Synthesis of 3’-Deoxy-3’-difluoromethyluridine and 2’-Deoxy-2’-difluoromethyluridine

Stéphane Marcotte, Baudoin Gérard, Xavier Pannecoucke, Christian Feasson, Jean-Charles Quirion*
Laboratoire d’Hétérochimie Organique associé au CNRS, IRCOF, INSA et Université de Rouen, Rue Tesnière, 76821 Mont Saint-Aignan cedex, France
Fax +33(2)35522959; E-mail: quilirion@ircof.insa-rouen.fr
Received 12 December 2000; revised 26 January 2001

Abstract: The synthesis of 3’-deoxy-3’-difluoromethyluridine (9) and 2’-deoxy-2’-difluoromethyluridine (7β) by hydrogenation of the corresponding difluoromethylene derivatives is described. A second synthesis of the latter has been performed. Starting from thymidine, a two-step procedure affords the benzylated furanoid glycal 12. Addition of dibromodifluoromethane gives the α-2’-deoxy-2’-bromodifluoromethylarabinose (13). This compound allowed an access to α- or β-2’-deoxy-2’-difluoromethyluridine via a S2 type reaction on a α-halodeoxyarabinose species.

Keywords: addition reactions, fluorine, nucleosides, carbohydrates

For the last two decades, many nucleosides analogues have been prepared and studied owing to their biological activities. It has been demonstrated that modifications of the ribose moiety are compatible with biological activity. These analogues often exhibit specific activities as well as better resistance toward enzymatic degradation. In parallel, fluorinated compounds have received a great interest for their biological and medical applications. Indeed, the introduction of a C-F bond in a molecule is of great importance for its physicochemical properties. For example, fluorine substituted nucleosides 1–4 are used in cancer and herpes therapies (Figure 1).

Replacement of an oxygen atom by a CF2 group is now widely used, especially in carbohydrate chemistry where the anemic oxygen atom has been replaced by such a group. The electronegativity of difluoromethane group should also stabilise the anemic bond and suppress a significant pathway of in vivo decomposition. Further, the difluoromethane group is a very good mimic of the hydroxyl group and so can interact in a better way with the receptor, but without the nucleophilic properties of the hydroxyl function. Finally, another interesting property of this group is that it can improve the bioavailability of the drug owing to increasing lipophilicity.

Considering all these aspects and the necessity to find new series of modified nucleosides having an increased activity and less toxicity, we decided to prepare new difluoromethylated nucleosides. In this paper first results dealing with the synthesis of title compounds by two different strategies are presented. We first studied the preparation of 2’- and 3’-difluoromethyluridine 7 and 9 by hydrogenation of the known protected difluoromethyluridine derivatives 6 and 8β (Scheme 1).

Scheme 1: (a) TPDS-CI, pyridine; (b) Dess–Martin periodinane; (c) [(Me2N)3PCF2Br]Br, Zn, THF; (d) TBAF, THF; (e) H2, Pd/C, EtOH; (f) TBDMSOT, pyridine

Compound 6 was prepared according to literature using a Wittig type reaction on a ketonucleoside synthesised in a two-step process (46% yield) using uridine 5 as the starting material. We first tried to perform hydrogenation with the protected compound 6. However, efforts to reduce the double bond were unsuccessful. In order to suppress the steric hindrance in the vicinity of the difluoromethylene group, the two hydroxyl groups were deprotected prior to hydrogenation. We then realised this reaction under classical conditions (H2, Pd/C, EtOH) and obtained an inseparable mixture of diastereoisomers in a 3:1 ratio in favour of the arabinose isomer 7β. A similar sequence was applied to the synthesis of isomer 9. Hydroxyl groups 2’ and...
5′ of uridine were selectively protected using TBDMSCl. 3′-Hydroxyl was then oxidised and afterwards submitted to Wittig type reaction furnishing the known difluoromethylene derivative. 8,9 Hydrogenation of the deprotected 3′-difluoromethylenenucleoside gave a mixture (2.7:1) of isomers in favour of compound 9.

Although this method allowed the preparation of the desired compounds, it appeared not applicable for an efficient synthesis of difluoromethylene nucleosides. Especially for the synthesis of the most interesting product 7β, the use of an expensive protecting group in the first step, the lack of stereoselectivity in the last one and the difficulties to separate the two isomers prompted us to develop a more versatile strategy in which the base would be introduced during the last steps. This would allow the preparation of a series of analogues from a common intermediate.

In search of a more straightforward method, we turned our attention to a method described by Mietchen et al. in glycosyl series.7 These authors investigated the diastereoselective synthesis of 2-deoxy-2-bromodifluoromethylglycosyl glucose or galactose by a radical reaction of a pyranoid glycal with dibromodifluoromethane in the presence of sodium dithionite. The transposition of this synthetic pathway to the preparation of desired compounds required the preparation of the corresponding furanoid glycal. Several approaches to such glycals have been previously described. Most of them used multistep reactions starting from ribose8 or deoxyribose.9 Pedersen and then Hammer10 designed a high yielding method involving treatment of protected or unprotected thymidine with an excess of HMDS in the presence of (NH₄)₂SO₄. In a first attempt, we applied this approach to di-O-benzylated thymidine but we were unable to detect the presence of the corresponding glycal from the reacting mixture. However, when this method was applied directly to thymidine 10, we were pleased to observe the formation of silylated glycal 11 in 70% yield (Scheme 2) resulting from the concomitant elimination of the base and protection of the hydroxy groups.

This unstable product was immediately reacted with benzyl bromide to afford dibenzylated product 12 in 80% yield as described by Abramski.8 The overall yield from thymidine (56%) and the simplicity of the experimental procedure made our method the most effective synthesis for protected glycal 12 and can find applications to the preparation of different protected glycals.

Having in our hands a valuable method for the preparation of glycal 12, we then studied the application of the Mietchen method to the furanoid series. When applied to glycal 12, this procedure afforded a mixture of compounds. NMR analysis indicated the presence of different 1′-bromo and hydroxy isomers. But, when the crude reacting mixture was allowed to stay in an aqueous medium for a longer time, we observed the conversion of the different products to a single compound 13. The addition was completely stereoselective leading to the isomer resulting from the attack of the bromodifluoromethyl spe-

![Scheme 2](image)

In conclusion, we have developed two different methods to have an access to 3′ and 2′-deoxy-difluoromethylur-

In order to prepare a more stable compound and a more reactive substrate toward substitution, the free hydroxyl was acetylated leading to compound 14 (47% yield from 12). In a first attempt, we tried unsuccessfully to introduce the base at this stage. The only isolated product was the difluoromethylene derivative resulting from a dehydrobromination. Considering that the presence of a bromine atom was the major drawback in our synthesis, we then decided to reduce the bromodifluoromethyl group. Indeed, reduced product 15 was obtained in excellent yield (85%) via a radical reductive process (Bu₃SnH, AIBN). The final steps, involving introduction of the base, were first conducted directly with acetate 15 (Scheme 3).

Addition of silylated uracil 19 to 15 in the presence of TMSOTf furnished a 4:1 mixture of isomers in 76% yield. The major one 17α was proved to possess the α configuration by NMR studies.

In order to change the α/β ratio in favour of β, we decided to synthesise the α-halodeoxyarabinose 16 which was easily obtained by treatment of 15 with HCl. The NMR spectra of the crude material revealed the presence of a single diastereoisomer, which was presumed to be α. The condensation of 16 in dichloromethane with the silylated uracil gave a 57:43 mixture of 17β and 17α isomers, respectively. The two compounds were easily separated by flash chromatography and the stereochemical assignments of the two purified compounds are based on NMR spectroscopy studies and especially NOESY experiments (Figure 2).

This significant change is likely to be due to a S₉₂ type reaction on the α-arabinose species 16.11 The use of less polar solvent (CHCl₃ and CCl₄) to try to increase the S₉₂ pathway lead to low yields and no changes in the ratio of the isomers. Finally, the deprotection of the benzyl groups was easily achieved by hydrogenolysis to give the two desired nucleosides 7α and 7β with good yields.

In conclusion, we have developed two different methods to
dine. In the first one difluoromethylene nucleoside was used as starting material but with a limited applicability. The second one could be applied to the synthesis of various base-modified nucleosides. The key step of this new route is the addition of dibromodifluoromethane on a furanoid glycal. During this synthesis, we elaborated new methodology for the preparation of glycal 2 in two steps and 56% yield from uridine. We are currently evaluating the biological importance of these difluoromethylene nucleosides.

All commercial solvents were distilled before use. Flash chromatography column were done on silica gel SI 60 (40–63 μm) Merck. 1H NMR, 13C NMR and 19F NMR (CFCl3 as external reference) were taken on Bruker DPX-300 MHz.

**2'-Deoxy-2'-difluoromethylenuridine (7β); Typical Procedure**
A solution of 2'-deoxy-2'-difluoromethyleneuridine (25 mg, 0.09 mmol) in EtOH (5 mL) was hydrogenated in the presence of 10% Pd/C for 24 h. Filtration over millipore, concentration and chromatography (using preparative plates, CH2Cl2-MeOH, 9:1) afforded a mixture of isomers difluoromethylenuridine 7 (22 mg, 8%) as a white powder; mp 165–168 °C. The major product was found to be 7β.

**3'-Deoxy-3'-difluoromethyluridine (9)**
The same method of hydrogenation when applied to 3'-deoxy-3' difluoromethylenuridine gave 9 (90%) as a 2.7:1 mixture of diastereomers; white powder; mp 173–175 °C.

1,4-Anhydro-2-deoxy-3,5-di-O-trimethylsilyl-D-erythro-pent-1-enitol (11)
A solution of thymidine (1.2 g, 4.96 mmol) and (NH4)2SO4 (770 mg) in hexamethyldisilazane (60 mL) was refluxed under nitrogen for 9 h. The solution was concentrated under vacuum. The residue was dissolved in pyridine (10 mL) and then poured into cyclohexane (100 mL) and H2O (100 mL). After separation, the organic phases were washed again with H2O (100 mL), dried (MgSO4) and concentrated under vacuum to give a brown oily residue. Distillation (Kugelrohr, 40–60 °C/0.07 Torr) afforded the silylated glycal 11 (861 mg, 70%) as colourless oil with analysis identical to that reported in Ref. 8a.

2'-Deoxy-2'-bromodifluoromethyl-3', 5'-di-O-benzyl-D-arabinose (13)
Compound 12α (470 mg, 1.35 mmol) was dissolved in MeCN (12.7 mL) and H2O (7.6 mL). The solution was degassed by bubbling argon. At 0 °C under an argon atmosphere, NaHCO3 (480 mg, 5.71 mmol), Na2S2O4 (442 mg, 2.538 mmol) and finally CF3Br (434 μL, 4.73 mmol) were added to the degassed solution. After 1 h at 0 °C, Na2S2O4 (400 mg, 2.29 mmol) was added and the mixture was stirred vigorously overnight. The mixture was then poured in Et2O (200 mL) and washed with brine (100 mL) and then with H2O (100 mL). The organic layer was dried (MgSO4) and concentrated under vacuum to give 13 as colourless oil. NMR analysis of the crude material shows a sufficient purity and no further purification was undertaken.

1'-O-Acetyl-2'-deoxy-2'-bromodifluoromethyl-3', 5'-di-O-benzylarabinose (14)
To a stirred solution of the crude 13 in anhyd CH2Cl2 (20 mL) was added Ac2O (0.6 mL, 6.32 mmol), Et3N (41 μL, 0.29 mmol) and DMAP (10 mg, 0.08 mmol). After stirring overnight, a sat. solution of NaHCO3 (10 mL) was added. The organic layer was separated and washed with brine (10 mL), dried (MgSO4) and concentrated. Chromatography using cyclohexane–EtOAc (95:5) as eluent afforded 14 as a colourless oil (310 mg, 47% from 12).

1'-O-Acetyl-2'-deoxy-2'-difluoromethyl-3', 5'-di-O-benzylarabinose (15)
A solution of 14 (310 mg, 0.64 mmol), tributyltin hydride (230 μL, 0.832 mmol) and AIBN (5 mg, 0.06 mmol) in anhyd toluene (5 mL) was heated at 70 °C for 2 h. After cooling, Et3O (50 mL) was added. This layer was washed twice with 5% KF solution (2 × 10 mL) and finally with H2O (10 mL). After drying and concentration, the residue was purified by chromatography over silica gel (eluent: cyclohexane–EtOAc, 95:5) to give a colourless oil (220 mg, 85%).

**Figure 2** NOE correlations from NOESY spectra of 17α and 17β
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*Only the data for the major diastereoisomer are given.
Decoupled from $^1$H.
Coupled with $^1$H.
2′-Deoxy-2′-difluoromethyl-3′, 5′-di-O-benzyluridines (17a and 17b)

Method A: Compound 15 (155 mg, 0.382 mmol) was dissolved in anhyd MeCN (15 mL) containing 4 Å molecular sieves. At 0 °C, the silylated uracil (196 mg, 0.764 mmol) in MeCN (2 mL) and then TMSOTf (0.18 mL, 0.93 mmoL) were added. The mixture was then stirred at r.t. for 24 h. Aq sat. NaHCO₃ solution (50 mL) was then added. Extraction using CH₂Cl₂ (3 × 50 mL), drying (Na₂SO₄) and finally concentration gave a yellow oil. Purification by chromatography (eluent: 7:3 cyclohexane–EtOAc) afforded 17a (117 mg, 67%).

Method B: HCl was bubbled at 0 °C into a solution of 15 (90 mg, 0.22 mmol) in CH₂Cl₂ (5 mL) for 10 min. TLC monitoring (eluent: cyclohexane–EtOAc, 8:2) showed the disappearance of 15. The solution was concentrated under vacuum and coevaporated twice with anhyd toluene (5 mL) and dried under high vacuum for 2 h. Then anhyd CH₂Cl₂ (2 mL) and 4 Å molecular sieves were added, the mixture was then stirred for 20 min and a solution of the silylated uracil 19 (148 mg, 0.58 mmol) in CH₂Cl₂ (2 mL) was added. After 48 h, CH₂Cl₂ (10 mL) and aq sat. solution of NaHCO₃ (10 mL) were added. The organic layer was separated and washed with H₂O (10 mL), then dried (MgSO₄). Chromatography on silica gel using (cyclohexane–EtOAc, 6:4) afforded pure 17b (26 mg, 28%) and 17a (33 mg, 31%) as colourless oils.

2′-Deoxy-2′-difluoromethyluridines (7a and 7b)

A solution of the protected nucleoside 17a (60 mg, 0.13 mmol) was hydrogenated (H₂, 1 bar) in EtOAc using a catalytic amount of Pd/C for 24 h. After filtration, concentration gave 7a (31 mg, 85%) as a white powder; mp 183–185 °C.

The same procedure was applied to 17b to give 7b (89%) as a colourless solid (mp 172–174 °C).

References