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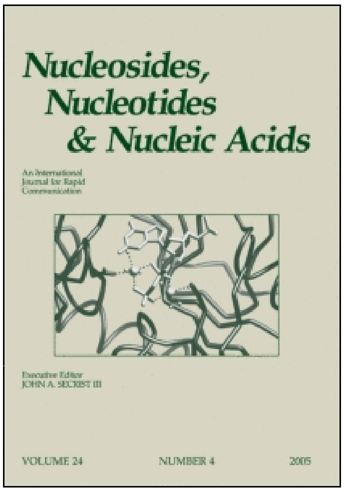

Nucleosides, Nucleotides and Nucleic Acids

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Synthesis of "Reversed" and "Double Headed" Nucleosides

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SYNTHESIS OF "REVERSED" AND "DOUBLE HEADED" NUCLEOSIDES

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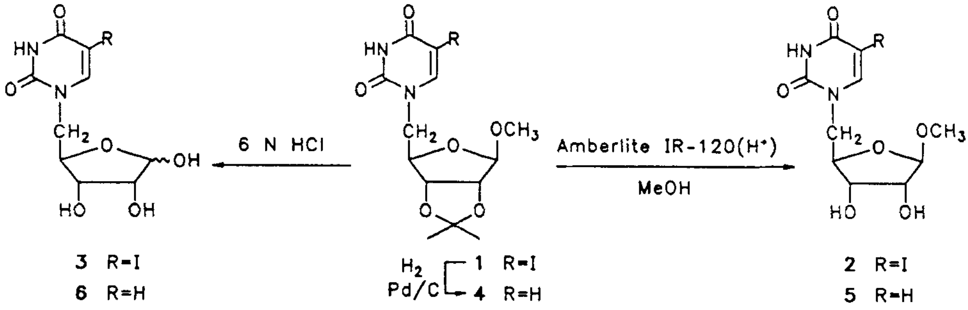
Abstract: The synthesis of several partially and fully deprotected "reversed" nucleosides are described starting from "reversed" 5-iodouracil-1-yl nucleoside 1. The preparation of a novel purine-purine and mixed purine-pyrimidine "double headed" nucleosides *via* "reversed" purine nucleoside 12 is also described.

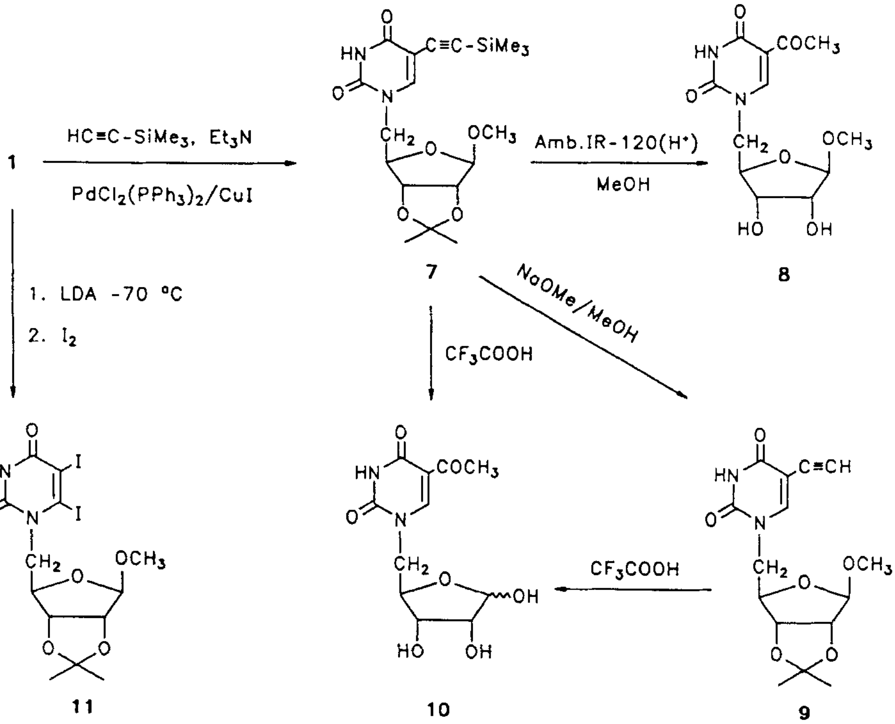
Continuing our studies on the synthesis of "reversed" nucleosides, we prepared C-5 substituted "reversed" nucleosides in the pyrimidine series as potential chemotherapeutic agents, lacking normal glycosyl linkage and hence being more stable to hydrolytic cleavage.

Recently we have found that the reaction of the sodium salt of 5-iodouracil with suitably protected 5-O-tosyl D-ribose gives approximately 20% better yield on the "reversed" 5-iodouracil-1-yl nucleoside 1 (58% yield) than other reported procedures.[1]

The isopropylidene group can be removed from 1 without altering the anomeric configuration, by treatment with acidic ion-exchange resin in methanol. The "reversed" nucleoside 2 was isolated in 85% yield.



On the other hand the hydrolysis of 1 with dilute hydrochloric acid afforded fully deprotected "reversed" nucleoside 3 in 72% yield. In both deprotection reactions small quantities of by-products 5 (3% yield) and 6 (17% yield) have been isolated as the consequence of substitution of 5-iodine by hydrogen in acidic media. The structures of 5 and 6 have been proved by the spectroscopic and analytical data and by the independent synthetic routes. The hydrogenation of 1 over palladium on carbon catalyst afforded the "reversed" nucleoside 4 in 82% yield, which on deprotection by Amberlite IR-120 (H^+) in methanol or dilute hydrochloric acid afforded 5 (89% yield) and 6 (86% yield), respectively.

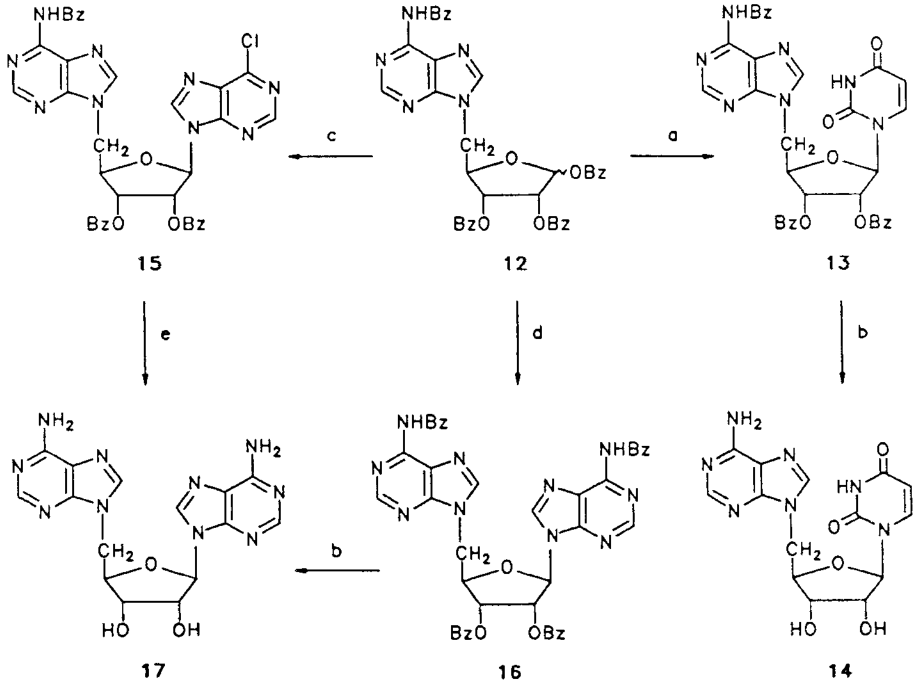


The 5-iodo "reversed" nucleoside 1 was suitable for further functionalisation of the uracil unit. Coupling of 11 and (trimethylsilyl)acetylene ($(Ph_3P)_2PdCl_2/CuI$ in triethylamine)[2] gave "reversed" nucleoside 7 in 71% yield. However, using acidic ion-exchange resin in methanol for deprotection of 7, we found that it was converted in 5-acetyl "reversed" nucleoside 8 in 78% yield. Apparently, besides the removal of isopropylidene and trimethylsilyl protections, the addition of water on triple bond took place. Treatment of 7 with 0.2 M sodium methoxide in dry methanol effected removal of the trimethylsilyl group giving 5-ethynyl "reversed" nucleoside 9 in 88% yield.

Complete deprotection of 9 and 7 occurred in 50% trifluoroacetic acid together with the addition of water molecule to the triple bond, giving 5-acetyl "reversed" nucleoside 10 in almost quantitative yield.

In addition the 5,6-diiodo "reversed" nucleoside 11 was synthesized *via* lithiation with LDA in THF below -70 °C, and subsequent electrophilic reaction with iodine in modest yield (15%). Treatment of 11 with Amberlite IR-120 (H^+) in methanol resulted in a complex mixture of products.

Based on our recently reported synthesis of "double headed" nucleosides[1] we have also prepared novel purine-purine 17 and mixed purine-pyrimidine 14 "double headed" nucleosides *via* suitably protected "reversed" intermediate 12.



a) 1.uracil/BSA/CH_3CN, 2.TMSOTf; b) NH_3/MeOH/25°C; c) 1.6-Cl-purine/BSA/CH_3CN, 2.TMSOTf; d) 1.NHBz-adenine/BSA/CH_3CN,2.TMSOTf; e) NH_3/MeOH/100°C.

Following the reported procedure, the sodium salt of adenine with 5-O-tosyl protected D-ribose gave the corresponding 9-substituted "reversed" nucleoside in 51% yield, and subsequent hydrolysis with dilute hydrochloric acid afforded fully deprotected "reversed" nucleoside in 76% yield.[3] We converted this nucleoside in perbenzoylated 12 (quantitative yield) which is suitably protected and functionalized for the glycosylation at C-1 by the Vorbrüggen method.[3] The reaction of trimethylsilylated uracil and 12 in the presence of trimethylsilyl triflate gave novel mixed "double headed" nucleoside 13 in 60% yield. The removal of the benzoyl protection groups gave 14 in 79% yield. Using the same set of reactions the protected purine-purine "double headed" nucleoside 15 (23% yield) and 16 (32% yield) have been prepared and deprotected giving 17 (70-85% yield). The assignments of the protons in "double headed" nucleosides were based on the 2D NMR COSY spectra, and stereochemistry around the anomeric centres was established from NOESY spectra.

In conclusion described synthetic route to "double headed" nucleosides *via* "reversed" nucleosides gives considerably better yields (60-90%) when the pyrimidine base is introduced in the glycosylation step of both 5-pyrimidine[1] and 5-purine "reversed" nucleosides. In contrast, if the purine base is attached in the glycosylation step the yields are only 20-60%.

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REFERENCES

1. B. Kašnar, V. Škarić, B. Klaić, and M. Žinić, *Tetrahedron Lett.*, 34, 4997 (1993).
2. M. J. Robins, R. S. Vinayak, and S. G. Wood, *Tetrahedron Lett.*, 31, 3731 (1990).
3. a) H. Vorbrüggen, K. Krolikiewicz, and B. Bennua, *Chem. Ber.*, 114, 1234 (1981);
   b) H. Vorbrüggen and G. Höfle, *Chem. Ber.*, 114, 1256 (1981).