A Slightly Shorter Route to Carbocyclic Nucleosides. Synthesis of (±)-*trans*-1-[2-(Hydroxymethyl)cyclopentylmethyl]uracil

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(±)-*trans*-1-[2-(Hydroxymethyl)cyclopentylmethyl]uracil (**1**) was prepared in two steps and 56% yield from 2-hydroxymethylcyclopentylmethylamine (**7**) and 3-methoxy-2-propenoylisocyanate (**6**). Isocyanate **6** was prepared from methyl 3-methoxy-2-propenoate in four steps and 38% overall yield.

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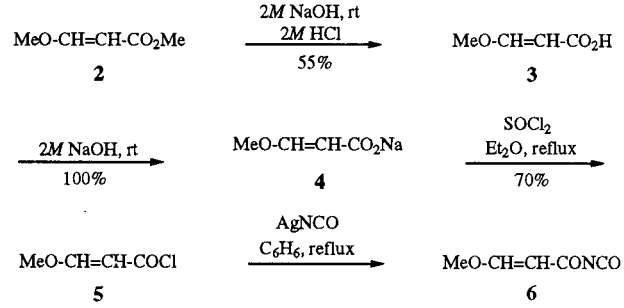
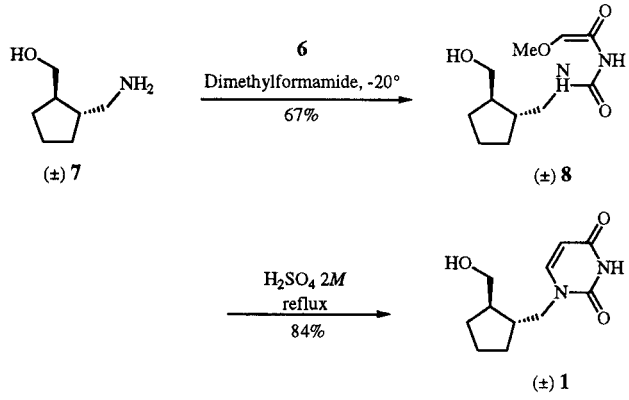
Nucleoside analogues are an interesting class of biologically active compounds [1], many of which have antiviral and/or antitumor activities [2,3]. In recent years our interest in these compounds has centered on the synthesis and biological evaluation of a subclass denominated the 1,2-disubstituted carbocyclic nucleosides [4,5]. In these analogues, the usual ribose or deoxyribose is replaced by a cyclopentane ring with a hydroxymethyl group and a heterocyclic base on adjacent carbons. In order to examine the effect of maintaining four atoms between N-1 of the base and the hydroxymethyl group, we required 1,2-disubstituted carbocyclic nucleosides with a methylene bridge between the cyclopentane ring and the heterocyclic base. Here, we report an approach to the synthesis of these compounds, applying it to the analogue (±)-*trans*-1-[2-(hydroxymethyl)cyclopentylmethyl]uracil (**1**), by way of example.

Our usual approach to the synthesis of these nucleoside analogues [6] is to construct the uracil base around an amino alcohol precursor. Hitherto, we have used a published procedure [7,8] involving reaction of the amino alcohol with 3-ethoxy-2-propenoyl isocyanate, which can be prepared in five steps from ethyl bromoacetate and triethyl orthoformate [8,9]. Recently, methyl 3-methoxy-2-propenoate (**2**) has become commercially available. In this work we used **2** to prepare 3-methoxy-2-propenoyl isocyanate (**6**), which is equally suitable for formation of the uracil base [6]. Compound **6** was obtained in 38% yield in a four step reaction sequence that avoids the low-yielding and laborious first step necessary in the synthesis of the ethoxy compound (Scheme 1).

Scheme 1



Scheme 2



Preparation of isocyanate **6** began with basic hydrolysis of methyl 3-methoxy-2-propenoate (**2**) at room temperature. The resulting acid **3**, as its sodium salt **4**, was treated with thionyl chloride in dry ether, to afford the corresponding acid chloride **5**, which was purified by vacuum distillation. Reaction of **5** with silver cyanate in benzene afforded the desired 3-methoxy-2-propenoyl isocyanate (**6**), which was not isolated due to its known instability.

The benzene solution of **6** was used directly in the condensation reaction with (±)-*trans*-2-hydroxymethylcyclopentylmethylamine (**7**, Scheme 2). The resulting disubstituted urea **8** was then cyclized in sulfuric acid to afford (±)-*trans*-1-[2-(hydroxymethyl)cyclopentylmethyl]uracil (**1**) in 56% yield from **7**; this yield compares well with the 58% yield obtained when **1** was prepared by this route using 3-ethoxy-2-propenoyl isocyanate [6].

Compound **1** is the parent compound of a series of carbocyclic analogues of nucleosides with modified pyrimidine bases which we plan to prepare. Evaluation of the biological activity of the first series of such analogues is in progress.

EXPERIMENTAL

Melting points were determined in a Reichert Kofler thermopan apparatus and are uncorrected. The ir spectra (potassium bromide disc) were recorded in a Perkin-Elmer 1640FT spectrometer (ν in cm^{-1}). The ^1H and ^{13}C nmr spectra were recorder in a Bruker AMX 300 nmr spectrometer, using tetramethylsilane as internal standard (δ in ppm, J in Hz). Mass spectrometry was carried out in a Hewlett Packard 5988A spectrometer. Elemental analyses were performed by a Perkin-Elmer 240B microanalyser. Flash chromatography was performed on silica gel (Merck 60, 230-400 mesh).

3-Methoxy-2-propenoic Acid (**3**).

A suspension of methyl 3-methoxy-2-propenoate (**2**) (20 ml, 29.02 g; 250 mmoles) in 2*M* sodium hydroxide (135 ml, 270 mmoles) was stirred at room temperature until the ester dissolved (*ca.* 2 hours), whereupon it was acidified with 2*M* hydrochloric acid. The solid precipitate filtered out was identified as acid **3** (14 g, 55%), mp 83-84°; ir: ν = 2958, 1734, 1654, 1616, 1256, 736; ^1H nmr (dimethyl-d_6 sulfoxide): δ = 3.65 (s, 3H, CH_3-), 5.14 (d, 1H, H-2, J = 12.62), 7.52 (d, 1H, H-3, J = 12.62), 11.75 (bs, 1H, -OH).

Anal. Calcd. for $C_4H_6O_3$: C, 47.06; H, 5.88. Found: C, 47.00; H, 5.83.

Sodium 3-Methoxy-2-propenoate (**4**).

A suspension of acid **3** (5 g, 49 mmoles) in water (100 ml) was adjusted to *p*H 7 with 2*M* sodium hydroxide. The solvent was evaporated under reduced pressure, maintaining the temperature below 40° (toluene and ethanol were added so as to form a low-boiling ternary azeotrope). After drying the solid residue over phosphorus pentoxide in a vacuum desiccator, it was identified as sodium salt **4** (5.95 g, 100%), mp > 330°; ir: ν = 1654, 1636, 1546, 1438, 1166, 932, 845; ^1H nmr (dimethyl-d_6 sulfoxide): δ = 3.63 (s, 3H, CH_3-), 5.13 (d, 1H, H-2, J = 12.58), 7.52 (d, 1H, H-3, J = 12.58).

Anal. Calcd. for $C_4H_5O_3Na$: C, 38.71, H, 4.03. Found: C, 38.66; H, 3.99.

3-Methoxy-2-propenoyl Chloride (**5**).

Thionyl chloride (1.51 ml, 23 mmoles) was added dropwise to a suspension of sodium salt **4** (2 g, 16 mmoles) in dry diethyl ether (30 ml) refluxing under Argon. After 4 hours at reflux, the reaction was allowed to cool to room temperature and was then allowed to stand overnight. The resulting suspended solid was filtered and washed with a little dry diethyl ether, and the combined filtrate and washings were evaporated under reduced pressure. The residue was vacuum distilled at 105-110° (35-37 mm Hg) to afford acid chloride **5** (0.72 g, 70%) as a colorless oil.

3-Methoxy-2-propenoyl Isocyanate (**6**).

Silver cyanate (3.3 g, 20 mmoles, previously dried over phosphorus pentoxide at 100° for 3 hours) was refluxed in dry benzene (20 ml) for 30 minutes, whereupon a solution of acid chloride **5** (1.2 g, 10 mmoles) in dry benzene (5 ml) was added dropwise. After addition of **5** was complete, the mixture was stirred under reflux for 30 minutes before allowing the solid to settle out. The supernatant was then decanted and used directly in the next reaction.

(±)-*trans*-*N*-2-(Hydroxymethyl)cyclopentylmethylcarbamoyl-3-methoxy-2-propenamide (**8**).

A solution of (±)-*trans*-2-(hydroxymethyl)cyclopentylmethylamine (**7**) [6] (400 mg, 3.10 mmoles) in dimethylformamide (12 ml) was stirred at -20° over 4 Å molecular sieves and under an Argon atmosphere. A benzene solution of isocyanate **6** (8 ml, 3.5 mmoles, assuming a quantitative yield in the last reaction) was added, and the mixture was allowed to reach rt while stirring overnight. The molecular sieves were filtered and the solvent was evaporated under reduced pressure, maintaining the temperature below 40° (toluene and ethanol were added so as to form a low-boiling ternary azeotrope). The solid residue was column chromatographed with chloroform as eluant, which afforded disubstituted urea **8** (532 mg, 67%) as a white solid, mp 55-57°; ir: ν = 3312, 2938, 1718, 1685, 1654, 1618, 1560, 1543, 1534, 1458, 1154; ^1H nmr (dimethyl-d_6 sulfoxide): δ = 1.22-1.77 (m, 8H, $(-CH_2-)_3$ + >CH-C-O + >CH-C-N), 3.00-3.41 (m, 4H, $-CH_2-O$ + $-CH_2-N$), 3.66 (s, 3H, $-CH_3$), 4.47 (t, 1H, -OH, J = 5.12), 5.51 (d, 1H, =CH-CO, J = 12.30), 7.56 (d, 1H, O-CH=, J = 12.30), 8.54 (t, 1H, -NH- amide, J = 5.18), 10.01 (bs, 1H, -NH- imide).

Anal. Calcd. for $C_{12}H_{20}O_4N_2$: C, 56.25; H, 7.81; N, 10.94. Found: C, 56.28; H, 7.84; N, 10.90.

(±)-*trans*-1-[2-(Hydroxymethyl)cyclopentylmethyl]uracil (**1**).

A solution of disubstituted urea **8** (530 mg, 2.07 mmoles) in 2*M* sulfuric acid (20 ml) was refluxed for 3 hours. The mixture was allowed to cool, and then the solvent was evaporated under reduced pressure (toluene and ethanol were added so as to form a low-boiling ternary azeotrope). The residue was chromatographed with 97:3 dichloromethane/methanol as eluant, which afforded (±)-*trans*-1,2-(hydroxymethyl)cyclopentylmethyluracil (**1**) (389 mg, 84%) as a white solid, mp 139-140°; ir: ν = 3033, 2945, 1727, 1689, 1482, 1390, 796; ^1H nmr (dimethyl-d_6 sulfoxide): δ = 1.22-2.01 (m, 7 + 1H, $(-CH_2-)_3$ + >CH-C-O + >CH-C-N), 3.23 (m, 2H, $-CH_2-O$), 3.55 (dd, 1H, -*H*CH-N, J = 13.20 and 8.22), 3.68 (dd, 1H, -HC*H*-N, J = 13.20 and 6.87), 4.47 (t, 1H, -OH, J = 4.66), 5.51 (d, 1H, H-5, J = 7.71), 7.63 (d, 1H, H-6, J = 7.71), 11.16 (bs, 1H, -NH-); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ = 24.2 (4'), 29.1 (3'), 30.2 (5'), 41.6 (1'), 45.2 (2'), 51.8 (6'), 64.6 (7'), 100.9 (5), 146.3 (6), 151.5 (2), 164.0 (4); ms: EI m/z (relative intensity) 224 (M^+, 3), 206 (M^+-H_2O, 37), 126 ($M^+-C_6H_{10}O$, 32), 113 ($M^+-C_7H_{11}O$, 100), 94 (94), 82 (44), 79 (34), 67 (18).

Anal. Calcd for $C_{11}H_{16}O_3N_2$: C, 58.93; H, 7.14; N, 12.50. Found: C, 58 90; H, 7.16; N, 12.49.

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