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A NEW ROUTE TO 1,1-DIFLUORO OLEFINS: APPLICATION TO THE SYNTHESIS OF 2'-DEOXY-2'-DIFLUOROMETHYLENE NUCLEOSIDES.

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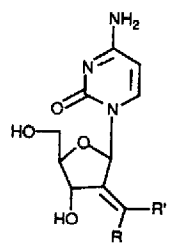
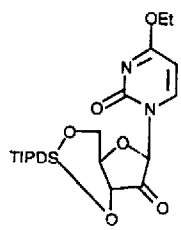
Abstract: Methodology has been developed for the difluoromethylenation of ketone 2, resulting in the synthesis of cytidine derivative 1c.

A recent report from these laboratories described the stereospecific synthesis of 2'-deoxy-2'fluoromethylene nucleosides, and the effect of fluoro olefin geometry on cytotoxic activity.[1] Fluoro olefin 1a is a potent cytotoxic agent (IC_{50} = 58 nM), whereas the geometric isomer 1b is substantially less active (IC_{50}=3870 nM). These



1a R=F; R'=H
1b R=H; R'=F
1c R=F; R'=F



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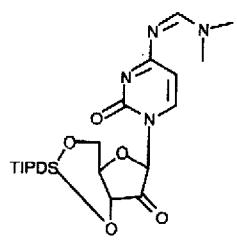

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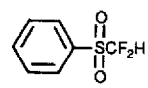

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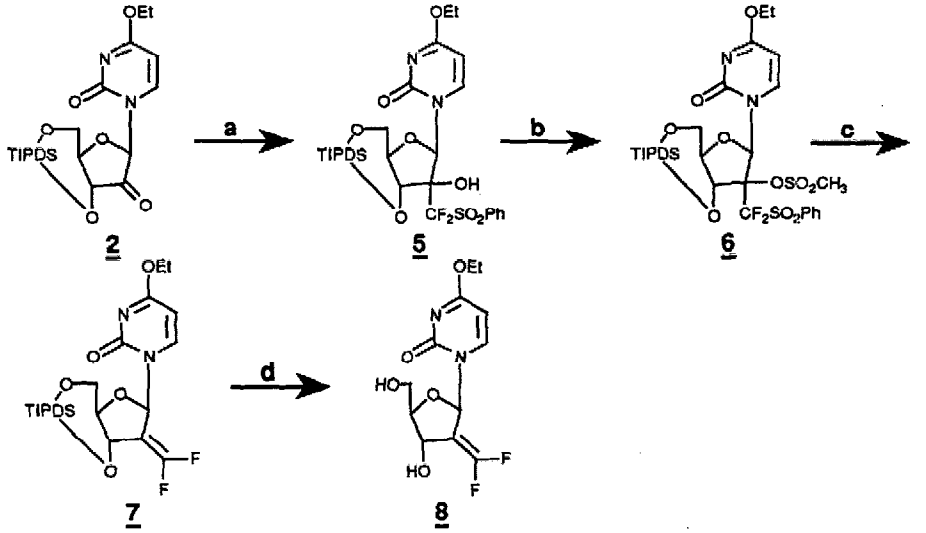
compounds were designed to inhibit ribonucleotide diphosphate reductase (RDR), and 1a demonstrated potent enzyme inhibition.[2] An intriguing question is how the conversion of 1a to the difluoro olefin 1c would affect antitumor activity and inhibition of RDR. In this letter, we report the synthesis of cytidine analog 1c, employing a modified Julia olefin synthesis using the electron transfer system, SmI_2-THF.[3] This synthesis of 1c provides a new route to highly functionalized, sensitive difluoro olefins.

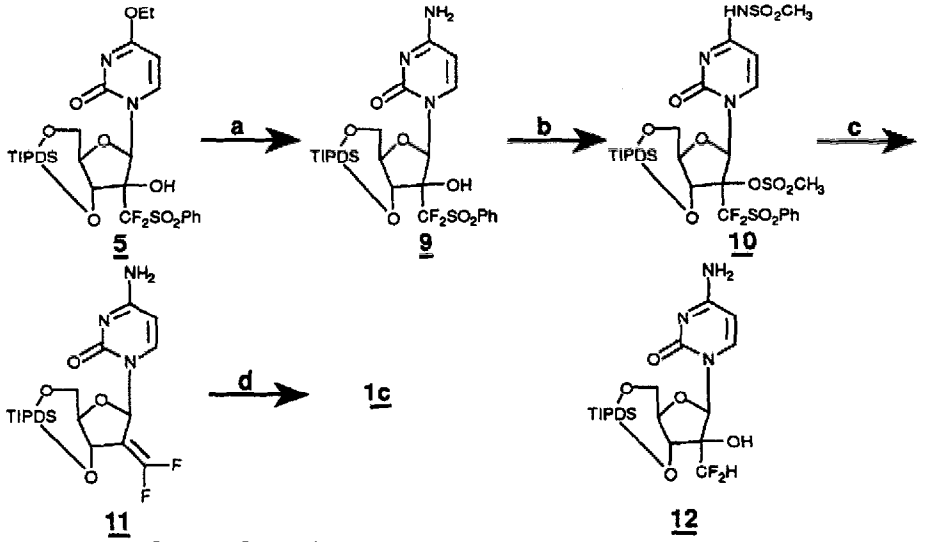
Our initial efforts focused on conventional difluoromethylenation strategies. Attempted Wadsworth-Emmons olefinations of either 2[4] or 3[5] using difluoromethyldiphenylphosphine oxide[6] were unsuccessful, as were attempts at Wittig olefination with the reagent generated *in situ* from $CF_2Br_2/(Me_2N)_3P$.[7] Inspired by a recent publication,[8] a modified Julia[9] approach was considered. Numerous attempts at the addition of the carbanion of difluoromethyl phenyl sulfone 4[10] to protected cytidine ketone 3 resulted in destruction of starting material. However, (Scheme I), addition of two equivalents of lithium hexamethyldisilazane to a mixture of sulfone 4 and ketone 2 in THF-HMPA at -70°C afforded an 85% yield of 5 after chromatography, with carbanion addition occurring mainly from the

Scheme I



(a) 4, 2 equiv. $LiN(Si(CH_3)_3)_2$, 10:1 THF-HMPA, -70°C (0.5h);
(b) $LiN(Si(CH_3)_3)_2$, THF, CH_3SO_2Cl, 55°C (2h);
(c) 2 equiv. SmI_2, THF, rt (5 min);
(d) $[CH_3(CH_2)_3]_4NF$, THF, 0°C (1h).

Scheme II



(a) NH_3, EtOH, 70°C (16h);
(b) 2 equiv. $LiN(Si(CH_3)_3)_2$, THF -70°C then 2.5 equiv CH_3SO_2Cl, 55°C (2h);
(c) 4 equiv. SmI_2, THF, 55°C (1h);
(d) $[CH_3(CH_2)_3]_4NF$, THF, 0°C (0.5h).

α-face. Reductive elimination of tertiary mesylate 6, prepared from 5 in 69% yield, using two equivalents of freshly prepared SmI_2-THF[11] was extremely facile; the olefin 7 was isolated in 62% yield after flash chromatography.[12] Removal of the 3'5'-O-tetraisopropyldisoloxane-1,3-diyl(TIPDS) group from 7 was accomplished using 1M tetrabutylammonium fluoride (TBAF) in THF, affording diol 8[12] in 59% yield. Treatment of either 7 or 8 with ammonia-saturated ethanol at a variety of temperatures gave none of the desired cytidine 1c and resulted only in cleavage of the base, presumably by an S_N2' process.

In order to circumvent this problem (Scheme II), 5 was first converted to the cytidine derivative 9 in 69% yield by treatment with ammonia-saturated ethanol at 70°C. Attempted reductive elimination of 9 with four equivalents of freshly prepared SmI_2-THF gave a mixture of recovered starting material and 12, the product of reductive desulfonylation.[13] Attempted mono-O-mesylation of 9 afforded a mixture of di-mesylate 10, and small amounts of both O-and N-mono-mesylates. Subsequently, the di-mesylate 10 was prepared in quantitative yield from 9 using excess methanesulfonyl chloride. Reductive elimination of 10 with four equivalents of SmI_2-THF required heating at 55°C for complete reaction to occur, with olefin 11[12] produced in 46% yield after purification. Removal of the (TIPDS) group from 11 was accomplished in 53% yield using TBAF, completing the synthesis of 1c.[12]

In conclusion, methodology has been developed from the difluoromethenylation of nucleosides, culminating in the syntheses of 8 and 1c. Evaluation of the biological activity of 1c, and a study of the applicability of this methodology are currently under way.

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REFERENCES AND NOTES

1. McCarthy, J.R.; Matthews, D.P.; Stemerick, D.M.; Huber, E.W.; Bey, P.; Lippert, B.J.; Snyder, R.D.; Sunkara, P.S. J. Am. Chem. Soc. 1991, 113, 7439.

2. The diphosphate of 1a has been prepared and irreversibly inhibited purified RDR, private communication, Lippert, B.J.

3. For a review see, Soderquist, J.A. Aldrichimica Acta. 1991, 24, 15.

4. Matsuda, A.; Itoh, H.; Takenishi, K.; Susuki, T.; Ueda, T. Chem. Pharm. Bull. 1988, 36, 945.

5. Matthews, D.P.; Persichetti, R.; Sabol, J.S.; McCarthy, J.R., manuscript in preparation.

6. Edwards, M.L.; Stemerick, D.M.; Jarvi, E.T.; Matthews, D.P.; McCarthy, J.R. Tetrahedron Lett. 1990, 31, 5571.

7. Fried, J.; Kittisopikul, S.; Halliman, E.A. Tetrahedron Lett. 1984, 25, 4329.

8. Kende, A.A.; Mendoza, J.S. Tetrahedron Lett. 1990. 31, 7105.

9. Julia, M.; Paris, J.M. Tetrahederon Lett. 1973, 14, 4833.

10. (a) Stahly, J.P. J. Fluorine Chem., 1989, 43, 53; (b) Miller, T.G.; Thanassi, J.W. J. Org. Chem. 1960, 25, 2009.

11. Our reagent was prepared as follows: A mixture of samarium powder and 1,2-diiodoethane was placed in a dried flask which was first evacuated and then placed under an Ar atmosphere. THF (0.1M, distilled from sodium benzophenone ketyl) was added, and after an initial induction period (1-2 min), stirring was continued at room temperature for 1.5 h. A solution of the substrate in THF was added to the above deep blue solution and the progress of the reaction was monitored by TLC. On occasion, addition of commercially available 0.1M SmI_2 in THF was used to maintain the blue color. Workup consisted of pouring the reaction mixture into a 10% solutio of $Na_2S_2O_3$ and extracting with ethyl acetate.

12. 7: ^{19}NMR ($CDCl_3$, 282 MHz), δ -84.54 (d, J=35.5 Hz), -79.27 (d, J=36.9 Hz). 8: ^{19}F NMR ($CDCl_3$, 282 MHz), δ -84.39 (d, J=36.9 Hz), -80.54 (d, J=36.7 Hz). 11: ^{19}F NMR ($CDCl_3$, 282 MHz), δ -84.39 (d, J=35.6 Hz), -79.26 (d, J=35.9 Hz). 1c: ^{19}F NMR (CD_3OD, 282 MHz), δ -85.0 (d, J=39.2 Hz), δ -82.78 (d, J=39.7 Hz).

13. Kunzer, H.; Stahnke, M.; Sauer, G.; Wiechert, R. Tetrahedron Lett. 1991, 32, 1949. The relative stereochemistry of 12 was confirmed using Nuclear Overhauser Enhancemen (NOE) difference spectroscopy, done on a Varian 300 MHz spectrometer by Dr. Edward Huber of MMDRI, Cincinnati.

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