A Short and Convenient Synthesis of New 1,2-Disubstituted Carbocyclic Nucleoside Analogues of Pyrimidine Based on a Cyclopentene Ring

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Abstract: The synthesis of a new series of 1,2-disubstituted carbocyclic nucleoside analogues, pyrimidines of general structure I, is reported. These compounds were prepared in good yield from (±)-6-azabicyclo[3.2.0]hept-3-en-7-one (1) via two synthetic routes that involve NaBH₄-mediated C-N bond cleavage as the key step. The uracil derivative Ia was halogenated with Cl, Br, and I at position 5 by treatment with the corresponding N-halosuccinimide.

Key words: nucleosides, reductions, amino alcohols, carbocycles, heterocycles

Nucleoside analogues display a wide range of biological activities and have attracted particular attention as antiviral and antitumor agents. The synthesis of new modified nucleosides represents an important and increasingly active area of interest for organic chemists in the search for compounds with improved biological properties. Within this area, systems of particular interest include carbocyclic nucleosides and 2',3'-dideoxynucleosides. Carbocyclic nucleosides are compounds in which the furanose oxygen atom of a classical nucleoside is replaced by a methylene group. These compounds possess greater metabolic stability toward the nucleoside phosphorylases and a higher lipophilicity, two properties that are potentially beneficial in terms of increased in vivo half life, oral efficiency and cell wall penetration. On the other hand, a number of 2',3'-dideoxynucleosides are currently the drugs of choice for the treatment of certain viral infections (including AIDS). Indeed, the potent HIV-1 inhibitor carbovir and its prodrug, abacavir, combine the two types of structural modification described above. On the basis of the factors outlined above, and as part of our study of the therapeutic potential of 1,2-disubstituted carbonucleosides (OTCs), we describe now the synthesis of (±)-cis-1-(2-hydroxymethyl-4-cyclopentenyl)-2,4-pyrimidine-2,6-diones of structure I (Schemes 1 and 3). We previously developed another series of pyrimidine-based OTCs in which the pseudosugar is a cyclopentane ring, and in this present study unsaturation has now been incorporated into the 2',3'-position of the carbocycle. Such a structural modification also allows versatility in the functionalization of the ring. 5-Halopyrimidines ( Ib–d, Scheme 3) are not only of interest for their potential chemotherapeutic properties but also as synthetic intermediates in the formation of new carbon–carbon or carbon–heteroatom bonds. Our usual approach to the synthesis of uracil-based OTCs is to construct the heterocyclic base on an appropriate amino alcohol by reaction with a β-aloxaacyroyl isocyanate followed by acid-catalyzed cyclization according to published procedures.

The preparation of the uracil derivative Ia, which is the precursor for the other compounds in the series, employed β-lactam 1 as the starting material. Compound I was obtained in 46% yield by a [2 + 2]-cycloaddition between cyclopentadiene and chlorosulfonyl isocyanate, two commercially available compounds, and Ia was subsequently prepared following the two synthetic routes outlined in Scheme 1. The first route represents the conventional methodology for the construction of the heterocyclic base using the amino group of the amino alcohol. This path required the initial synthesis of (±)-cis-2-amino-3-cyclopentenylmethanol (2), which was previously described by us. The second route involves initial reaction of 1 with 3-methoxyacryloyl isocyanate or with 3-ethoxyacryloyl isocyanate in anhydrous benzene affording the corresponding carbamoyl derivatives 3a–b. Reduction of compounds 3 with an excess of NaBH₄ in methanol gave the corresponding acyclic ureides with cis stereochemistry (4a–b) and subsequent acidic ring closure afforded the desired uracil derivative Ia. The key step in the second route is the reductive opening of the amide bond of 1 using an open-chain uracil precursor as the requisite electron-withdrawing N-substituent. Such an approach has not been used previously with β-lactam systems. This strategy allows the transformation of 1 into the uridine analogue Ia in three steps with overall yields in the range 30–33% and gives rise to the desired precursor Ia in a more direct way. It also avoids the preparation of amino alcohol 2, which is an unstable compound that is difficult to isolate and purify.

This approach also proved suitable for the preparation of amino alcohol 2 from β-lactam 1. In this case the ethoxycarbonyl group was selected as the labile electron-withdrawing group (Scheme 2). The LDA-assisted ethoxycarbonylation of 1 with ethoxycarbonyl chloride afforded carbamate 5 and subsequent reductive amide bond cleavage of 5 gave the cis-1,2-disubstituted cyclopentene derivative 6 as the major product. The ethoxycarb-
bonyl group was removed by treatment with aqueous KOH in methanol. Although this new synthetic approach does not represent a reduction in the number of steps compared to the previously reported method for the synthesis of amino alcohol 2 from 1, it is far more convenient in terms of the isolation, manipulation and purification of the products and intermediates. Furthermore, the new route allows the synthesis of amino alcohol 2 in good overall yield (43%).

The synthesis of pyrimidine analogue 1a using the amino alcohol leads to a longer synthetic strategy, but it also allows greater versatility given that amino alcohol 2 can be converted into a range of different heterocyclic bases. On the other hand, the second synthetic strategy is more direct for compound 1a and allows access to a diverse series of pyrimidine-based OTCs.

We proceeded to investigate the halogenation at position 5 of the uracil in compound 1a, bearing in mind that the presence of the double bond in the carbocycle could interfere with this reaction. Given this possibility, the use of the corresponding α-halosuccinimide was investigated and found to be suitable for the generation of the electrophile (Scheme 3). The chlorination reaction was carried out with NCS in DMF at 50 °C and the bromination was carried out with NBS in DMF at room temperature. These reactions gave yields of 71% and 99%, respectively. However, as one would expect, iodination of 1a under the same conditions was not possible and it was necessary to replace DMF with acetic acid and heat the reaction at 80 °C for 8 h. These reaction conditions gave rise to a mixture of three products in similar proportions due to simultaneous esterification of the hydroxyl group. The products formed were identified as the 5-iodouridine analogue 1d (41%), its acetyl derivative 7 (24%) and the acetylated product 8 (34%). These products were separated by column chromatography. Better results were obtained by carrying out an in situ deacetylation on the reaction mixture by treatment with NaOH (0.5 M) at room temperature. This approach allowed the iodinated product 1d to be isolated in 67% yield. The use of the synthetic strategy outlined above should allow the synthesis of a wide variety of pyrimidine derivatives for pharmacological evaluation.

Scheme 1 Reagents and conditions: a) 3-methoxyacryloyl isocyanate or 3-ethoxyacryloyl isocyanate, anhyd benzene, 60 °C, 60–68%; b) NaBH₄, MeOH, r.t., 74–75%; c) 3-methoxyacryloyl isocyanate, anhyd DMF–benzene, –20 °C to r.t., 29%; d) H₂SO₄ (2 M) reflux, 68–65%.

Scheme 2 Reagents and conditions: a) LDA, THF, CICO₂Et, –78 °C to r.t., 86%; b) NaBH₄, MeOH, r.t. (83%); c) KOH (10 M), MeOH, reflux (62%).

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Scheme 3 Reagents and conditions: a) NCS, DMF, 50 °C (1b, 71%); b) NBS, DMF, r.t. (1c, 99%); c) NIS, HOAc, reflux (1d, 41%; 7, 24%; 8, 34%); d) NIS, HOAc, reflux, NaOH (0.5 M), r.t. (1d, 67%).

Mps are uncorrected and were determined in capillary tubes using a Gallenkamp apparatus. IR spectra were recorded using a Bruker IFS 28 Equinox and a FTIR Bruker Vector 22 spectrometer. 1H and 13C NMR spectra were recorded on a Bruker ARX-400 instrument, using TMS as internal standard [chemical shifts (δ) in ppm, J in Hz]. Complete assignment of the signals was performed by NOE, DEPT, HMQC or HMBC experiments. Mass spectra were recorded using a Hewlett-Packard 5988A spectrometer. Microanalyses were performed at the Microanalysis Service, University of Santiago, using a Perkin–Elmer 240B elemental analyzer. Silica gel (Merck 60, 230–400 mesh) was used for flash chromatography (FC). Analytical TLC was performed on plates precoated with silica gel (Merck 60 F254, 0.25 mm).

(1R,2R,3S)-6-Aza-6-ethoxycarbonylbicyclo[3.2.0]hept-3-en-7-one (5) A solution of 1 (200 mg, 1.83 mmol) in anhyd THF (3.3 mL) was added dropwise to a stirred mixture of LDA–hexane suspension (10%; 3.34 mL, 3.12 mmol) and anhyd THF (3.3 mL) at –78 °C under Ar. The mixture was stirred at –78 °C for 1 h and ethyl chloroformate (0.23 mL, 2.44 mmol) was added. The reaction temperature was raised gradually to r.t. and the mixture stirred for 12 h. The solvent was evaporated under vacuum and the residue was purified by FC (hexane–EtOAc, 6:1) to give 5.

Yield: 272 mg (82%); colourless oil.

IR (KBr): 2980, 1799, 1717, 1320, 1178, 1060, 907, 875, 781, 732 cm⁻¹.
(t)-Aza-6-(3-ethoxyacryloylaminocarbonyl) bicyclo[3.2.0]hept-3-en-7-one (3b)

According to the procedure described for the preparation of 3a, a solution of 3-ethoxyacryloyl isocyanate\(^{15}\) (5.86 g, 41.51 mmol) in anhyd benzene (140 mL) was treated with a solution of 1 (3.02 g, 27.69 mmol) in anhyd benzene (30 mL). The solid residue was purified by FC (hexane–EtOAc, 4:1) to give 3b.

Yield: 4.73 g (68%); white solid; mp 94–96 °C.

\(^{1}H\) NMR (CDCl\(_3\)): \(\delta = 6.85 \text{ (s, 1 H, H-1)}, 2.11 \text{ (m, 1 H, H-2)}, 1.58 \text{ (m, 1 H, H-5)}\).

\(^{13}C\) NMR (CDCl\(_3\)): \(\delta = 170.3 \text{ (C-7)}, 166.2 \text{ (NHCO)}, 165.4 \text{ (CHOCH)}, 146.1 \text{ (COCN)}, 138.2 \text{ (C-3)}, 128.4 \text{ (C-4)}, 97.6 \text{ (COCH\(_3\))}, 62.7 \text{ (C-5)}, 57.7 \text{ (OCH\(_2\))}, 51.6 \text{ (C-1), 30.8 (C-2).}

MS: \(m/z = 236 \text{ (M\(^+\)}, 205 \text{ (M\(^+\) – CH\(_3\)O, 100), 138 \text{ (M\(^+\) – C\(_3\)H\(_5\)NO\(_3\), 47).}

Anal. Calcd for C\(_{10}\)H\(_{13}\)NO\(_2\): C, 69.8; H, 7.6; N, 10.8. Found: C, 69.2; H, 7.7; N, 10.9.

(t)-Aza-6-(2-Hydroxymethyl-4-cyclopentenyl)-N-3-(methoxyacryloyl)urea (4a)

Method A

To a stirred solution of 2 (692 mg, 6.12 mmol) in anhyd DMF (20 mL) at \(-20^\circ\text{C}\) was added dropwise a solution of 3-methoxyacryloyl isocyanate (857 mg, 6.75 mmol) in anhyd benzene (30 mL). The mixture was allowed to warm up to r.t., stirred overnight and filtered. The filtrate was concentrated under reduced pressure and the residue purified by FC (hexane–EtOAc, 1:2) to obtain 4a.

Yield: 431 mg (29%); white solid; mp 139–142 °C.

IR (KBr): 3362, 3181, 1646, 1523, 1255, 1190, 1153, 1124, 808 cm\(^{-1}\).

\(^{1}H\) NMR (DMSO-\(d_6\)): \(\delta = 10.07 \text{ (s, 1 H, D,O exchange, CONH)}, 8.45 \text{ (d, 1 H, } J = 8.9 \text{ Hz, D,O exchange, CONH)}, 7.55 \text{ (d, 1 H, } J = 12.3 \text{ Hz, CHOCH\(_3\))}, 5.94–5.92 \text{ (m, 1 H, H-1), 5.69–5.67 (m, 1 H, H-5)}, 5.52 \text{ (d, 1 H, } J = 12.3 \text{ Hz, COCH\(_3\))}, 4.83–4.81 \text{ (m, 1 H, H-1)}, 4.43 \text{ (t, 1 H, } J = 4.9 \text{ Hz, D,O exchange, OCH\(_3\))}, 3.66 \text{ (s, 3 H, OCH\(_3\))}, 3.49–3.42 \text{ (overlapped with the H\(_2\)O signal) (1 H, HCHO\(_3\))}, 2.38–2.22 \text{ (m, 2 H, H-2, H-3)}, 2.19–2.14 \text{ (m, 1 H, H-3)}.

\(^{13}C\) NMR (DMSO-\(d_6\)): \(\delta = 167.5 \text{ (NHCO)}, 162.7 \text{ (CHOCH\(_3\))}, 153.5 \text{ (NCONH)}, 133.5 \text{ (C-4), 130.9 (C-5), 97.8 (COCH\(_3\)), 60.8 (CHO\(_2\))}, 57.9 \text{ (CH\(_3\))}, 55.1 \text{ (C-1), 41.9 (C-2), 34.3 (C-3).}

MS: \(m/z = 240 \text{ (M\(^+\)}, 225 \text{ (M\(^+\) – CH\(_3\)), 222 \text{ (M\(^+\) – H\(_2\)O)}, 210 \text{ (M\(^+\) + 1\(^+\)} – \text{CH\(_3\)}\(_2\)), 145 \text{ (M\(^+\) + 2\(^+\)} – \text{CH\(_3\)}\(_2\)), 112 \text{ (M\(^+\) – C\(_3\)H\(_6\)NO\(_3\), 47).}

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Yield: 71 mg (74%).

(±)-cis-N-2-Hydroxymethyl-4-cyclopentenyl)-N'-(3-ethoxyacryloyl)urea (4b)

According to the procedure described for the preparation of 4a (Method B), a solution of 3b (1.01 g, 4.03 mmol) in MeOH (50 mL) was treated with NaBH₄ (763 mg, 20.17 mmol). The solid residue was purified by FC (hexane–EtOAc, 1:1) to afford 4a.

Yield: 71 mg (74%).

Method C

A solution of compound 4a (226 mg, 0.94 mmol) in aq H₂SO₄ (2 M; 7.57 mL) was heated under reflux for 3 h and the mixture was neutralized with aq NaOH (2 M). The residue obtained after evaporation of the solvent was purified by FC (CH₂Cl₂–MeOH 98:2) to give 4b.

Yield: 772 mg (75%); white solid; mp 113–116 °C.

1H NMR (CDC₁₅N): δ = 8.95 (s, 1 H, D₂O exchange, CONH), 138.0 (C-4), 136.2 (C-4), 130.0 (C-5), 100.1 (CO₂CH₃), 113.9 (C-1), 51.9 (C-2), 40.8 (C-2), 35.7 (C-3), 128.5 (C-5), 127.6 (C-6): 168.3 (NHCO), 163.4 (C-4), 151.3 (C-2), 143.2 (C-6), 138.2 (C-4), 128.5 (C-5), 100.6 (C-5), 60.6 (CH₂OH), 41.8 (C-2): 35.7 (C-3).

IR (KBr): 3361, 3033, 1686, 1471, 1260, 1073, 805 cm⁻¹.


Method B

NaBH₄ (75 mg, 1.99 mmol) was carefully added to a stirred solution of 3a (94 mg, 0.398 mmol) in MeOH (5 mL) at 0 °C. The suspension was stirred at r.t. for 20 min. Excess NaBH₄ was decomposed by the addition of H₂O (3 mL) and the stirring was continued for 20 min. The mixture was extracted with CH₂Cl₂ (5 × 3 mL). The extract was dried (Na₂SO₄), the solvent was removed and the residue purified by FC (hexane–EtOAc, 1:1) to afford 4a.

Yield: 133 mg (68%); white solid; mp 153–155 °C.

1H NMR (DMSO-d₆): δ = 8.95 (s, 1 H, D₂O exchange, CONH), 138.0 (C-4), 136.2 (C-4), 130.0 (C-5), 100.1 (CO₂CH₃), 113.9 (C-1), 51.9 (C-2), 40.8 (C-2), 35.7 (C-3), 128.5 (C-5), 127.6 (C-6): 168.3 (NHCO), 163.4 (C-4), 151.3 (C-2), 143.2 (C-6), 138.2 (C-4), 128.5 (C-5), 100.6 (C-5), 60.6 (CH₂OH), 41.8 (C-2): 35.7 (C-3).

IR (KBr): 3473, 3054, 1618, 1461, 1245, 743 cm⁻¹.

1H NMR (DMSO-d₆): δ = 11.68 (br s, 1 H, D₂O exchange, NH), 7.30 (s, 1 H, H-6), 6.19–6.17 (m, 1 H, H-4'), 5.63–5.61 (m, 1 H, H-5'), 5.44–5.42 (m, 2 H, H-1'), 4.46 (t, 1 H, J = 4.6 Hz, D₂O exchange, OH), 3.21–3.17 (m, 2 H, CH₂OH), 2.59–2.50 (m, 1 H, H-2'), 2.38–2.34 (m, 1 H, H-3'), 2.26–2.19 (m, 1 H, H-4').

13C NMR (DMSO-d₆): δ = 159.1 (C-4), 150.4 (C-2), 139.9 (C-6), 138.2 (C-5'), 105.5 (C-5), 62.2 (C-1), 45.6 (C-2), 32.8 (C-3), 14.4 (OCH₂CH₃).

MS: m/z = 244 ([M + 2]+, 4), 242 (M⁺, 14), 225 ([M + 2]⁺, 12), 212 (M⁺ – CH₂OH, 4), 149 ([M + 2]⁺ – C₂H₅OH, 13), 148 ([M + 2]⁺ – C₂H₅OH, 12), 147 ([M⁺ – C₂H₅OH, 37), 146 ([M⁺ – C₆H₄NO₂, 31), 79 (M⁺ – C₆H₅CON₂O₂), 100), 67 (M⁺ – C₆H₅CON₂O₂, 33), 66 (M⁺ – C₆H₅CON₂O₂), 78), 53 (25) (12), 51 (16).

Anal. Calcd for C₁₀H₁₀N₂O₃: C, 57.68; H, 5.81; N, 11.66. Found: C, 57.72; H, 6.01; N, 13.41.

[The rest of the content continues with similar descriptions of reactions, products, and yields.]
(±)-cis-1-(2-Hydroxyethyl-4-cyclopentenyl)-5-iodouracil (Id)

Method E
To a solution of compound Ia (250 mg, 1.20 mmol) in HOAc (20 mL) was added dropwise a solution of NIS (297 mg, 1.32 mmol) in HOAc (12 mL). The mixture was heated at 80 ºC for 8 h. After evaporation of the solvent under vacuum the residue was purified by FC (CH₂Cl₂–MeOH, 98:2) to give 7, 8 and Id.

Compound Id
Yield: 163 mg (41%); yellow solid; mp 202–204 ºC (decomp).

IR (KBr): 3448, 3027, 1668, 1601, 1455, 1245, 1044, 447 cm⁻¹

MS: m/z = 334 (M⁺, 9), 239 (M⁺ – CH₃O, 36), 238 (M⁺ – CO₂H), 195 (16), 127 (M⁺ – C₆H₅NO₂, 18), 97 (M⁺ – C₅H₇NO₂), 96 (M⁺ – C₄H₃NO₂, 29), 84 (54), 79 (M⁺ – C₄H₄NO₂, 63), 78 (M⁺ – C₃H₂NO₂, 16), 77 (M⁺ – C₃H₃NO₂), 67 (M⁺ – C₃H₂NO₂, 50), 66 (M⁺ – C₃H₃NO₂, 100); 53 (26).


Method F
According to the procedure described in Method E, a solution of compound Ia (1.95 g, 9.37 mmol) in HOAc (100 mL) was treated with a solution of NIS (2.32 g, 10.30 mmol) in HOAc (80 mL). The residue was treated with aq NaOH (0.5 M; 100 mL), neutralized with aq HCl (0.5 M) and purified by FC (CH₂Cl₂–MeOH, 98:2) to give Id.

Yield: 2.11 g (67%).

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