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SYNTHESIS OF 1-(3-R-AMINO-4-HYDROXY BUTYL)THYMINE ACYCLONUCLEOSIDE. ANALOGS AS POTENTIAL ANTI-AIDS DRUGS

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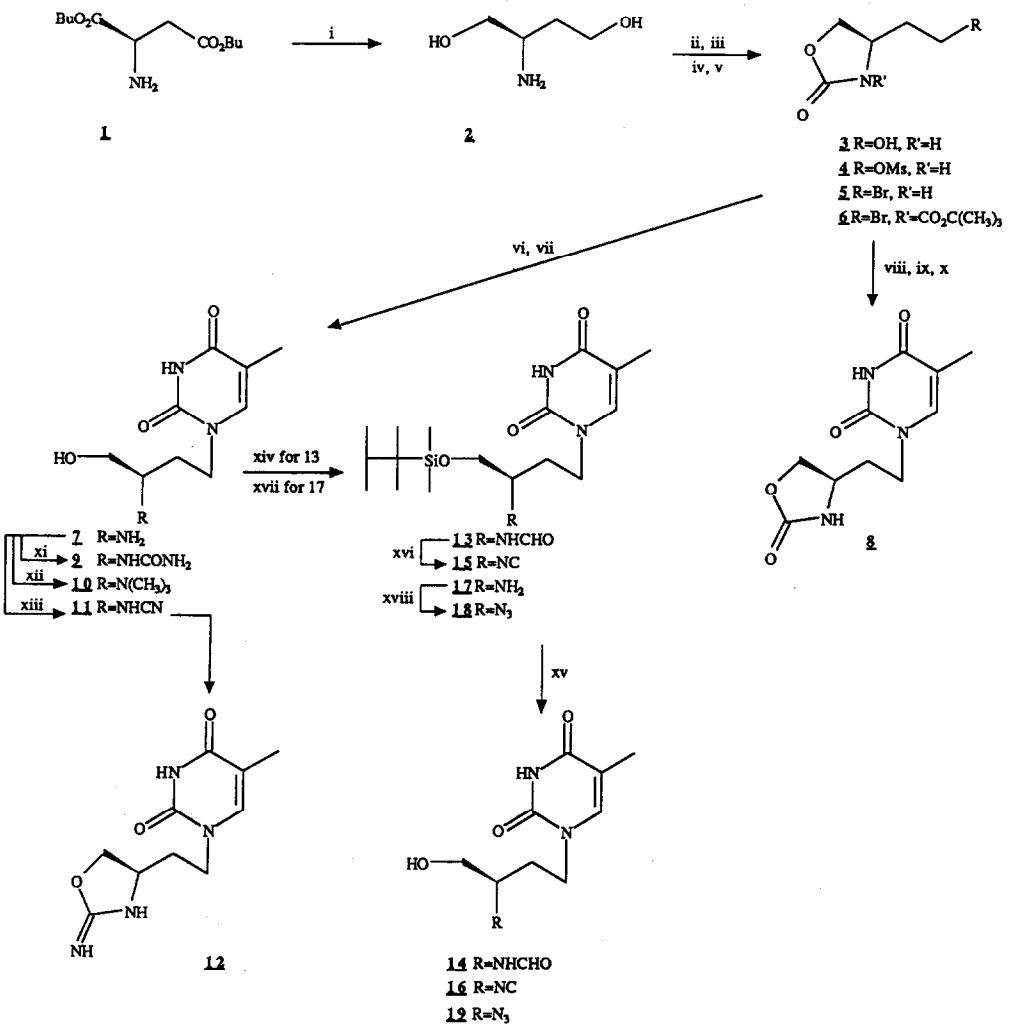
Abstract : The 1-(3-R-amino-4-hydroxybutyl)thymine acyclonucleoside analogs 8-12, 14, 16, 19, and the corresponding 3-aminomethyl derivatives 24-26 were prepared from the di-n-butyl ester of R-(-)-aspartic acid.

3'-Azido-3'-deoxythymidine (AZT) is at present the only drug used clinically for the treatment of AIDS. The duration of treatment and the efficiency of this drug is limited, however, by its hematologic toxicity[1], its short lifetime in vivo[2], and the emergence of AZT resistant HIV strains[3]. Enormous efforts are thus being made to discover superior nucleoside or acyclonucleoside based therapeutic agents. As regards the latter class of compounds, in this communication we describe the synthesis of a new series of acyclonucleoside analogs derived from R-(-)-aspartic acid and thymine which lack the C-2' carbon of thymidine, and in which the sugar oxygen and C-3' atoms have been replaced by a carbon and nitrogen atom, respectively (scheme 1).

In the initial steps, the di-n-butylester 1 of R-(-)-aspartic acid was reduced to the diol 2 (LAH, THF, < 90%)[4,5], and 2 was converted to the oxazolidinone 3 by reaction with phosgene in toluene-H_2O (Y = 91%)[5]. Subsequent elaboration to the N-Boc protected bromide 6 was achieved through displacement of the mesylate group in 4 by bromide ion (LiBr, acetone ; 90%), and reaction of 5 with Boc carbonate in THF containing DMAP and Et_3N (6 ; 91%).

Regioselective formation of the desired N-1 alkylated thymine derivative 7 was achieved in three operations involving : i) reaction of 6 with 4-methoxy-5-methyl-2-pyrimidinone in DMF using K_2CO_3 as the base, ii) evaporation of the solvent and continued reaction in CH_3OH, which effects opening of the oxazolidinone ring, and iii) N-Boc deprotection and concomitant liberation of the C-4 amide carbonyl by reaction in CH_2Cl_2-2N HCl. Compound 7[5], a highly hygroscopic colourless solid ($[\alpha]_D$+10°(CH_3OH)), was obtained pure after ion exchange chromatography using IRN-77 (H^+) (25% yield from 1).

Alternatively, by skipping the treatment of the coupling reaction product with



i: $LiAlH_4$, THF, reflux (>90%); ii: Cl_2CO, NaOH, toluene, H_2O, 0-5°C (91%); iii: MsCl, DMAP, pyridine, -10 to -5°C (43%); iv LiBr, acetone, 20°C (90%); v: $((CH_3)_3COCO)_2O$, DMAP, Et_3N, THF, 20°C (91%); vi: 5- Methyl-4-methoxy-2-pyrimidinone, K_2CO_3, 18-C-6, DMF, 40°C then K_2CO_3, 18-C-6, MeOH, 20°C (81%); vii: HCl, H_2O, CH_2Cl_2, 20°C (98%); viii: 5-Methyl-4-methoxy-2-pyrimidinone, K_2CO_3, 18-C-6, DMF, 40°C (74%); ix: TFA, CH_2Cl_2, 0°C (100%); x: HCl 0.1N, CH_2Cl_2, 20°C (81%); xi: KOCN, H_2O, 60°C (98%); xii: HCHO, HCO_2H, H_2O, 70-80°C (83%); xiii: BrCN, $NaOAc{\cdot}3H_2O$, MeOH, 20°C (70%); xiv: $ThexylMe_2SiCl$, imidazole, 55-60°C, DMF, (75%); xv: For 14: Dowex-50 (H^+), MeOH, 20°C (65%). For 16: $(nBu)_4NF$, THF, 20°C (94%). For 19: Dowex-50 (H^+), MeOH, 20°C (83%); xvi: PPh_3, CCl_4, Et_3N, CH_2Cl_2, 60°C (74%); xvii: $ThexylMe_2SiCl$, Et_3N, pyridine, 20°C (76%); xviii: TfN_3, aliquat, CH_2Cl_2, 20°C (53%)

SCHEME 1

CH_3OH, and by carrying out the N and O-deprotection steps independantly the oxazolidinone 8 (m.p. 253-256°C (H_2O) ; $[\alpha]_D$ + 46° (DMSO))[5] was obtained as colourless crystals.

Analog 9 (m.p. 210-211°C (H-2O) ; $[\alpha]_D$ + 79° (DMSO))[5], prepared by reaction of 7 with KOCN in H_2O, was isolated in 98% yield after flash silica column chromatography, and the dimethylamino compound 10, a colourless oil ($[\alpha]_D$+34° (CH_3OH))[5], was obtained in 83% yield by treatment of 7 with H_2CO-HCO_2H. Compound 11 (Y = 73%)[5] was prepared by reaction of 7 with CNBr. However, this sensitive product readily cyclizes in methanol solution giving compound 12 (m.p. 198-200°C (CH_3OH) ; $[\alpha]_D$ + 59° (CH_3OH))[5].

For the preparation of analogs 14 and 16 from 7, protection of the 4'-hydroxyl group and conversion of the 3'-NH_2, to the corresponding formamide was required. This was achieved in one step by reaction of 7 with thexyldimethylsilyl chloride in DMF at 60°C[6]. Subsequent reaction of 13 with CCl_4, Et_3N, and triphenylphosphine in CH_2Cl_2 produced intermediate 15 (y = 74%)[7], whereas treatment of 13 with DOWEX-50 (H^+) for 30 min gave analog 14 (m.p. 183-184°C (CH_3OH) ; $[\alpha]_D$ + 22° (CH_3OH)) in 65% yield[5]. The isonitrile 16 (m.p. 124-126°C (acetone-heptane) ; $[\alpha]_D$ + 60° (CH_3OH))[5] was obtained in high yield from 13 using Bu_4NF in THF to cleave off the O-silyl protecting group.

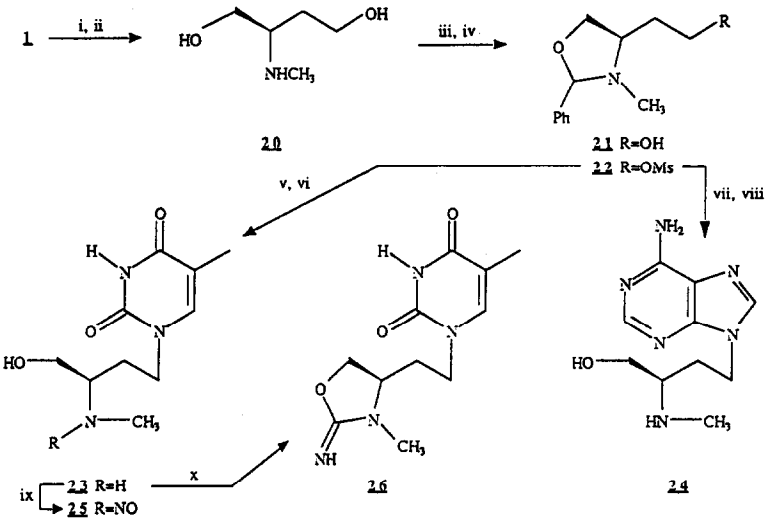
The 3'-azido analogs 19 (viscous oil ; $[\alpha]_D$ + 55° (CH_3OH))[5] was prepared in 45% overall yield by reacting the O-protected amine 17 with freshly prepared triflyl azide (caution) in CH_2Cl_2[8], followed by liberation of the 4'-hydroxyl group in 18 using DOWEX-50 (H^+).

Due to problems of insolubility, and sensitivity of the base component to certain reagents, efforts to obtain the N-methylamino derivative 23 from amine 7 or oxazolidinone 8 failed. For this reason an alternative route to 23 was followed (scheme 2) which involved preparation of the N-methyl diol 20 from 1, its conversion to the mesylate 22 via the sensitive oxazolidine 21 (90:10 mixture of two isomers ; not purified), and the reaction of 22 with 4-methoxy-5-methyl-2-pyrimidinone in DMF containing Cs_2CO_3 and NaI (cat)[9] followed by treatment with O.1 N HCl and column chromatographic purification (silica, EtOAc : CH_3OH : NH_4OH , 70:20:5, then Sephadex LH20 (CH_3OH)). It is noteworthy that, whereas intramolecular cyclization of the iodide generated in situ from 22 was avoided in the coupling reaction using Cs_2CO_3 as the base, the regioselectivity of the coupling reaction was poor, as an equimixture of the N(1)-alkylation product (30%) (precursor to 23) and the O(2)-alkylation product (28%) was formed. Under nearly identical conditions compound 24 (m.p. 127-129°C (CH_3OH) ; $[\alpha]_D$-3° (CH_3OH))[5] was prepared from oxazolidine 22 and adenine (Y = 22%).

The N-nitroso analog 25 (m.p. 149-151°C (CH_3OH) ; $[\alpha]_D$ + 26° (H_2O))[5] was isolated in quantitative yield, after purification (silica ; EtOAc : CH_3OH 8%), from the reaction of 23 with $NaNO_2$ in NHCl. However, attempts to isolate the cyanamide formed in the reaction of 23 with CNBr were unsuccessful as this product cyclized completely to 26[5]

during column purification.

The anti-HIV activity of our acyclonucleoside analogs will be reported at a later date.[10]



i: NaOH, CH_2Cl_2 then AcOCHO, THF (100%); ii: $LiAlH_4$, THF (81%); iii: PhCHO, molec. sieves 4A (100%); iv: MsCl, Et_3N, DMAP, CH_2Cl_2 (98%); v: 5-Methyl-4- methoxy-2-pyrimidinone, Cs_2CO_3, NaI, DMF (30%); vi: HCl 0.1N, CH_2Cl_2 (89%); vii: Adenine, Cs_2CO_3, NaI, DMF (22%); viii: HCl 0.1N, THF (91%); ix: $NaNO_2$, HCl, H_2O (98%); x: BrCN, $NaOAc3H_2O$, MeOH then EtOAc-MeOH (98%)

SCHEME 2

References, Footnotes, and Acknowledgements

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5 The spectral data for all compounds were in accord with their proposed structure. Satisfactory microanalyses were obtained for all analogs.

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