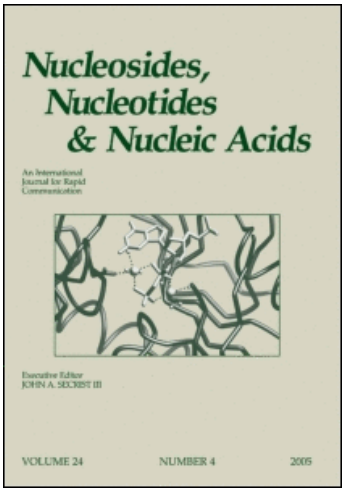

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Serafinowski, Pawel , Dorland, Erwin , Balzarini, Jan and De Clercq, Erik(1995) 'The Synthesis and Antiviral Activity of Some New S-Adenosyl-L-homocysteine Derivatives and Their Nucleoside Precursors', Nucleosides, Nucleotides and Nucleic Acids, 14: 3, 545 — 547
To link to this Article: DOI: 10.1080/15257779508012423
URL: http://dx.doi.org/10.1080/15257779508012423

NUCLEOSIDES & NUCLEOTIDES, 14(3-5), 545-547 (1995)

THE SYNTHESIS AND ANTIVIRAL ACTIVITY OF SOME NEW S-ADENOSYL-L-HOMOCYSTEINE DERIVATIVES AND THEIR NUCLEOSIDE PRECURSORS

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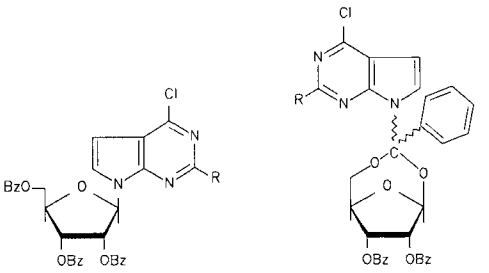
S-Adenosyl-L-homocysteine (SAH) and some of its analogues are potent inhibitors of transmethylation reactions catalysed by S-adenosyl methionine dependent methyltransferases.[1]
S-Tubercidinyl-L-homocysteine (STH) is the most potent and metabolically stable inhibitor of several methyltransferases described to date.[2,3] In order to examine the effect of various structural modifications to the heterocyclic moiety on the compound's biological activity, S-2-methyltubercidinyl-L-homocyteine (**10a**) and S-2-chlorotubercidinyl-L-homocysteine (**10b**) were prepared.

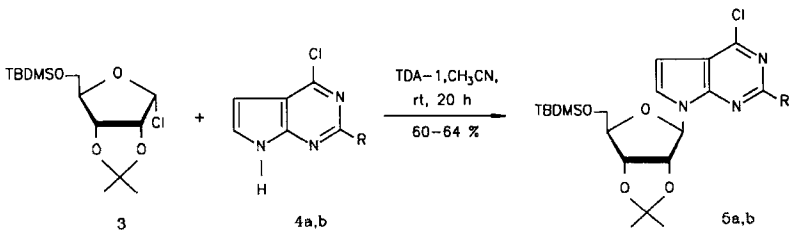
The synthesis of compunds **10a** and **10b** is presented in the Scheme. Initially, the synthesis of the required nucleoside precursors 2-methyltubercidin (**7a**) and 2-chlorotubercidin (**7b**) was attempted via ribosylation of 4-Chloro-2-methylpyrrolo[2,3-d]pyrimidine (**4a**)[4] and 2,4-dichloropyrrolo[2,3-d]pyrimidine (**4b**)[5] respectively, with 2,3,5-tri-O-benzoyl-α,β-D-ribofuranosyl chloride. The reaction was carried out under the solid-liquid phase transfer conditions using acetonitrile containing powdered potassium hydroxide and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) as a catalyst[6]. However, instead of the expected products of glycosylation **1a** and **1b**, compunds of type **2**[7] were isolated in 60-70% yield. The same products were obtained when the heterocyclic bases were ribosylated with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in the presence of stannic chloride[8] or trimethylsilyl iodide[9].

Compounds **4a** and **4b** were therefore condensed with 5-O-t-butyl-dimethylsilyl-2,3-O-isopropylidene-α-D-ribofuranosyl chloride (**3**)[10] under the solid liquid phase-transfer conditions similar to those applied during the condensations described above. The ribosylations showed a high preference for the required N-9 isomer and accordingly compounds **5a** and **5b** were isolated by column chromatography on silica gel in 70 and 60% yield, respectively.

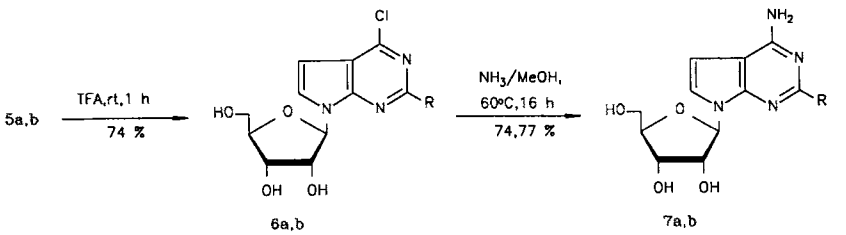
The protecting groups were removed from **5a** and **5b** by the action of trifluoroacetic acid. The resulting products of deprotection **6a** and **6b** were then aminated with 8 M methanolic ammonia to afford crystalline 2-methyltubercidin (**7a**)[11] and 2-chlorotubercidin (**7b**).



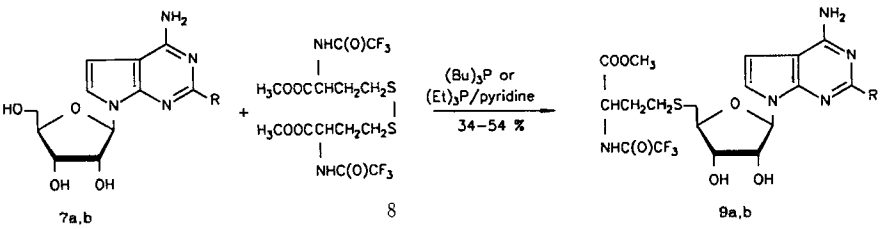
1a, b 2a, b



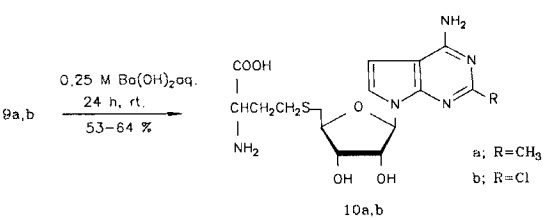
3 4a,b 5a,b



5a,b 6a,b 7a,b



7a,b 8 9a,b



10a,b

SCHEME

The nucleosides **7a** and **7b** were subsequently condensed with N,N'-bis-trifluoroacetyl-L-homocystine dimethyl ester (**8**) in the presence of triethylphosphine.[12,13] The N-trifluoroacetyl-S-tubercidinyl-L-homocysteine methyl esters **9a** and **9b** , obtained as a result, were isolated in 34 and 54% yield, respectively, by column chromatography on silica gel. Finally, the carboxyl and amino functions in **9a** and **9b** were deprotected with 0.25 M barium hydroxide in 50% aqueous methanol[12,13] to give S-2-methyltuberdicinyl-L-homocysteine (**10a**) in 53% yield, and S-2-chlorotubercidinyl-L-homocysteine (**10b**)[14] in 63% yield, after anion exchange chromatography on Sephadex A-25.

The compounds were evaluated for their activity against several viruses such as herpes simplex, vaccinia, vesicular stomatitis, Coxsackie, polio, parainfluenza, reo, Sindbis and Semliki forest in Vero, HeLa and E_6SM cell cultures. A minimum inhibitory concentration of 20μg/mL was noted in some cases, *ie* with compound **7b** against Coxsackie B4 and polio-1, but otherwise no antiviral activity was observed.

ACKNOWLEDGEMENT

This investigation was supported by the Cancer Research Campaign.

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14. All the compounds were fully characterised by their analytical and spectroscopic data.