Synthesis of 3'-Fluoromethylthio-, 3'-Fluoromethylsulfinyl- and 3'-Fluoromethylsulfonyl-substituted 3'-Deoxythymidine

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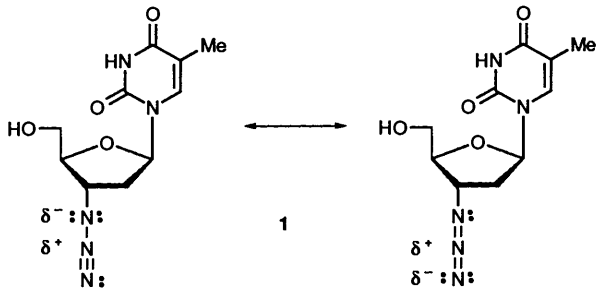
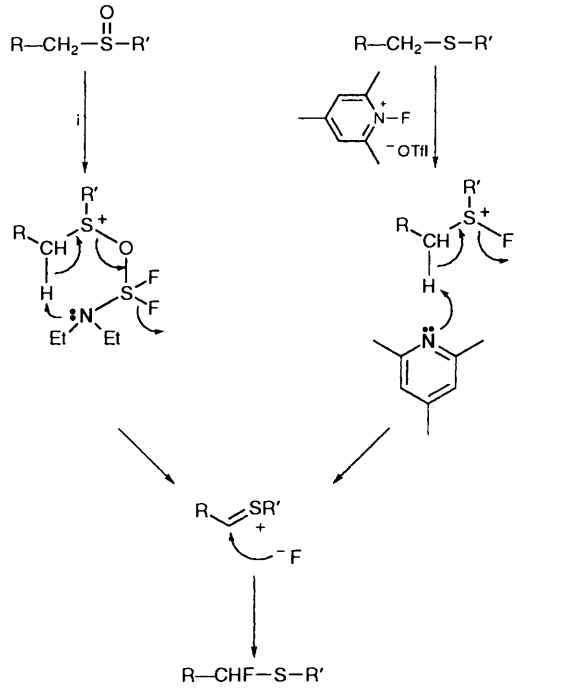
3'-Deoxy-3'-(fluoromethylthio)thymidine **2** is synthesized from 5'-*O*-benzoyl-3'-deoxy-3'-(methylsulfinyl)thymidine **9** by using DAST. 5'-*O*-Benzoyl-3'-deoxy-3'-(fluoromethylthio)thymidine is used as starting material for the synthesis of the sulfoxide **3** and the sulfone **4**. Both sulfoxides **3A** and **3B** show a C3'-*endo* sugar conformation.

3'-Azido-3'-deoxythymidine **1** is one of the most active anti-HIV agents[1] and it is still the most widely used drug to treat AIDS patients. The compound, however, suffers from significant toxicity. Efforts to mimic the azido group of 3'-azido-3'-deoxythymidine have led to the synthesis of a wide variety of 3'-substituted 3'-deoxythymidine analogues with a three-atom functionality.[2,3] Until now, this approach had little success. It is known, however, that minor chemical modifications of 3'-substituted 2',3'-dideoxynucleosides could give rise to tremendous differences in anti-HIV activity. In extension to our previous work in the field of fluorinated nucleoside analogues,[2,4] we have now synthesized 3'-deoxythymidine derivatives with a α-fluoro sulfide function in the 3'-position (compound **2**) together with the sulfoxides (**3**) and sulfone (**4**) derivatives. Also, the non-fluorinated analogues **5**, **6** and **7** were synthesized. These molecules can be considered as isosteres of 3'-azido-3'-deoxythymidine, although the shape of the C-3' substituent is different.



The synthesis of α-fluoro sulfides can be carried out by reaction of sulfides with XeF_2,[5] of α-chloro sulfides with potassium fluoride,[6] and of dithio-acetals and ketals with HgF_2.[7] Two Pummerer-type rearrangements are described which lead to α-fluoro sulfides: reaction of sulfides with *N*-fluoropyridinium trifluoromethanesulfonates (triflates)[8] and reaction of sulfoxides with diethylaminosulfur trifluoride (DAST).[9] While DAST is a relatively unstable liquid, *N*-fluoropyridinium triflate is a stable, white, crystalline material. Both reagents, however, are easily handled, mild fluorinating agents. The conversion of sulfoxides into α-fluoro sulfides using DAST[9] was believed to involve the formation of a sulfenium cation *via* a concerted mechanism. The reaction is catalysed by Lewis acids.[9,10] α-Fluorination of sulfides with *N*-fluoropyridinium triflate occurs *via* fluorination of sulfur followed by Pummerer-type rearrangement.[8] The proposed intermediates are depicted in Scheme 1.

We explored the possibilities of synthesizing 3'-deoxy-3'-



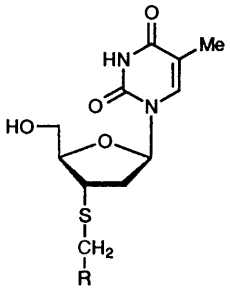
Scheme 1 *Reagents:* i, DAST

(fluoromethylthio)thymidine by using both Pummerer-type reactions. Therefore two starting products were needed: 5'-*O*-benzoyl-3'-deoxy-3'-(methylthio)thymidine **8** and 5'-*O*-benzoyl-3'-deoxy-3'-(methylsulfinyl)thymidine **9**.

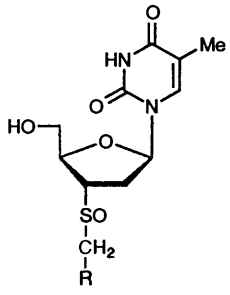
Results

Reaction of thymidine **10** with trityl chloride in pyridine at 40 °C, followed by addition of mesyl chloride at room temperature, in a one-pot procedure, afforded 3'-*O*-mesyl-5'-*O*-tritylthymidine **11** in 90% yield (Scheme 2). This compound was converted into the O^2,3'-anhydronucleoside **12** by being heated to reflux in tetrahydrofuran (THF) for 3 h in the presence of 1 mol equiv. of NaOH. The yield of this reaction was only 75%, due to the formation of 1-(2-deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine **13** as side-compound in 20% yield. The O^2,3'-anhydronucleoside **12**[11] was treated with a mixture of methanethiol and its sodium salt in a mixture of dimethylformamide (DMF) and ethanol at 100 °C for 8 h. This reaction, when performed in anhydrous conditions, gave 3'-deoxy-3'-methylthio-5'-*O*-tritylthymidine **14** in 85% yield. Traces of

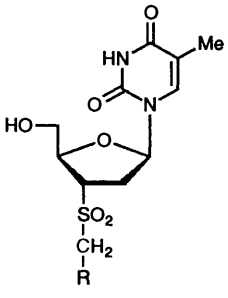
water increased the formation of 1-(2-deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine **13** as side-compound. The isolation and purification of the O^2,3'-anhydronucleoside **12** is necessary since a one-pot conversion of 3'-*O*-mesyl-5'-*O*-tritylthymidine **11** into 3'-deoxy-3'-methylthio-5'-*O*-tritylthymidine **14**, without purification of the intermediates (by reaction with NaOEt–EtOH followed by addition of NaSMe–HSMe–DMF), is low yielding. Removal of the trityl group was performed with formic acid for 5 min at room temperature. Benzoylation of 3'-deoxy-3'-(methylthio)thymidine **5** with 1.5 mol equiv. of benzoyl chloride in pyridine at 40 °C gave 5'-*O*-benzoyl-3'-deoxy-3'-(methylthio)thymidine **8**. Removal of the trityl group of intermediate **14** followed by benzoylation of the 5' hydroxy function was carried out because we expected that removal of the benzoyl protecting group at the end of the synthesis might give a cleaner reaction product than that of the trityl protecting group, due to the expected acid lability of the 3'-(fluoromethylthio)nucleosides.



2 R = F
5 R = H



3 R = F
6 R = H



4 R = F
7 R = H

Treatment of 5'-*O*-benzoyl-3'-deoxy-3'-(methylthio)thymidine **8** with *N*-fluoro-2,4,6-trimethylpyridinium triflate in dichloromethane gave 5'-*O*-benzoyl-3'-deoxy-3'-(fluoromethylthio)thymidine **17** (see Scheme 3, later). This compound was debenzoylated with ammonia in methanol to give 3'-deoxy-3'-(fluoromethylthio)thymidine **2**. This reaction sequence suffers, however, from the disadvantage of similar R_f-values (TLC) for 5'-*O*-benzoyl-3'-deoxy-3'-(methylthio)thymidine **8** and 5'-*O*-benzoyl-3'-deoxy-3'-(fluoromethylthio)thymidine **17**. This makes it very difficult to monitor the reaction on TLC, and often inseparable mixtures of compounds **8** and **17** were obtained. Also, the presence of water should be excluded as much as possible, since this leads to the formation of a mixture of *R*- and *S*-methylsulfinyl derivatives.

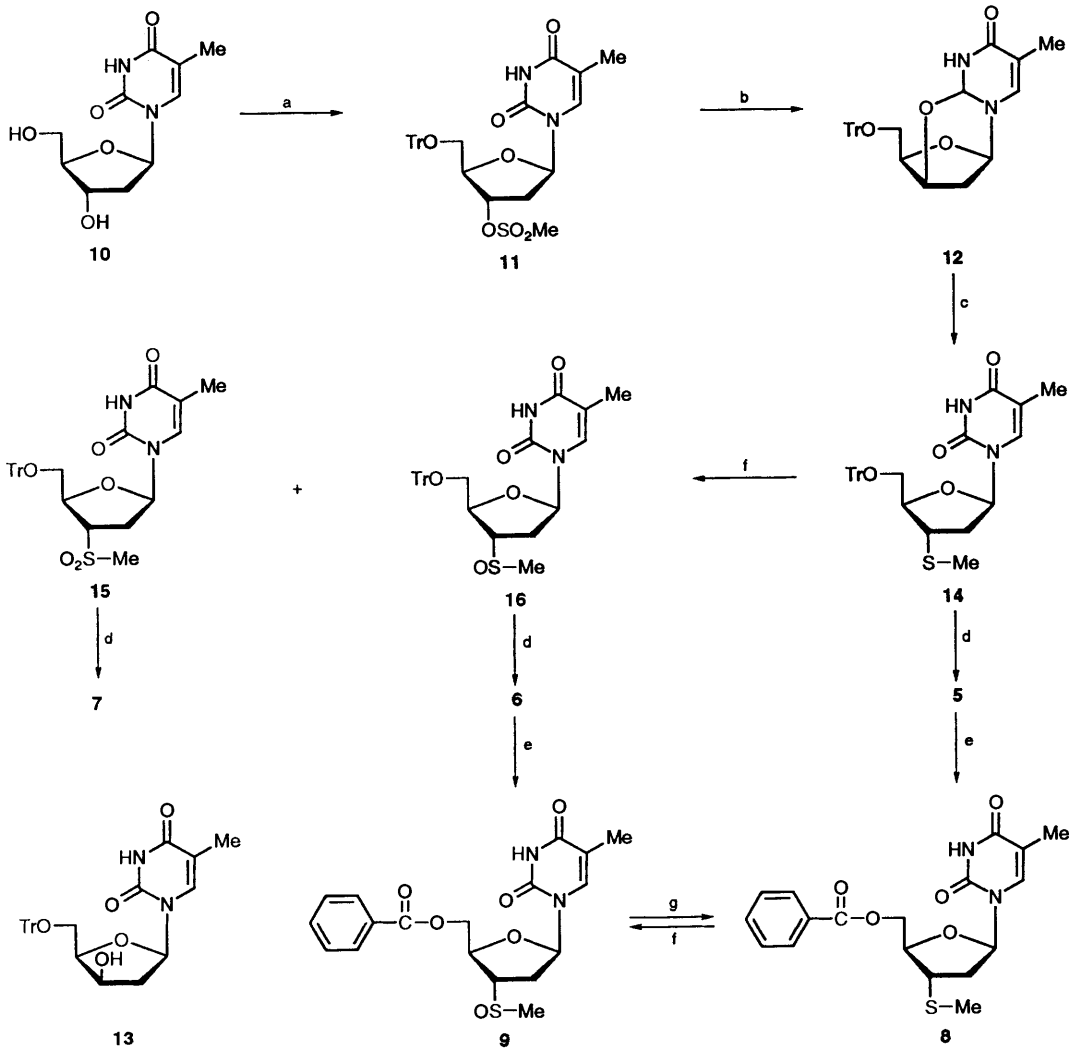
Therefore we turned our attention to the synthesis of the α-fluoro sulfides starting from the sulfoxides. Sulfoxides are more polar than sulfides and a better separation between the starting material **9** and the product of the reductive fluorination (**17**) could be expected. This would allow us to monitor the reaction easily on TLC by following the disappearance of the starting material. Oxidation of 3'-deoxy-3'-(methylthio)-5'-*O*-tritylthymidine **14** with 1 mol equiv. of *m*-chloroperbenzoic acid (MCPBA) in dichloromethane gave 3'-deoxy-3'-methylsulfinyl-5'-*O*-tritylthymidine **16** in 85% yield (Scheme 2). According to NMR spectroscopy, this product is a mixture of *R* and *S* sulfoxide and could not be resolved by using conventional chromatographic techniques. The solution of MCPBA in dichloromethane was added dropwise in order to minimise overoxidation to 3'-deoxy-3'-methylsulfonyl-5'-*O*-tritylthymidine **15**. The sulfoxide **16**, as well as the sulfone **15**, was detritylated with formic acid at room temperature for 5 min to give compounds **6** and **7** respectively. The sulfoxide **6** was obtained as a single isomer after crystallisation from ethanol, but the absolute configuration, however, could not be definitely assigned. Benzoylation of 3'-deoxy-3'-(methylsulfinyl)thymidine **6** with benzoyl chloride in pyridine afforded 5'-*O*-benzoyl-3'-deoxy-3'-(methylsulfinyl)thymidine **9**.

For the synthesis of larger amounts of sulfoxide **9**, however, we preferred to oxidise 5'-*O*-benzoyl-3'-deoxy-3'-(methylthio)thymidine **8** with MCPBA. This procedure is more convenient because the unprotected sulfoxide **6** is quite polar and is more difficult to purify by chromatography than is sulfide **5**. Reaction of 5'-*O*-benzoyl-3'-deoxy-3'-(methylsulfinyl)thymidine **9** with DAST in dichloromethane at room temperature afforded 5'-*O*-benzoyl-3'-deoxy-3'-(fluoromethylthio)-thymidine **17** in 55% yield (see Scheme 3). The deoxygenated sulfide, 5'-*O*-benzoyl-3'-deoxy-3'-(methylthio)thymidine **8**, was formed as side-compound in only minor amounts (< 5%).

5'-*O*-Benzoyl-3'-deoxy-3'-(fluoromethylthio)thymidine **17** was used as starting material for the synthesis of the sulfoxide **3** and the sulfone **4** (see Scheme 3). Oxidation of compound **17** with 1.2 mol equiv. MCPBA in dichloromethane at −25 °C afforded 5'-*O*-benzoyl-3'-deoxy-3'-(fluoromethylsulfinyl)-thymidine **18** in 58% yield. The reaction product is a mixture of the R_S and S_S isomers (**18A** and **18B**). In contrast with the isomers of sulfoxide **9**, isomers **18A** and **18B** are clearly separated on TLC [CH_2Cl_2–MeOH (95:5)] and both isomers could be obtained in pure form. Deprotection with ammonia in methanol afforded both isomers of 3'-deoxy-3'-(fluoromethylsulfinyl)thymidine (**3A** and **3B**) in 80–85% yield. Oxidation of a mixture of sulfide **17** with 2 mol equiv. of MCPBA or further oxidation of a mixture of sulfoxides **18A** and **18B** afforded 5'-*O*-benzoyl-3'-deoxy-3'-(fluoromethylsulfonyl)thymidine **19**, which was debenzoylated with ammonia in methanol to give 3'-deoxy-3'-(fluoromethylsulfonyl)thymidine **4** (Scheme 3).

In an attempt to determine the absolute configuration of the two isolated sulfoxides **3A** and **3B**, the 360 MHz NMR spectra were recorded. The results are collected in Table 1. Most of the coupling constants were measured directly in a first-order fashion from the expanded patterns. For the overlapping multiplets, the important missing values could be obtained by simple elimination and careful comparison and matching of the whole coupling set (see the Experimental section). The coupling constants for both diastereoisomers are very similar and definitely point to a C3'-*endo* (close to $^3T_2$) sugar conformation for both isomers. This, it should be noted, is clearly distinct from the usual C2'-*endo* conformation observed for 3'-substituted 2'-deoxypyrimidine nucleosides, and may have a decisive influence on its antiviral activity.

Although there are a few striking shift differences in the NMR spectra of the two isomers, no definite conclusions could be drawn about their absolute configuration. However, from a consideration of the rotational preferences around the C3'–S bond as seen in Newman projections, we tentatively assigned the R_S stereochemistry to the more polar compound **3B** and the S_S configuration to **3A**. Indeed, since the sugar backbone conformations of the two isomers are very similar as evidenced from ^{1}H NMR spectral data, the shift changes can be accounted for only by a different rotameric behaviour of the 3'-fluoromethylsulfinyl group. Now, this behaviour seems to be not influenced by any specific H-bonding interaction with the



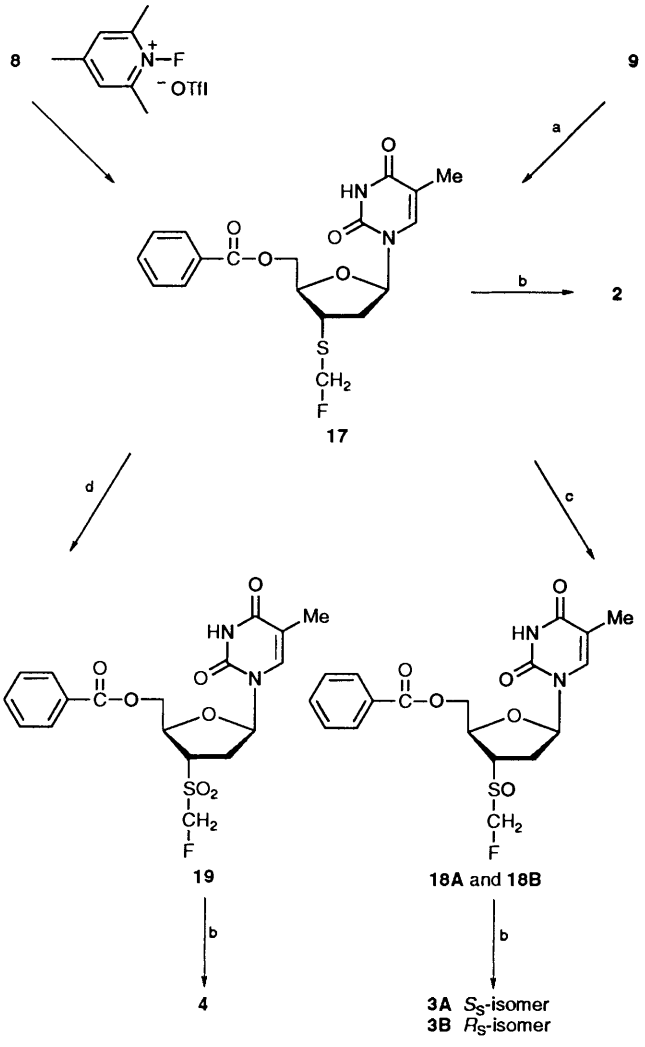
Scheme 2 a, TrCl, pyridine, 40 °C, MesCl, pyridine, room temp. (90%); b, NaOH, THF, reflux (75%); c, MeSH, MeSNa, DMF–EtOH, 100 °C (85%); d, HCO_2H, 5 min, room temp. (92%); e, BzCl, pyridine, 40 °C (90%); f, MCPBA, CH_2Cl_2, 1 h, −25 °C (84% **16**, 10% **15**; 61% **9**); g, as side-compound during formation of the 3′-fluoromethylthio derivative **17** from **9** by using DAST

nearby 5′-OH function, and thus mainly steric effects are to be considered. This follows from the observation that the ^{13}C shift differences (and especially that of C-2′) between the two isomers **3A** and **3B** having a free 5′-OH function are almost identical with those between the two 5′-*O*-benzoyl analogues **18A** and **18B** or between the two 5′-OH, 3′-SO-Me derivatives **6A** and **6B**.

Further, from a comparison of the ^{13}C NMR spectra of compounds **3** and **4**, it is immediately evident that the C-2′ shift of one of the isomers (**3B**) is similar to that of the sulfone, so that it may be assumed that their most populated conformers should be also very similar. Now, if one considers mainly the surroundings of C-2′, the only possible rotamer of stereoisomer **3B** which can be similar to a sulfone rotamer is represented by **a** (if sulfoxide *R*-isomer) or by **b** (if sulfoxide *S*-isomer) in Fig. 1.

However, in view of the fact that the CH_2F substituent may be considered as the largest group of the three, the preferential rotamer of the *S*-isomer should not be as in rotamer **b**, but rather as in rotamer **c**, with the electron pair (••) between the two carbon substituents. Hence, in this *S*-configuration, as far as C-2′ is concerned, there is no evidence for similarity with one of the sulfone conformations, and on this basis the preferred rotamer **a** (and thus *R*-configuration) is retained for stereoisomer **3B**. Confirmatory evidence for this tentative assignment may be found in the downfield ^1H shift of the axially situated 4′-H and 2′-H^B protons of stereoisomer **3B**, compared with the other isomer **3A**. This could be due to the *syn*-1,3-diaxial deshielding effect[12] of the anisotropic sulfoxide bond, as is visible in rotamer **a**. In the same way, the characteristic highfield shift of C-2′ in the less polar isomer **3A** (which is thus assigned the *S*-configuration and a rotameric preference as in **c**) can now be explained by the fact that this carbon is situated in the shielding region of the sulfoxide bond.

The ^1H NMR study clearly demonstrated the preference for a C3′-*endo* conformation for the deoxyribose moiety of compounds **3A** and **3B** (Fig. 2). This conformation is not in agreement with the preferred conformation normally found in the crystal structure[4b] of 3′-azido- and 3′-fluoro-substituted 3′-deoxythymidine analogues. These biologically active compounds show a preference for the C2′-*endo* conformation. In solution state, 2′,3′-dideoxy-3′-fluororibonucleosides adopt an *S*-type conformation. This *S*–*N* equilibrium is shifted in the direction of the *N*-form in 3′-azido-3′-deoxythymidine.[13] Although still speculative, together with the size of the 3′-substituent, the pseudoequatorial orientation of the 5′-hydroxy position in isomers **3A** and **3B** (C3′-*endo* conformation) might contribute to the inactivity of these compounds against HIV-1 (data not shown) when compared with the pseudoaxial orientation of the 5′-hydroxy group in the highly active 3′-azido-and 3′-fluoro-nucleosides (C2′-*endo* conformation).[14,15]



Scheme 3 *Reagents and conditions:* a, DAST; b, NH_3, MeOH, 16 h, room temp. (91% **2**, 80% **3a**, 85% **3b**, 50% **4**); c, MCPBA, CH_2Cl_2, 1 h, −25 °C (58%); d, MCPBA, CH_2Cl_2, 16 h, room temp.

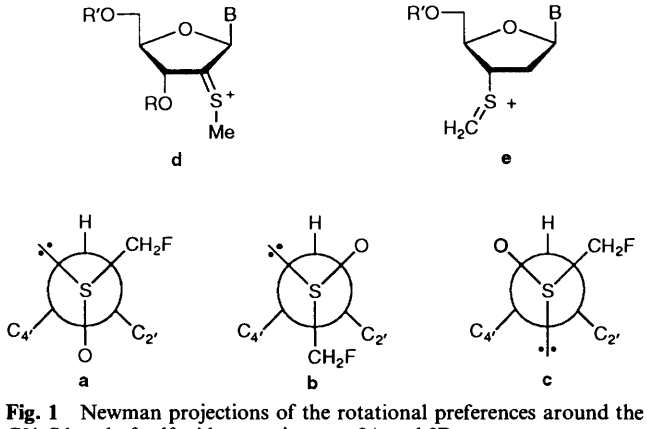


Fig. 1 Newman projections of the rotational preferences around the C3′–S bond of sulfoxide stereoisomers **3A** and **3B**

Discussion

The observation that the reaction of DAST with 5′-*O*-benzoyl-3′-deoxy-3′-(methylsulfinyl)thymidine **9** gives 5′-*O*-benzoyl-3′-deoxy-3′-(fluoromethylthio)thymidine **17** and not 5′-*O*-benzoyl-3′-deoxy-3′-fluoro-3′-methylthiothymidine is of interest. McCarthy suggested in his original publication[9] that the regioselectivity of the reaction is sterically controlled. This was based on the exclusive formation of fluoromethyl ethyl sulfide from methyl ethyl sulfoxide. However, his explanation is restricted to the described reaction. The results with methyl ethyl sulfoxide are not in agreement with the results of Sufrin *et al.*[16] By reaction of 2′,3′-di-*O*-acetyl-5′-deoxy-5′-(methylsulfinyl)adenosine with DAST, he obtained a mixture of three 2′,3′-di-*O*-acetyl-5′-deoxyadenosine analogues, *i.e.* the 5′-methylthio derivative, the 5′-deoxy-5′-fluoromethylthio analogue, and the 5′-deoxy-5′-fluoro-5′-methylthio congener, of which the last one predominates. Robins explored the reaction of 3′,5′-bis-*O*-(4-chlorobenzoyl)-2′-deoxy-2′-(methylsulfinyl)uridine with DAST–$SbCl_3$.[17] He observed the formation of 3′,5′-bis-*O*-(4-chlorobenzoyl)-2′-deoxy-2′(*S*)-fluoro-2′-(methylthio)uridine and no fluorination of the methyl carbon. It is clear from these results that, in this series of compounds, steric, as well as electronic, effects and the avoidance of formation of strained intermediates (strain-impeded effects) play a role in the regioselectivity of the reaction. The stability of the sulfonium

Table 1 ^{1}H NMR data of stereoisomers **3A** and **3B** (chemical shifts in δ *vs.* $SiMe_4$, coupling constants in Hz) in $(CD_3)_2SO$ solution

(a)	Chemical shift	
	Most polar isomer or **3B**	Less polar isomer or **3A**
1′-H	6.06	6.04
2′-H^{A} [a]	2.48	2.81
2′-H^{B} [a]	2.38	2.25
3′-H	3.77	3.72
4′-H	4.42	4.09
5′-H^{A} [a]	3.77	3.77
5′-H^{B} [a]	3.58	3.65
5′-OH	5.25	4.29
Sub A [b]	5.62	5.64
Sub B [b]	5.49	5.42
T_{Me} [b]	1.82	1.80
T_H [b]	7.75	7.72
T_{NH} [b]	11.65	11.35
(b)	Coupling constants $J_{H,H}$	
	Most polar isomer or **3B**	Less polar isomer or **3A**
^3J(1′,2′^{A})	6.1	7.1
^3J(1′,2′^{B})	6.7	5.2
^2J(2′^{A},2′^{B})	−15.0	−14.6
^3J(2′^{A},3′)	6.1	7.1
^3J(2′^{B},3′)	9.2	8.9
^3J(3′,4′)	~7.4	7.2
^3J(4′,5′^{A})	~3.5	3.5
^3J(4′,5′^{B})	~3.9	4.1
^2J(5′^{A},5′^{B})	−11.8	−12.2
^3J(5′-O*H*,5^{B})	~5.2	5.4
^3J(5′-O*H*,5′^{A})	~5.2	5.4
^2J(Sub A, Sub B)	−9.3	−9.1
^3J(Sub A, F)	47.0	46.8
^3J(Sub B, F)	47.9	47.9

[a] For geminal protons, A is the proton at highest frequency. [b] T: thymine, Sub: CH_2 of fluoromethylsulfinyl substituent.

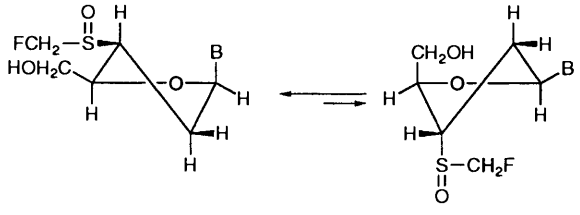


Fig. 2 Preference for C3′-*endo* conformation over the C2′-*endo* conformation for compounds **3A** and **3B**, as determined by ^{1}H NMR spectroscopy

cation intermediates, depicted in structures **d** and **e**, together with the acidity of the proton which is abstracted and steric factors, should be taken into account when explaining the difference in regioselectivity observed between the three types (2'-, 3'- and 5'-substituted) of nucleoside analogue.

Experimental

UV spectra were recorded with a Philips PU 8700 UV–VIS spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were determined with a JEOL FX 90Q spectrometer with tetramethylsilane as internal standard for the ^{1}H NMR spectra, $(CD_3)_2SO$ (δ_C 39.6) and $CDCl_3$ (δ_C 76.9) for the ^{13}C NMR spectra. A Bruker WH 360 spectrometer was used for compounds **3A** and **3B**. *J* Values are given in Hz. The ^{19}F chemical shift of hexafluorobenzene was taken as secondary reference at δ_F −163 from $CFCl_3$. Mass spectra were obtained using a Kratos Concept ^{1}H mass spectrometer. Precoated Machery-Nagel Alugram® Sil G/UV254 plates were used for TLC and the spots were examined with UV light and sulfuric acid–anisaldehyde spray. Column chromatography was performed on Janssen Chimica silica gel (0.060–200 nm). Extracts were dried over anhydrous Na_2SO_4.

3'-Deoxy-3'-(methylthio)thymidine **5**.—To a solution of sodium ethanolate (3.5 g, 50 mmol) in ethanol (50 cm^3) were added successively a solution of methanethiol (4.8 g, 100 mmol) in DMF (30 cm^3) and *O*^{2},3'-anhydro-1-(5-*O*-trityl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine (4.6 g, 10 mmol) **12**.[11] The reaction mixture was heated (bath temperature 100 °C) for 8 h, cooled to room temperature, evaporated, diluted with CH_2Cl_2, filtered and evaporated. The residual oil was purified by column chromatography using CH_2Cl_2 and then CH_2Cl_2–MeOH 98:2 as eluent. 3'-Deoxy-3'-methylthio-5'-*O*-tritylthymidine **14** was obtained as a foam (4.37 g, 85%); δ_C[$(CD_3)_2SO$] 11.9 (Me), 13.1 (SMe), 37.8 (C-2'), 42.0 (C-3'), 63.2 (C-5'), 83.4 and 83.6 (C-4' and -1'), 109.5 (C-5), 135.9 (C-6), 150.4 (C-2), 163.7 (C-4) and (trityl: 86.4, 127.2, 128.0, 128.3 and 143.5).

Detritylation was performed by dissolution of the tritylated compound (3.08 g, 6 mmol) in formic acid (30 cm^3). The solution was kept for 5 min at room temperature, evaporated, then co-evaporated twice with toluene, and this was followed by chromatographic purification [CH_2Cl_2–MeOH (97:3)]. This reaction yielded *3'-deoxy-3'-(methylthio)thymidine* **5** (1.5 g, 92%); λ_{max}(MeOH)/nm 268 (ε 9800 dm^3 mol^{-1} cm^{-1}); δ_H[$(CD_3)_2SO$] 2.11 (s, SMe); δ_C[$(CD_3)_2SO$] 12.3 (Me), 13.3 (SMe), 38.1 (C-2'), 41.7 (C-3'), 60.6 (C-5'), 83.6 and 85.4 (C-1' and -4'), 109.1 (C-5), 136.3 (C-6), 150.5 (C-2) and 163.8 (C-4) (Found: C, 48.6; H, 5.9; N, 10.4. $C_{11}H_{16}N_2O_4S$ requires C, 48.70; H, 5.57; N, 10.32%).

3'-Deoxy-3'-(methylsulfinyl)thymidine **6**.—A solution of 70% MCPBA (725 mg, 3 mmol) in dichloromethane (10 cm^3) was added dropwise to a solution of 3'-deoxy-3'-methylthio-5'-*O*-tritylthymidine (1.51 g, 3 mmol) in dichloromethane (20 cm^3) at −25 °C. The mixture was stirred for 1 h, washed with aq. sodium hydrogen carbonate (5%; 30 cm^3), dried, evaporated and purified by column chromatography [CH_2Cl_2–MeOH (98:2)] to give 3'-deoxy-3'-methylsulfinyl-5'-*O*-tritylthymidine **16** (1.3 g, 84%) as a mixture of the R_S and S_S isomers. The presence of two inseparable isomers hampers the interpretation of the NMR data: δ_C($CDCl_3$) 11.7 and 11.9 (Me), 28.8 and 34.4 (C-2'), 37.1 (SMe), 59.2 and 60.0 (C-3'), 62.8 and 64.8 (C-5'), 77.8 and 79.0 (C-4'), 85.7 and 87.5 (C-1'), 111.1 (C-5), 85.1, 127.3, 127.6, 127.9, 128.0, 128.4 and 143.0 (trityl), 135.0 and 135.5 (C-6), 150.0 (C-2) and 163.6 (C-4).

The product was detritylated by dissolution in formic acid (20 cm^3). After 5 min, the solution was evaporated, co-evaporated with toluene, and purified by column chromatography [CH_2Cl_2–MeOH (9:1)] to give, after crystallisation from ethanol, *3'-deoxy-3'-(methylsulfinyl)thymidine* (450 mg, 62%) as a single isomer: **6A**, m.p. 195–200 °C (decomp.); λ_{max}(MeOH)/nm 267 (ε 9900); *m/z* (CI) 289 (MH^+); δ_H[$(CD_3)_2SO$] 2.54 [s, S(O)Me]; δ_C[$(CD_3)_2SO$] 12.3 (Me), 27.8 (C-2'), 36.7 [S(O)Me], 58.3 (C-3'), 61.3 (C-5'), 80.8 (C-4'), 84.3 (C-1'), 109.3 (C-5), 136.3 (C-6), 150.4 (C-2) and 163.8 (C-4) (Found: C, 45.8; N, 5.4; H, 9.8. $C_{11}H_{16}N_2O_5S$ requires C, 45.82; H, 5.59; N, 9.72%).

From the filtrate the ^{13}C NMR values could be extracted for the other isomer (**6B**), δ_C[$(CD_3)_2SO$] 12.3 (Me), 33.5 (C-2'), 36.7 [S(O)Me], 58.9 (C-3'), 62.8 (C-5'), 78.8 (C-4'), 83.8 (C-1'), 109.5 (C-5), 136.1 (C-6), 150.4 (C-2) and 163.8 (C-4).

3'-Deoxy-3'-(methylsulfonyl)thymidine **7**.—During the oxidation of 3'-deoxy-3'-methylthio-5'-*O*-tritylthymidine with MCPBA, a compound was detected with slightly higher R_f-value on TLC than the sulfoxide. This compound was formed by overoxidation. It was detritylated with formic acid for 5 min at room temperature and the product was purified by column chromatography [CH_2Cl_2–MeOH (9:1)] (92 mg, 10%), λ_{max}(MeOH)/nm 266 (ε 9800); *m/z* 304 (M^+); δ_H[90 MHz; $(CD_3)_2SO$] 3.08 (s, SO_2Me); δ_C[$(CD_3)_2SO$] 12.6 (Me), 32.4 (C-2') and 39.8 (SO_2Me), 61.6 (C-3'), 62.6 (C-5'), 78.7 (C-4'), 84.2 (C-1'), 110.0 (C-5), 136.3 (C-6), 150.7 (C-2) and 164.1 (C-4) (Found: C, 43.4; H, 5.55; N, 8.8. $C_{11}H_{16}N_2O_6S$ requires C, 43.41; H, 5.30; N, 9.10%).

5'-O-Benzoyl-3'-deoxy-3'-(methylthio)thymidine **8**.—To a solution of 3'-deoxy-3'-(methylthio)thymidine **5** (272 mg, 1 mmol) in pyridine (20 cm^3) was added a solution of benzoyl chloride (212 mg, 0.175 cm^3, 1.5 mmol) in pyridine (5 cm^3). The reaction mixture was kept for 1 h at 40 °C, methanol (1 cm^3) was added, and the mixture was evaporated. The residual oil was diluted with CH_2Cl_2, washed with water, dried, evaporated, and purified by column chromatography [CH_2Cl_2–MeOH (98:2)] to yield *5'-O-benzoyl-3'-deoxy-3'-(methylthio)thymidine* **8** (364 mg, 92%); δ_H(90 MHz; $CDCl_3$) 1.67 (s, Me), 2.20 (s, SMe), 2.50 (dd, 2'-H_2), 3.37 (q, 3'-H), 4.25 (m, 4'-H), 4.66 (AB d, 5'-H_2), 6.16 (t, 1'-H) and 7.54 and 8.05 (2 m, benzoyl + 6-H); δ_C($CDCl_3$) 12.1 (Me), 14.3 (SMe), 39.3 (C-2'), 42.9 (C-3'), 63.5 (C-5'), 83.0 and 85.1 (C-4' and -1'), 110.8 (C-5), 128.9, 129.4 and 133.4 (phenyl), 134.8 (C-6), 150.1 (C-2), 163.6 (C-4) and 165.0 (C=O) (Found: C, 57.2; H, 5.1; N, 7.5. $C_{18}H_{20}N_2O_5S$ requires C, 57.43; H, 5.36; N, 7.44%).

5'-O-Benzoyl-3'-deoxy-3'-(methylsulfinyl)thymidine **9**.—(*a*) A mixture of 3'-deoxy-3'-(methylsulfinyl)thymidine **6** (400 mg, 1.39 mmol) and benzoyl chloride (0.22 cm^3, 2 mmol) in pyridine (30 cm^3) was kept at room temperature overnight. After addition of methanol (1 cm^3) the reaction mixture was evaporated and the residue was purified by column chromatography [CH_2Cl_2–MeOH (95:5)] to yield the title compound (485 mg, 89%).

(*b*) A solution of 70% MCPBA (1.23 g, 4 mmol) in dichloromethane (20 cm^3) was added dropwise to a solution of 5'-*O*-benzoyl-3'-deoxy-3'-(methylthio)thymidine **8** (1.96 g, 5 mmol) in dichloromethane (50 cm^3) at −25 °C. After being stirred for 1 h, the mixture was washed with aq. 5% sodium hydrogen carbonate, dried, evaporated, and purified by column chromatography [CH_2Cl_2–MeOH (98:2)] to yield compound **9** (1.2 g, 61% calculated on **8**) (Found: C, 55.3; H, 5.2; N, 7.05. $C_{18}H_{20}N_2O_6S$ requires C, 55.09; H, 5.14; N, 7.14%). For ^{13}C NMR data, see the next compound.

3'-Deoxy-3'-(fluoromethyl)thiothymidine **2**.—(*a*) A solution of 5'-*O*-benzoyl-3'-deoxy-3'-(methylthio)thymidine **8** (276 mg,

1 mmol) and 1-fluoro-2,4,6-trimethylpyridinium triflate (434 mg, 1.5 mmol) in dichloromethane (10 cm^3) was stirred for 48 h at room temperature. The reaction mixture was washed with water, dried, and evaporated. Column chromatographic purification [CH_2Cl_2–MeOH (98:2)] gave, in the first fraction, an oil (295 mg), which was identified by ^{13}C NMR and ^1H NMR spectroscopy as being a 1:1 mixture of 5'-*O*-benzoyl-3'-deoxy-3'-(fluoromethylthio)thymidine **17** and 5'-*O*-benzoyl-3'-deoxy-3'-(methylthio)thymidine **8**.

The more slowly eluting fraction, the amount of which was dependent on the reaction conditions, was identified as a 1:1 mixture of (R_S)- and (S_S)-5'-*O*-benzoyl-3'-deoxy-3'-(methylsulfinyl)thymidine **9**, $\delta_C(CDCl_3)$ 12.0 (Me), 27.8 and 33.9 (C-2'), 36.9 and 37.4 [S(O)Me], 59.5 and 60.1 (C-3'), 63.9 and 65.4 (C-5'), 110.9 and 111.0 (C-5), 128.0, 128.5, 129.4, 129.7, 132.5 and 133.4 (phenyl), 135.1 and 136.4 (C-6), 150.1 (C-2), 163.9 and 164.0 (C-4) and 165.8 and 166.0 (C=O).

(*b*) A solution of 5'-*O*-benzoyl-3'-deoxy-3'-(methylsulfinyl)-thymidine **9** (588 mg, 1.5 mmol) and DAST (1.86 cm^3, 15 mmol) in dichloromethane (10 cm^3) was refluxed (45 °C) for 36 h. The reaction mixture was cooled, washed with water, dried, and evaporated. Column chromatographic purification [CH_2Cl_2–MeOH (98:2)] yielded 5'-O-*benzoyl-3'-deoxy-3'-(fluoromethylthio)thymidine* **17** (350 mg, 59%); λ_{max}(MeOH)/nm 267 (ε 10 100); $\delta_C(CDCl_3)$ 12.0 (Me), 39.9 (C-2'), 42.3 (C-3'), 62.6 (C-5'), 83.4 and 85.1 (C-4' and -1'), 86.1 (d, *J* 216, CH_2F), 110.8 (C-5), 128.5, 129.4 and 133.4 (phenyl), 134.8 (C-6), 150.1 (C-2), 163.6 (C-4) and 165.8 (C=O) (Found: C, 55.1; H, 4.7; N, 6.9. $C_{18}H_{19}FN_2O_5S$ requires C, 54.81; H, 4.86; N, 7.10%).

A solution of 5'-*O*-benzoyl-3'-deoxy-3'-(fluoromethylthio)-thymidine **17** (300 mg, 0.76 mmol) in methanol, saturated with ammonia, was kept at room temperature overnight. The reaction mixture was evaporated and the residue was purified by column chromatography to give 3'-*deoxy-3'-(fluoromethylthio)thymidine* **2** (200 mg, 91%); λ_{max}(MeOH)/nm 268 (ε 9800); *m/z* (CI) 291 (MH^+); $\delta_C[(CD_3)_2SO]$ 12.3 (Me), 39.2 (C-2'), 41.2 (C-3'), 59.8 (C-5'), 83.5 and 85.7 (C-1' and -4'), 86.6 (d, *J* 210, CH_2F), 109.0 (C-5), 136.2 (C-6), 150.4 (C-2) and 163.7 (C-4); $\delta_F[(CD_3)_2SO]$ −182.0 (t, $^2J_{F,H}$ 52.5) (Found: C, 45.3; H, 5.1; N, 9.3. $C_{11}H_{15}FN_2O_4S$ requires C, 45.51; H, 5.21; N, 9.65%).

3'-*Deoxy-3'-(fluoromethylsulfinyl)thymidine* **3**.—A solution of 70% MCPBA (296 mg, 1.2 mmol) in dichloromethane (5 cm^3) was added dropwise to a cooled solution (−25 °C) of 5'-*O*-benzoyl-3'-deoxy-3'-(fluoromethylthio)thymidine **17** (394 mg, 1 mmol) in dichloromethane (10 cm^3). The reaction mixture was stirred for 1 h, washed successively with aq. sodium hydrogen carbonate (5%) and water, dried, and evaporated. Column chromatographic purification [CH_2Cl_2–MeOH (98:2)] yielded the less polar isomer **18A** (110 mg, 27%) separated from the more polar isomer, **18B** (130 mg, 32%).

Fast eluting isomer, **18A**: $\delta_C(CDCl_3)$ 12.1 (Me), 28.0 (C-2'), 56.0 (d, *J* 4.8, C-3'), 63.7 (C-5'), 78.3 (C-4'), 88.2 (C-1'), 93.4 (*J* 223, CH_2F), 111.0 (C-5), 128.5, 129.0, 129.5 and 133.4 (Ar), 136.5 (C-6), 150.0 (C-2), 163.6 (C-4) and 166.0 (C=O).

Slow eluting isomer, **18B**: $\delta_C(CDCl_3)$ 12.0 (Me), 33.4 (C-2'), 54.9 (d, *J* 7.4, C-3'), 65.1 (C-5'), 77.3 (C-4'), 86.0 (C-1'), 93.2 (*J* 223, CH_2F), 111.1 (C-5), 128.5, 129.1, 129.4 and 133.4 (Ar), 135.0 (C-6), 150.2 (C-2), 163.8 (C-4) and 165.8 (CO).

Both isomers were further identified after debenzoylation with ammonia in methanol, overnight at room temperature. The compounds were crystallised from MeOH.

Less polar isomer, **3A**: m.p. 176–178 °C (decomp.); λ_{max}-(MeOH)/nm 266 (ε 9600); *m/z* (CI) 307 (MH^+); $\delta_F[(CD_3)_2SO]$ −221.7 (t, $^2J_{F,H}$ 47.4); $\delta_C[(CD_3)_2SO]$ 12.2 (Me), 28.2 (C-2'), 53.9 (C-3', $^3J_{F,C}$ 6.1), 61.0 (C-5'), 80.6 (C-4'), 84.5 (C-1'), 95.8 (CH_2F, ^1J 208.8), 109.5 (C-5), 136.2 (C-6), 150.3 (C-2) and 163.6 (C-4) (Found: C, 42.7; H, 5.0; N, 8.8. $C_{11}H_{15}FN_2O_5S$ requires C, 43.13; H, 4.94; N, 9.15%).

More polar isomer, **3B**: m.p. 198–200 °C (decomp.); λ_{max}-(MeOH)/nm 266 (ε 9800) *m/z* (CI) 307 (MH^+); $\delta_F[(CD_3)_2$-SO] −223.3 (t, $^2J_{F,H}$ 47.4); $\delta_C[(CD_3)_2SO]$ 12.2 (Me), 32.8 (C-2'), 53.6 (C-3', $^3J_{F,C}$ 7.4), 62.2 (C-5'), 79.2 (C-4'), 83.9 (C-1'), 95.2 (CH_2F, ^1J 208.7), 109.5 (C-5), 136.0 (C-6), 150.3 (C-2) and 163.7 (C-4) (Found: C, 43.05; H, 4.95; N, 8.8%).

3'-*Deoxy-3'-(fluoromethylsulfonyl)thymidine* **4**.—To a solution of 5'-*O*-benzoyl-3'-deoxy-3'-(fluoromethylthio)thymidine **17** (130 mg, 0.25 mmol) in dichloromethane (5 cm^3) was added dropwise a solution of 70% MCPBA (100 mg) in dichloromethane (3 cm^3) at −20 °C. The reaction mixture was stirred overnight at room temperature, poured into 5% aq. sodium hydrogen carbonate (10 cm^3) and extracted with dichloromethane (10 cm^3). The organic layer was dried, evaporated, and purified by column chromatography [CH_2Cl_2–MeOH (98:2)] to yield 5'-*O*-benzoyl-3'-deoxy-3'-(fluoromethylsulfonyl)thymidine **19** (55 mg, 50%); $\delta_C(CDCl_3)$ 11.9 (Me), 32.6 (C-2'), 59.3 (C-3'), 64.4 (C-5'), 76.1 (C-4'), 86.9 (C-1'), 90.3 (d, *J* 218.5, CH_2F), 111.2 (C-5), 128.5, 129.4 and 133.4 (phenyl), 135.6 (C-6), 150.0 (C-2), 163.8 (C-4) and 165.9 (C=O).

Debenzoylation was carried out by dissolution of 5'-*O*-benzoyl-3'-deoxy-3'-(fluoromethylsulfonyl)thymidine in methanol (5 cm^3) saturated with ammonia. The solution was kept at room temperature overnight, then was evaporated, and the residue was purified by preparative TLC [CH_2Cl_2–MeOH (90:10)], and the *title compound* **4** was crystallised from MeOH (20 mg, 50%), m.p. 230–235 °C (decomp.); λ_{max}(MeOH)/nm 266 (ε 9700); *m/z* (CI) 323 (MH^+); $\delta_C[(CD_3)_2SO]$ 12.2 (Me), 31.5 (C-2'), 58.9 (C-3'), 62.0 (C-5'), 77.9 (C-4'), 84.0 (C-1'), 90.4 (d, *J* 212, CH_2F), 109.7 (C-5), 135.9 (C-6), 150.3 (C-2) and 163.6 (C-4); $\delta_F[(CD_3)_2SO]$ −213.9 (t, $^2J_{F,H}$ 46.4) (Found: C, 38.3; H, 4.6; N, 7.6. $C_{15}H_{15}FN_2O_6S$·MeOH requires C, 38.71; H, 4.95; N, 7.52%).

NMR Study of Stereoisomers **3A** *and* **3B**.—A solution of stereoisomer **3A** or **3B** (~30 mg) in $(CD_3)_2SO$ (0.4 cm^3) was used. For the ^1H NMR spectra the methyl resonance of $(CD_3)_2SO$ *vs.* $SiMe_4$ (δ 2.50) was used as secondary reference; for the ^{19}F NMR spectra the ^{19}F resonance of hexafluorobenzene (δ_F −163.0 *vs.* $CFCl_3$) was used as secondary reference. The ^1H NMR spectra at 19 °C were obtained with a Bruker WH 360 spectrometer operating at 360.136 MHz, using a pulse angle of 19° (2 μs), 160 scans, and a resolution of 0.37 Hz/point. The ^{19}F NMR spectra at 19 °C were obtained with the same apparatus operating at 338.795 MHz, using a pulse angle of 47° (5 μs), 40 scans, and a resolution of 0.24 Hz/point.

The coupling constants $J(1',2'^A)$, $J(1',2'^B)$, $J(2'^A,3')$, $J(2'^B,3')$ and $J(2'^A,2'^B)$ for compound **3B**, the more polar isomer, were measured in a first-order fashion from the patterns of 2'-H^A (that unfortunately partly collapsed with the solvent resonance) and 2'-H^B, and assigned by comparison with the sum of the constants [$\Sigma J(1',2'^A) + J(1',2'^B) = 13.1$ Hz] obtained from the separation of the outer lines of 1'-H. A value of 9.2 Hz can be excluded for $J(1',2')$.

The patterns for 3'-H (a coupling constant of 9.2 Hz does not fit in the pattern for 4'-H, which allows us to discriminate between the patterns for 3'-H and 4'-H) and 5'-H^A fully collapsed, so that no assignment of the lines was possible with certainty. 4'-H gave a doublet of triplets, with 2 × ~3.5 Hz and 1 × ~7–8 Hz.

From the pattern of 5'-H^B we extracted coupling constants of ~3.9, ~5.2 and ~−11.8 Hz.

The pattern of 5'-OH was a triplet with 2 × ~5.2 Hz. Consequently J(5'-OH, 5'-H^B) ~ J(5'-OH, 5'-H^A) ~ 5.2 Hz and $J(4',5'^B)$ is 3.9 Hz.

For further assignment of the coupling constants we must consider the conformation of the deoxyribose ring. Values of 9.2 and 6.1 Hz for $J(2',3')$ can only agree with a conformation in the C-3'-*endo* region (close to $^{3'}T_{2'}$). In the case of the C-2'-*endo* conformation, small values for $^3J(2'^A,3'^A)$, $^3J(2'^B,3')$ and $^3J(3',4')$ are expected. That means that 2'-H^B is the *exo* proton on C-2'. This also means (by consideration of a Fieser model) that a value of 7–8 Hz is expected for $J(3',4')$. Consequently a value of ~3.5 Hz must be attributed to $J(4',5'^A)$.

The methylene protons of the substituent were called Sub A and Sub B (A the proton at the highest frequency). They appear in the spectrum as two distinguished AB subspin systems which together form the AB-part of an ABX spin system with X the fluorine. The geminal coupling constant (which occurs four times in the AB-part of the ABX spin system) was −9.3 Hz (a rather positive value for a geminal coupling constant, but caused by the electronegativity of the fluorine and in agreement with the data given by Cookson *et al.*).[18] The coupling constants between the fluorine and the two protons were, respectively, 47.0 and 47.8 Hz (in agreement with the data given by Bovey).[19]

For the analysis of the less polar compound **3A**, we considered again first the coupling constants of 2'-H^A and 2'-H^B. In the pattern for 2'-H^A we measured coupling constants of 2 × 7.2 and 1 × 14 Hz. That means that $J(1,2'^A) \sim J(2'^A,3') \sim 7.1/7.2$ Hz (a value also measured in the pattern of 1'-H). In the pattern of 2'-H^B we measured coupling values of 5.2 and 8.9 Hz for the vicinal coupling constants. As a value of 5.1 Hz was found in the pattern for 1'-H, we may assume that this is the value for $J(1',2'^B)$ and that $J(2'^B,3')$ is 8.9 Hz.

Although the patterns for 3'-H, 5'-H^A and 5'-H^B overlap, the respective lines for each pattern can unequivocally be assigned. Besides the value −12.2 Hz for the geminal coupling constant, we measured in the pattern for 5'-H^A couplings of 3.5 and 5.4 Hz. In the pattern for 5'-H^B we measured vicinal coupling constants of 4.1 and 5.1 Hz. The pattern for 5'-OH was almost a triplet with 2 × ~5.4 Hz. That means that the coupling of 5'-H^A with 4'-H is 3.5 Hz, and the coupling of 5'-H^B with 4'-H is 4.1 Hz.

With the values known for $J(4',5'^A)$ and $J(4',5'^B)$ we can extract the value for $J_{3',4'}$ from the pattern for 4'-H, namely 7.2 Hz. From the pattern of the methylene protons of the substituent we extracted a geminal coupling of −9.1 Hz, and two $J_{F,H}$ geminal coupling constants of, respectively, 46.8 and 47.9 Hz.

In general we can say that, for this compound, also, a conformation close to the C3'-*endo* form can be proposed for the deoxyribose moiety.

The ^{19}F NMR spectra for both isomers were also run. The fluorine of the more polar isomer **3B** resonated at a lower frequency (by 1.6 ppm) than did that for the less polar isomer **3A**. In both cases approximate heteronuclear coupling constants of 47.4 Hz were measured.

Acknowledgements

We are indebted to Miss D. Brabants for fine editorial help. We thank Prof. Dr. W. Pfleiderer for the elemental analyses and Dr. G. Janssen for coordinating the mass analyses.

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Paper 3/05803D
Received 27*th September* 1993
Accepted 28*th September* 1993