectra were performed on a Q-TOFMICRO spectrometer (Micromass, now Waters, Manchester UK) equipped with an ESI source, that was operated in the negative and/or positive ion mode. The flow rate of sample injection was 10µL/min. With 100 acquisition per spectrum. Data were analyzed using Masslynx software developed by Waters.

Chromatography

Products were purified by solid-liquid column chromatography on Merck 0.063-0.20 mm silica gel; eluent was chosen case by case. TLC on plates precoated with Kiesel-

Gel 60 F₂₅₄ (Merck) was used to monitor the progress of the reaction; spots were developed by spraying with 2 N H₂SO₄ and heating to 120 °C for 1 min.

Compound 1

(Loganic Acid)

(1*S*,6*S*,7*R*)-6-hydroxy-7-methyl-1-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)-1,4*a*,5,6,7,7*a*-hexahydrocyclopenta[*c*]pyran-4-carboxylic acid.

¹H-NMR, (300 MHz, D₂O), δ : 0.88 (3H, d, J=6.1 Hz, H-10), 1.60 (1H, m, H-8), 1.74 (1H, m, H-9), 1.97 (1H, m, H-5), 2.86 (1H, m, H-5'), 3.13 (1H, m, H-3'), 3.25 (1H, m, H-4'), 3.58 (2H, m, H-5''), 3.98 (1H, m, H-7), 4.58 (1H, d, J=9.2 Hz, H-1'), 5.22 (1H, d, J=9.0 Hz, H-1), 6.90 (1H, s, H-3). ¹³C-NMR, (75 MHz, D₂O), δ : 14.4 (C-10), 32.9 (C-5), 42.3 (C-6), 42.7 (C-8), 47.9 (C-9), 63.3 (C-6'), 72.2 (C-4'), 75.2 (C-2'), 76.9 (C-7), 78.1 (C-3'), 78.7 (C-5'), 98.2 (C-1), 100.8 (C-1'), 121.4 (C-4), 147.4 (C-3), 178.3 (C-11).

ESI-MS: m/z = 399.1060 [M+Na]⁺ (calculated mass C₁₆H₂₄O₁₀ (376.5580)).

Compound 2 (Loganin)

(1*S*,6*S*,7*R*)-methyl-6-hydroxy-7-methyl-1-(((2*S*,3*R*,4*S*,5*S*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)-1,4*a*,5,6,7,7'*a*hexahydrocyclopenta[*c*]pyran-4-carboxylate.

S.1 ¹H-NMR spectrum of 2

^1H -NMR, (330 MHz, CD_3OD), δ : 1.08 (H-10, d, $J=7.5$ Hz), 1.60 (H-6, ddd, $J=14.0$ Hz, $J=7.5$ Hz, $J=4.5$ Hz), 1.86 (H-8, m), 2.03 (H-9, m), 2.25 (H-6, ddd, $J=14$ Hz, $J=8.0$ Hz, $J=1.5$ Hz), 3.10 (H-5, m), 3.20 (H-2', d, $J=8.1$ Hz), 3.67 (-OMe), 4.04 (H-7, m), 4.65 (H-1', d, $J=8.0$ Hz), 5.73 (H-1, d, $J=4.5$ Hz), 7.37 (H-3, d, $J=0.5$ Hz).

S.2 ^{13}C -NMR spectrum of **2**

^{13}C -NMR, (75 MHz, CD_3OD), δ : 12.8 (C-10), 30.7 (C-5), 40.1 (C-8), 40.3 (C-6), 45.0 (C-9), 52.6 (-OMe), 61.5 (C-6'), 70.4 (C-4'), 73.6 (C-2'), 74.4 (C-7), 76.5 (C-3'), 77.1 (C-5'), 97.6 (C-1), 99.4 (C-1'), 113.2 (C-4), 151.0 (C-3).

S.3 ESI-MS spectrum of **2**

ESI-MS: $m/z = 413.1824$ $[M+Na]^+$ (calculated mass $C_{17}H_{26}O_{10}$ (390. 3850)).

S.4 1H -NMR spectrum of **3**

S.5. ^{13}C -NMR spectrum of **3**

S.6 ESI-MS spectrum of **3**

S.7 ^1H -NMR spectrum of **4**

S.8 ^{13}C -NMR spectrum of **4** (^{13}C -NMR original format)

S.9 ESI-MS spectrum of **4**

S.13 ^1H -NMR spectrum of **6**

S.14 ^1H -NMR spectrum of **6**

S.15 ESI-MS spectrum of **6**

S.16 ¹H-NMR spectrum of **7**

S.17 ^{13}C -NMR spectrum of **7**

S.18 ESI-MS spectrum of **7**

S.19 ^1H -NMR spectrum of **8**

S.20 ¹³C-NMR spectrum of **8**

S.21 ESI-MS spectrum of **8**