SCIENTIFIC LETTER N°13

Edito

Pour la 13ème lettre Scientifique d’AtlanChim Pharma, le Professeur Jacques LEBRETON vous donne un aperçu des différentes stratégies permettant la synthèse de nucléosides modifiés. En effet ces dernières années nos chimistes ont acquis une forte expertise dans la chimie des sucres et les projets de nos clients nous enrichissent toujours d’avantage lors de la réalisation de leurs projets.

Tout au long de l’année 2019, nous vous avons fait partager notre savoir-faire et nos expertises à travers des webinaires au cours desquels nous avons pu traiter de sujets tels que les « Récentes avancées pour la synthèse de molécules biologiquement actives marquées (D, ^{13}C, ^{15}N, ^{18}O) », « Les synthèses de stéroïdes d'hier à aujourd'hui » et enfin les « récentes méthodologies pour la construction de pyrroles polysubstitués ». Nous vous avons également fait part de nos dernières publications scientifiques et publié mensuellement des posts sur la page linkedIn d’Atlanchim pharma intitulés «#TheMinuteOfChemistry»

Ce travail est nourri par une veille scientifique régulière et l’envie de partager avec vous notre passion pour notre métier et nos valeurs que sont : l’expertise scientifique, la transparence, l’échange et les défis de synthèse.

Avant le début de votre lecture, nous profitons de ce début d ’année pour vous souhaiter une très belle année 2020, qu’elle soit remplie de créativité et nous resterons à votre disposition pour vos challenges chimiques !

Editorial

For the 13th Scientific letter of AtlanChim Pharma, Professor Jacques LEBRETON gives you an overview of the different strategies allowing for the synthesis of modified nucleosides. Indeed in those recent years our chemists have acquired a strong expertise in sugar chemistry and our clients' projects always enrich us by carrying out their projects.

Throughout 2019, we shared with you our know-how and expertise through webinars during which we have discussed subjects such as « Recent advances in the synthesis of labeled biologically active molecules (D, ^{13}C, ^{15}N, ^{18}O) », « Syntheses of steroids from yesterday to today » and finally « Recent methodologies for the construction of polysubstituted pyrroles ». We also shared with you our latest scientific publications and we have started to publish monthly posts on the linkedIn page of AtlanChim Pharma entitled «#TheMinuteOfChemistry»

This work is based on regular scientific monitoring and the wish to share with you our passion for our profession and our values such as scientific expertise, transparency, exchange and synthesis challenges.

Before the beginning of your reading, we take this opportunity to wish you a very happy and creative new year 2020, we stay at your disposal for your chemical challenges!

Synthesis of modified nucleosides : a “walk” around the sugar ring.*

Jacques Lebreton
jacques.lebreton@atlanchimpharma.com

** This microreview is dedicated to my friend and colleague, Dr. Arnaud Tessier, on the occasion of his 40th birthday.*

Over the years, nucleoside analogues emerged as powerful therapeutic agents for the treatment of viral infections and cancers[1], and also for gene-based therapeutics[2] such as antisense oligonucleotides, silence RNA (siRNA) and RNA interference (RNAi). In this context, numerous modifications have been made on the nucleoside scaffolds to evaluate the impact on their biological properties.

The aim of this microreview is to provide, to the non-specialist, an overview of the different strategies giving efficiently access to various nucleosides with modified sugar rings[3].

Anhydronucleosides

Introduction of a correctly configured substituent at C2’ and C3’ positions of the sugar ring in pyrimidine series could be achieved from their corresponding anhydronucleosides as discussed in this paragraph. It should be pointed out that the use of anhydronucleoside intermediates is not available to stereoselectively functionalize these positions in purine series, due to the lack of exocyclic oxygen which is essential for the formation of the ether linker.

2,3’-Anhydro derivative of thymidine **2** was prepared in 1990 by Czernecki[4] from thymidine **1** using an elegant one-pot transformation involving a sequential protection of the 5’OH as an ester function under Mitsunobu conditions followed by an intramolecular Mitsunobu reaction to achieve the 2,3’-cyclisation.

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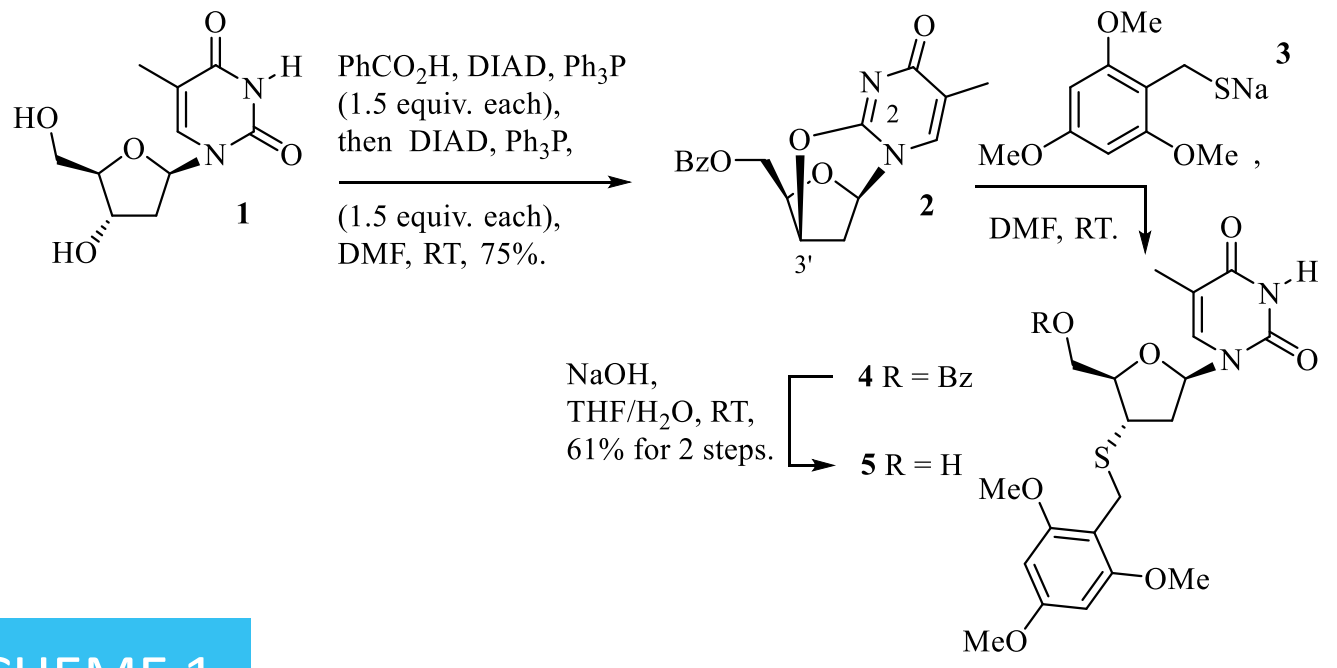
[1] E. De Clercq, *J. Med. Chem*. **2019**, *62*, 7322, and cited literature.
[2] R. Kole, A. R. Krainer, S. Altman, *Nat Rev Drug Discov*. **2012**, *11*, 125, and cited literature.
[3] For a recent review on this topic, see: S. Singh, D. Bhattarai, G. Veeraswamy, Y. Choi, K. Lee, *Curr. Org. Chem*. **2016**, *20*, 856.
[4] S. Czernecki, J.-M. Valéry, *Chem. Comm*. **1990**, 801.

This sequence has been recently applied by Bowman and coll[5]. to prepare the thioether derivative **5** as outlined in Scheme 1. Ring opening of the 2,3'-anhydro derivative of thymidine **2** was cleanly achieved with the sodium salt **3** of the labile acid 2,4,6-trimethoxybenzyl thiol with complete inversion.



SCHEME 1

As an alternative to previous Czernecki's procedure, treatment of mesylate **6** with only 1.06 equivalent of NaH provided the desired 2,3'-anhydro derivative **7** in 80% yield, as presented in Scheme 2.[6] In sharp contrast, when in this previous transformation 2.0 equivalents of NaH were added only the unsaturated nucleoside **11** was isolated in quantitative yield. In these conditions, the 2,3'-anhydro derivative **7** is formed *in situ*, and the excess of base promoted a base-mediated *trans*-elimination in which the uracilyloxy moiety behaved as nucleofuge to create the 2'-3' double bond in compound **11**. Azidation of 2,3'-anhydro derivative **7** with NaN_3 in DMF gave the expected azide **10** in only 26% yield. Alternatively, the 2,3'-anhydro derivative **7** was reacted in 1 M aqueous NaOH to furnish the inverted alcohol at C4' **8** in 93% yield. The inversion of configuration at C4' is the result of nucleophilic addition of the hydroxide ion at the 2-position of the pyrimidine in the 2,3'-anhydro derivative **7**. From this later alcohol **8**, classical mesylation followed by treatment with NaN_3 gave *via* a SN_2 displacement the targeted azide **10** in 97% yield.

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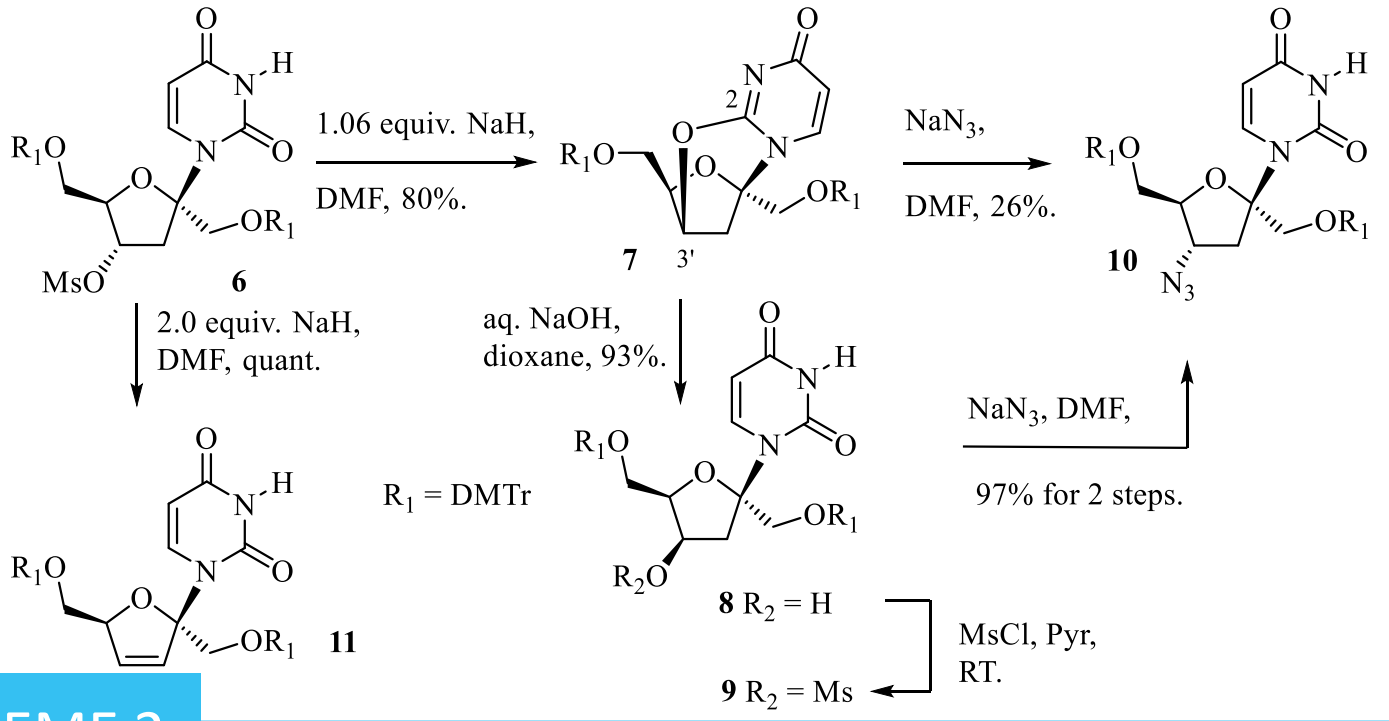
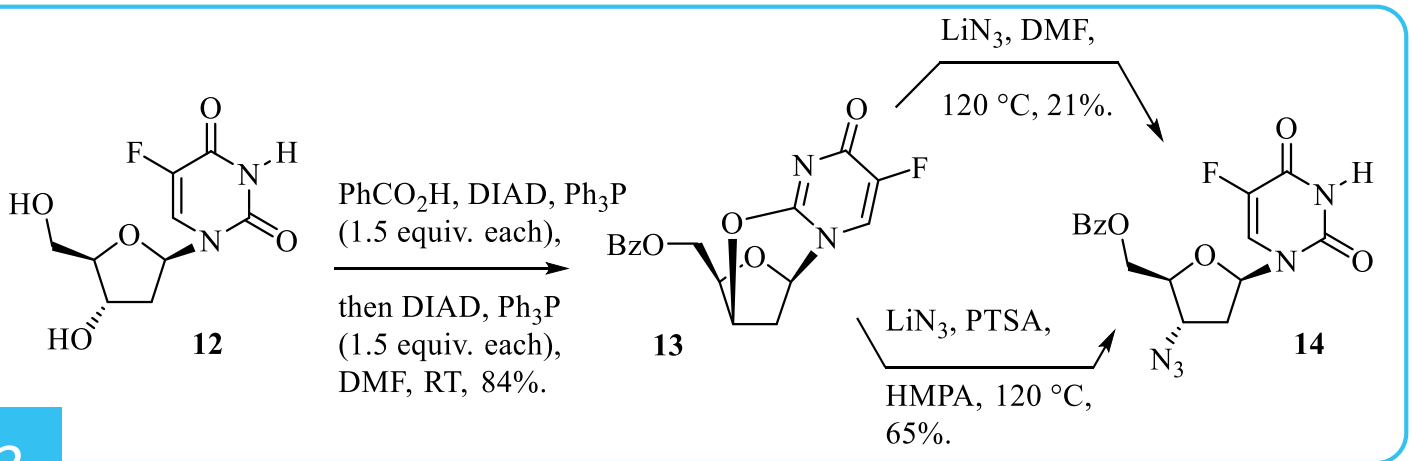
[5] S. Mavila, B. T. Worrell, H. R. Culver, T. M. Goldman, C. Wang, C.-H. Lim, D. W. Domaille, S. Pattanayak, M. K. McBride, C. B. Musgrave, C. N. Bowman, *J. Am. Chem. Soc*. **2018**, *140*, 13594.
[6] L. Kværnø, R. H. Wightman, J. Wengel, *J. Org. Chem*. **2001**, *66*, 5106.



SCHEME 2

To complete this discussion, it is worth to notice that the one-pot azidation of 2,3'-anhydro derivatives into their corresponding azides has been recently investigated. As outlined in Scheme 3, treatment of 2,3'-anhydro derivative **13** with LiN_3 in DMF at 120 °C gave the 3'-azido-5'-*O*-benzoyl-5-fluoro-2'-deoxyuridine **14** in only 21% yield, whereas the yield was increased up to 65% in HMPA containing 1.0 equivalent of PTSA at 120 °C.[7]

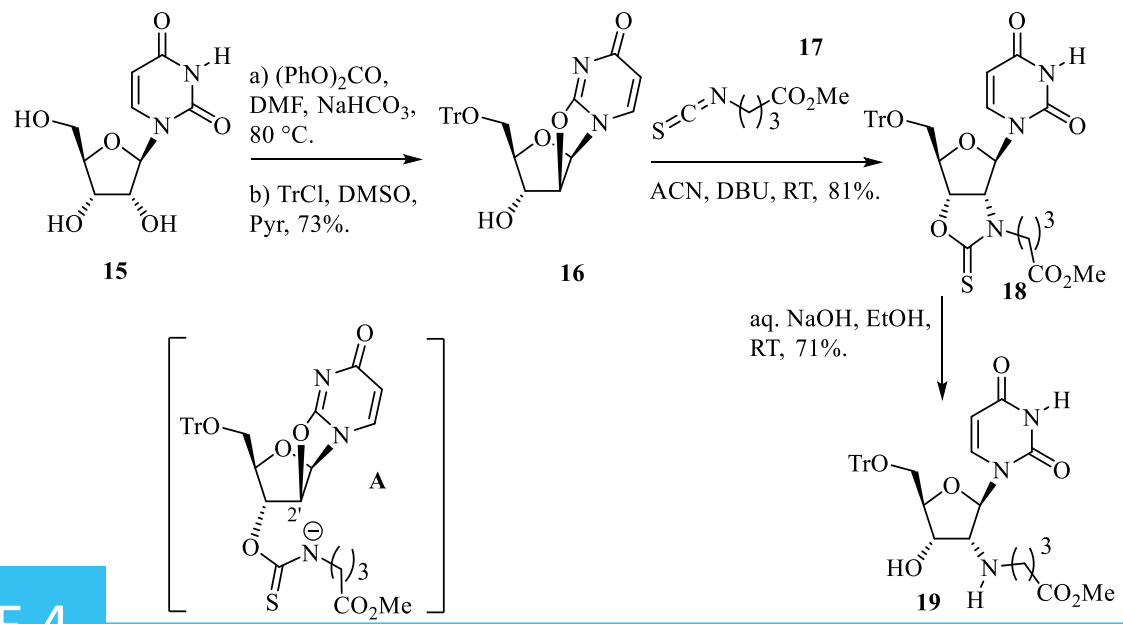


SCHEME 3

Recently, Walczak and coll. reported a versatile approach to 2'-amino-2'-deoxyuridine derivatives from 5'-*O*-trityl-2,2'-anhydrouridine **16** (readily prepared in 2 steps with 73% overall yield from uridine **15**, for a discussion concerning this transformation, see Scheme 6)

[7] M. Lewandowska, P. Ruszkowski, D. Baraniak, A. Czarnecka, N. Kleczewska , L. Celewicz, *Eur. J. Med. Chem*. 2013, *67*, 188.

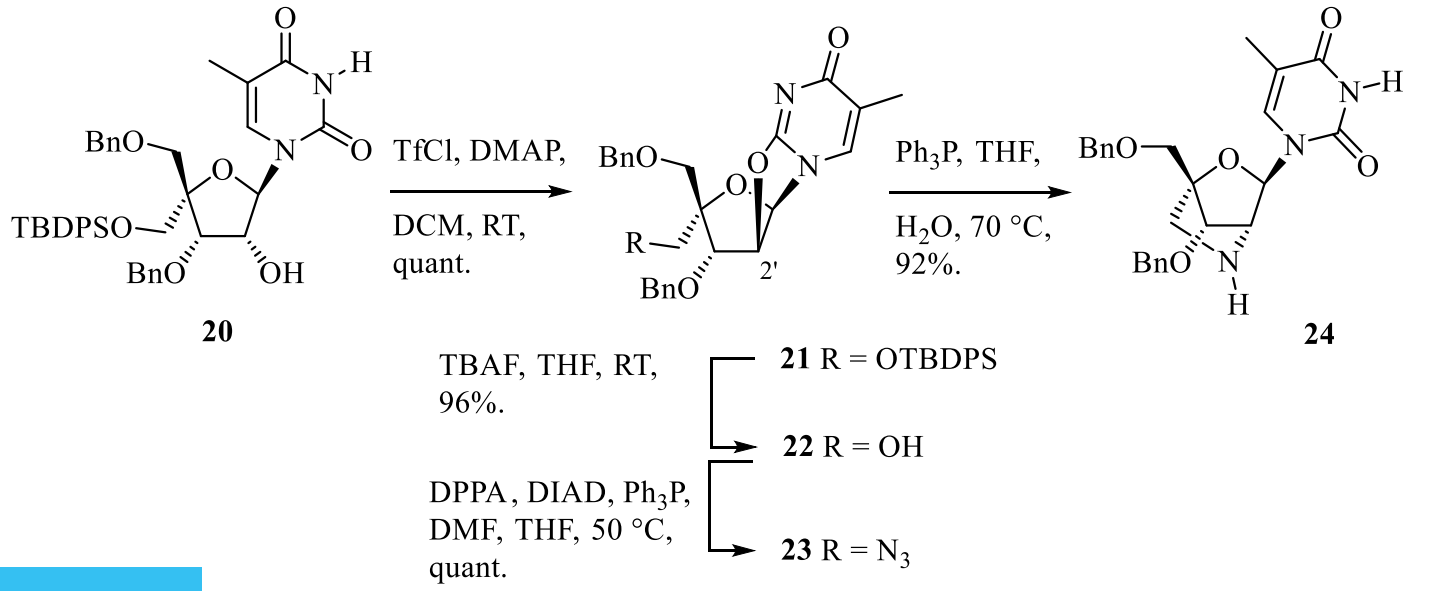
as outlined in Scheme 4.[8] The 2,2'-anhydrouridine **16** was reacted with isothiocyanate **17** in ACN in the presence of DBU as a base to furnish the expected oxazolethione derivative **18** in 81% yield. In this transformation, the free 3'-OH group of **16** reacted with the isothiocyanate **17** and the thiocarbamate formed *in situ* is subsequently deprotonated by DBU resulting in intramolecular nucleophilic attack on the carbon C2' of anhydrouridine intermediate **A**. Finally, the oxazolethione moiety of **18** was cleaved upon treatment with aqueous solution of NaOH to provide the desired 2'-amino-2'-deoxyuridine derivative **19** in 71% yield.



SCHEME 4

In the context of the preparation of new locked nucleic acids (LNA), a 2'-*N*,4'*C*-methylene bridged thymidine analogue **24** was synthetized as illustrated in Scheme 5 *via* the key 2,2'-anhydro intermediate **21**.[9] Compound **20** upon treatment with trifluoromethanesulfonyl chloride (TfCl) and DMAP in DCM yielded efficiently the fully protected 2,2'-anhydro derivative **21**. Reaction of this latter intermediate **21** with TBAF followed by azidation of the resulting primary alcohol **22** using a Mitsunobu reaction with diphenylphosphoryl azide (DPPA) afforded the desired azide **23** in 96% overall yield for the 3 steps. Finally, reduction of the azido group of **23** was achieved under Staudinger conditions and the resulting amino intermediate, by *in situ* intramolecular nucleophilic addition at C2' position, provided the targeted bridged nucleoside **24** in 92% yield.

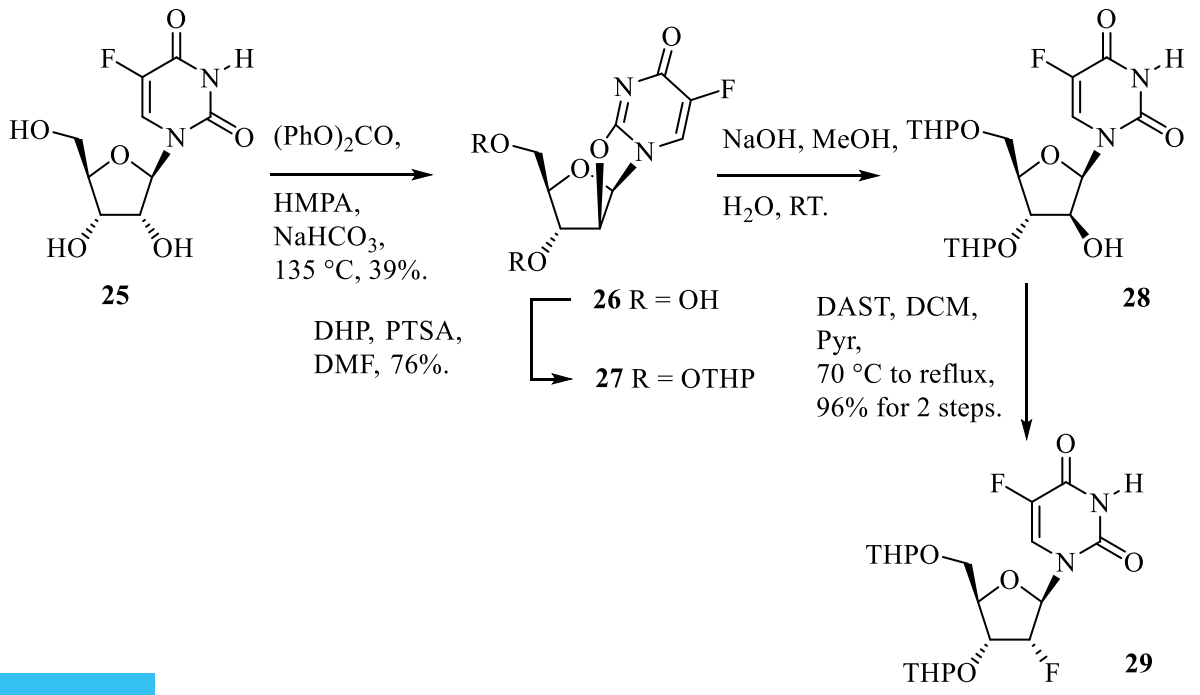
[8] A. Gondela, M. D. Tomczyk, L. Przypis, K. Z. Walczak, *Tetrahedron* **2016**, *72*, 5626.
[9] H. Sawamoto, Y. Arai, S. Yamakoshi, S. Obika, E. Kawanishi, *Org. Lett*. **2018**, 20, 1928.



SCHEME 5

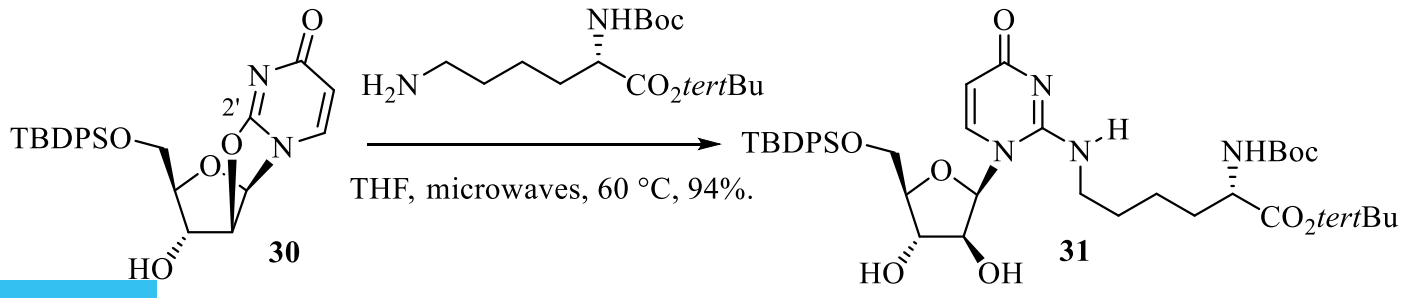
Another example of synthesis involving a 2,2'-anhydro derivative is presented in Scheme 6.[10] Treatment of 5-fluorouridine **25** with diphenylcarbonate in hot HMPA led to the formation of the 2,2'-anhydrouridine **26** in modest yield (39%). It should be pointed out that a more convenient and efficient procedure using diphenylcarbonate in DMF at 100 °C in the presence of catalytic amount of dry Na_2CO_3 has been published[11] leading to 2,2'-anhydrouridine **26** in 86% yield (3.32 g). Then, after protection of the alcohol functions of **26** as tetrahydropyranyl acetal (THP), cleavage of the anhydro ring of the resulting protected intermediate **27** was achieved under alkaline hydrolysis to give the *arabino*-nucleoside **28**. Finally, this latter compound **28** was treated with diethylaminosulfur trifluoride (DAST) to furnish the 2'-deoxy-2'-fluoro nucleoside **29** in good overall yield.

[10] J. Shi, J. Du, T. Ma, K. W. Pankiewicz, S. E. Patterson, P. M. Tharnish, T. R. McBrayer, L. J. Stuyver, M. J. Otto, C. K. Chu, R. F. Schinazi, K. A. Watanabe, *Bioorg. Med. Chem*. **2005**, *13*, 1641.
[11] J. Roivainen, I. A. Mikhailopulo, H. Eickmeier, H. Reuter, *Nucleos. Nucleot. Nucleic Acids* **2007**, *26*, 1015.



SCHEME 6

To complete this previous strategy, it should be pointed out that the tendency of some nucleophiles to attack at the 2-position of the pyrimidine moiety in 2,2'-anhydro derivatives has been recently exploited by Sweeney and coll. in the preparation of various *arabino-iso*cytosine nucleoside derivatives such as **31**, as reported in Scheme 7.[12]

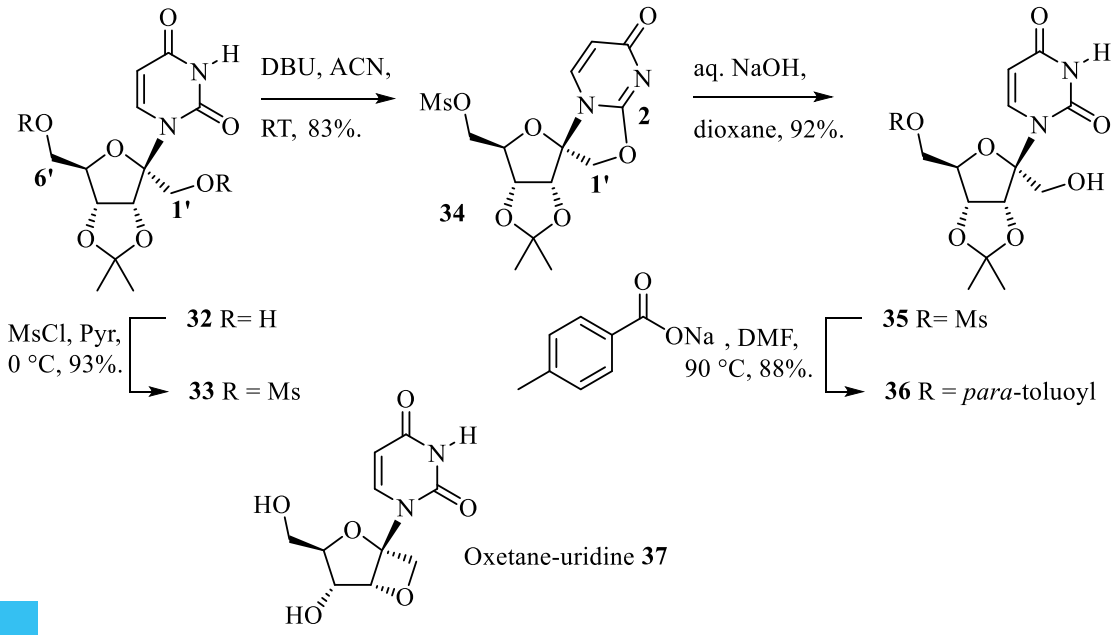


SCHEME 7

To end this session, several points should be discussed about the chemistry of anhydronucleosides. To the best of our knowledge, only one example of 2,1'-anhydro nucleoside **34**[13] has been reported in the literature as a building block in the synthesis of oxetane-nucleoside uridine derivative **37** (see Scheme 8). In this work, treatment of the 1',6'-*bis*-mesylate derivative **33** (prepared by classical mesylation of the corresponding diol **32**) with DBU provided the formation of the 2,1'-anhydro nucleoside **34** in 83% yield, in which the 5-

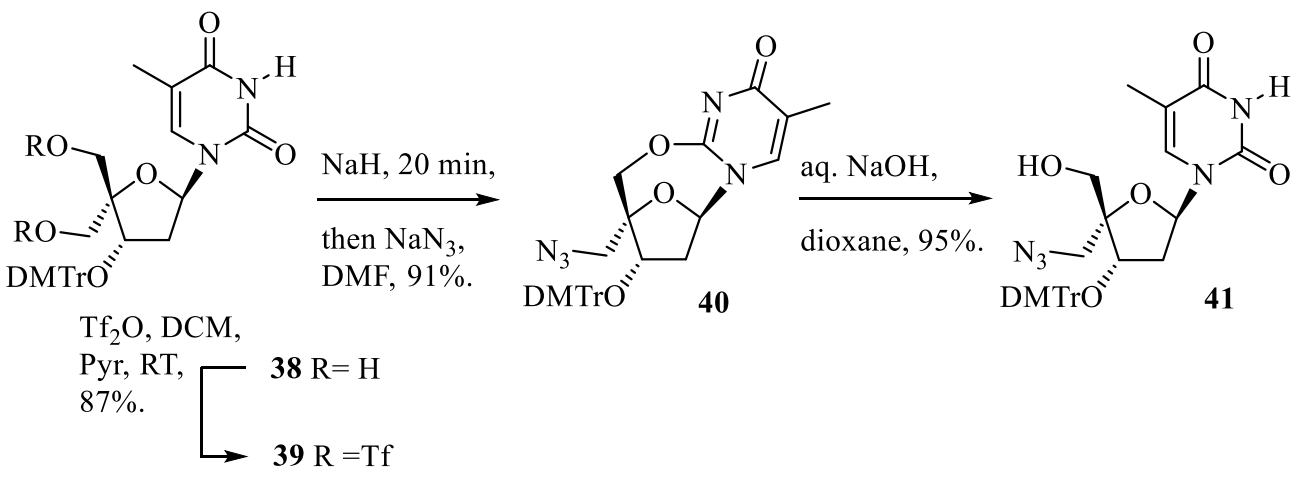
[12] J. B. Sweeney, P. A. Bethel, D. M. Gill, A. M. Ochocinska, E. J. Walsh, S. M. Walton, *Org. Lett.* **2019**, *21*, 2004.
[13] In this example, numbering convention for the psicofuranose ring is used.

membered spirocyclic ring is thermodynamically preferred over the corresponding 7-membered 2,6'-anhydro derivative (not shown). Then, the ring opening of the 2,1'-anhydro moiety of **34** was carried out in aqueous NaOH to provide the intermediate **35** which was treated with sodium *para*-methylbenzoate to promote the displacement of the mesylate at C6' leading to the key intermediate **36** in 81% overall yield for the 2 steps. From **32**, this sequence should be regarded as an orthogonal protection strategy of alcohol functions at C6' *versus* C1'.



SCHEME 8

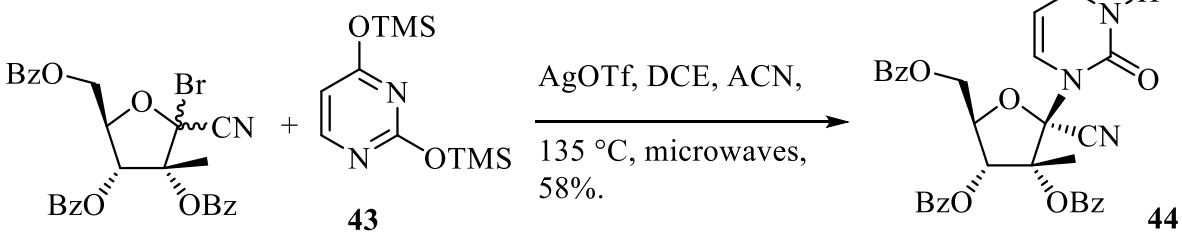
A similar strategy was applied in the preparation of the 4′-*C*-azidomethyl thymidine **41** from its 4′-*C*-hydroxymethyl precursor **38** *via* the 2,5′-anhydronucleoside intermediate **40** (see Scheme 9).[14]



SCHEME 9

[14] A. Kiviniemi, P. Virta, H. Lönnberg, *Bioconjugate Chem*. **2008**, *19*, 1726.

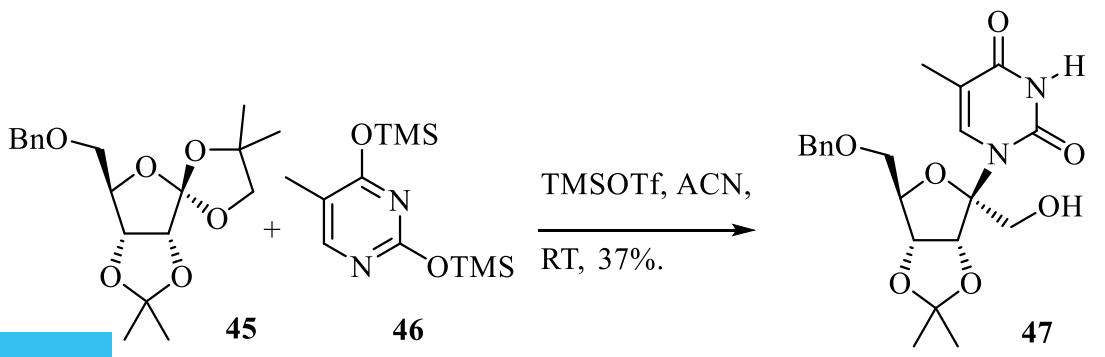
An efficient and stereocontrolled synthesis of 1'-*C*-cyano-2'-*C*-methyl pyrimidine nucleosides has been recently published by Mish and coll. from Gilead Sciences, as outlined in Scheme 10.[15] The 1'-bromo ribosyl donor **42** (prepared from the corresponding ribofuranosyl cyanide by photobromination using *N*-bromosuccinimide as a radical source)[16] was engaged in coupling reaction with the persilylated uridine **43** using AgOTf as promoter upon heating in a mixture of DCE and ACN under microwaves activation providing the 1'-*C*-CN-nucleoside pyrimidine **44** in 58% yield. Due to the anchimeric stabilization of the oxonium intermediate by the 2'-benzoate substituent only the β-anomer **44** was detected in the crude mixture.



SCHEME 10

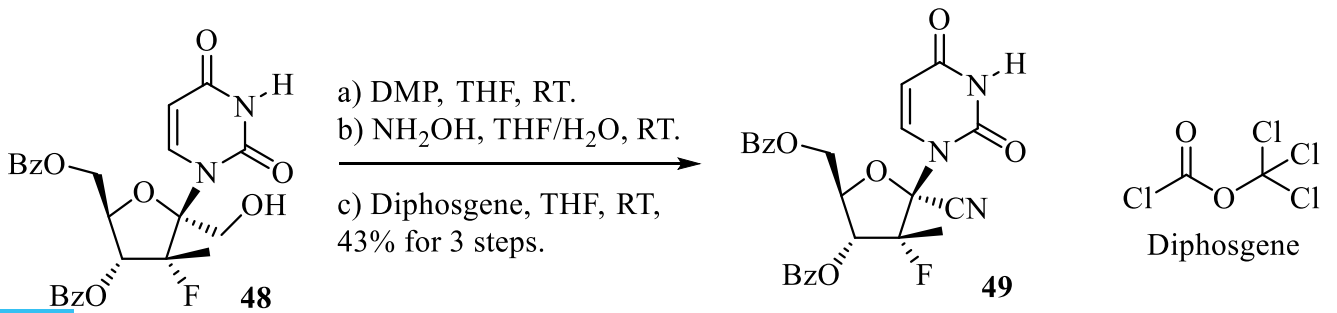
In the other hand, 1,2:3,4-di-*O*-isopropylidene-β-psicofuranose **45** (readily prepared from D-fructose following known procedures)[17] has been used as a versatile chiral building block to construct various modified nucleosides such as 1'*C*-derivatives as shown in Scheme 11.[18] This protected sugar **45** was directly coupled in ACN with persilylated thymine **46**, in the presence of TMSOTf as Lewis acid to provide the protected psiconucleosides **47** as an anomeric mixture in 1/1 ratio. The desired β-anomer **47** was isolated in 37% yield after separation by silica gel chromatography.

[15] M. R. Mish, A. Cho, T. Kirschberg, J. Xu, C. S. Zonte, M. Fenaux, Y. Park, D. Babusis, J. Y. Feng, A. S. Ray, C. U. Kim, *Bioorg. Med. Chem. Lett*. **2014**, *24*, 3092.
[16] V. Uteza, G.-R. Chen. J. Le Quan Tuoi, G. Descotes, B. Fenet, A. Gmuiller, *Tetrahedron* **1993**, *49*, 8579.
[17] E. J. Prinsbe, J. Smejkal, J. P. H. Verheyden, J. G. Moffatt, *J. Org. Chem*. **1976**, *41*, 1836.
[18] D. Honcharenko, O. P. Varghese, O. Plashkevych, J. Barman, J. Chattopadhyaya, *J. Org. Chem*. **2006**, *71*, 299.



SCHEME 11

It should be pointed out that such psiconucleosides could be used as intermediates in the synthesis of 1'-*C*-cyano-pyrimidine nucleosides as outlined in Scheme 12.[19] In this example, the hydroxymethyl group of **48** was converted to the desired nitrile **49** in a 3 step-sequence starting by a mild oxidation with Dess-Martin periodinane reagent (DMP) followed by treatment of the resulting aldehyde with hydroxylamine to provide the corresponding oxime which was finally dehydrated with diphosgene.



SCHEME 12

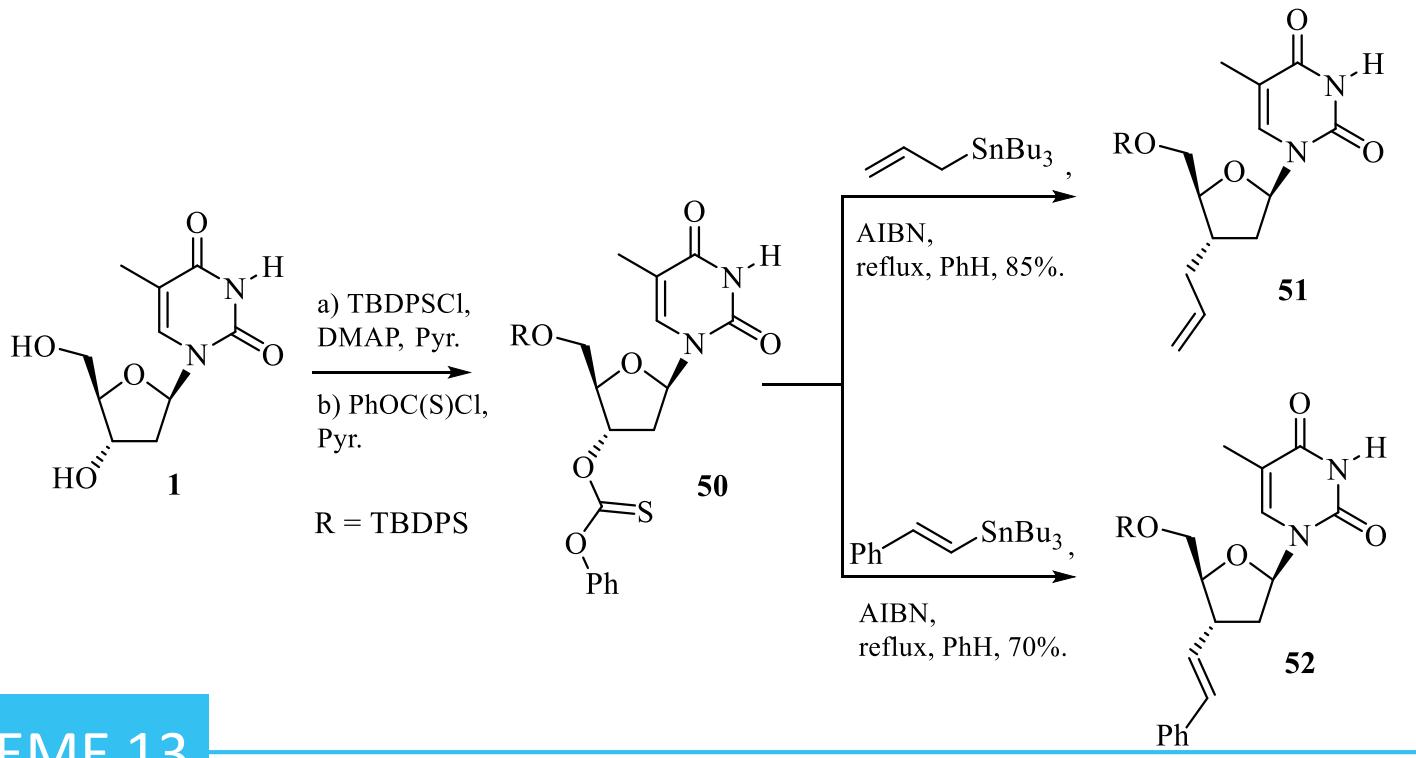
Free radical chemistry: 3'-*C*- and 2'-*C*-nucleosides.

Over the years, free-radical chemistry has become an attractive tool for the synthesis of nucleoside derivatives, due to mild reaction conditions, high levels of regio-, stereo- and chemoselectivity as well as excellent functional group tolerance.

Numerous 3'-α-*C*-branched nucleoside derivatives[20] have been obtained from their corresponding 3'-α-*C*-allyl- or 3'-α-*C*-styryl-precursors **51** and **52**, which were prepared from the easily accessible thiocarbonate **50**, obtained in 2 steps from thymidine **1** by selective protection of the primary alcohol followed by treatment of the remaining secondary alcohol

[19] T. A. Kirschberg, M. R. Mish, L. Zhang, N. H. Squires, K.-Y. Wang, A. Cho, J. Y. Feng, M. Fenaux, D. Babusis, Y. Park, A. S. Ray, C. U. Kim, *Bioorg. Med. Chem. Lett*. **2015**, *25*, 1040.
[20] For recent applications, see: (a) S. A. S. Audat, C. Trzasko Love, B. A. S. Al-Oudat, A. C. Bryant-Friedrich, *J. Org. Chem.* **2012**, *77*, 3829. (b) N.-S. Li, J. A. Piccirilli, *J. Org. Chem.* **2007**, *72*, 1198. (c) I. Van Daele, H. Munier-Lehmann, M. Froeyen, J. Balzarini, S. Van Calenbergh, *J. Med. Chem*. **2007**, *50*, 5281.

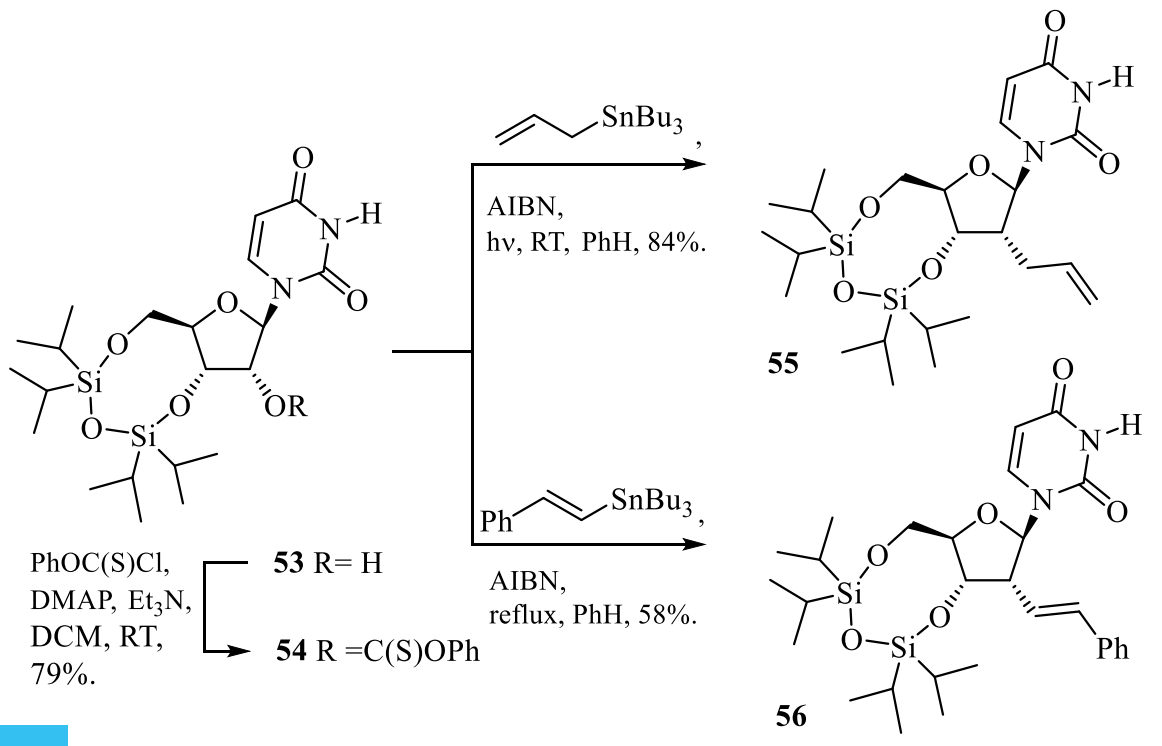
with the phenyl chlorothioformate (see Scheme 13). The radical reaction of **50** with either allyltributyltin or with β-tributylstannylstyrene was initiated by 2,2′-azobis(2-methylpropionitrile) (AIBN) providing the corresponding 3'-α-*C*-allyl- or 3'-α-*C*-styryl-adducts **51** and **52** in 85% and 70% yields, respectively. It is worth noting that these reactions resulted in the exclusive formation of the 3'-α-*C*-diastereoisomers **51**[21] and **52**[22] due to the stereoselective addition of the organotin reagents from the less hindered α-face of the 3'-carbon-centered radical intermediate.



SCHEME 13

This strategy has been applied with success to the preparation of 2'-α-*C*-allyl- or 2'-α-*C*-styryl-derivatives **55** and **56**, as reported in Scheme 14.[23,24]

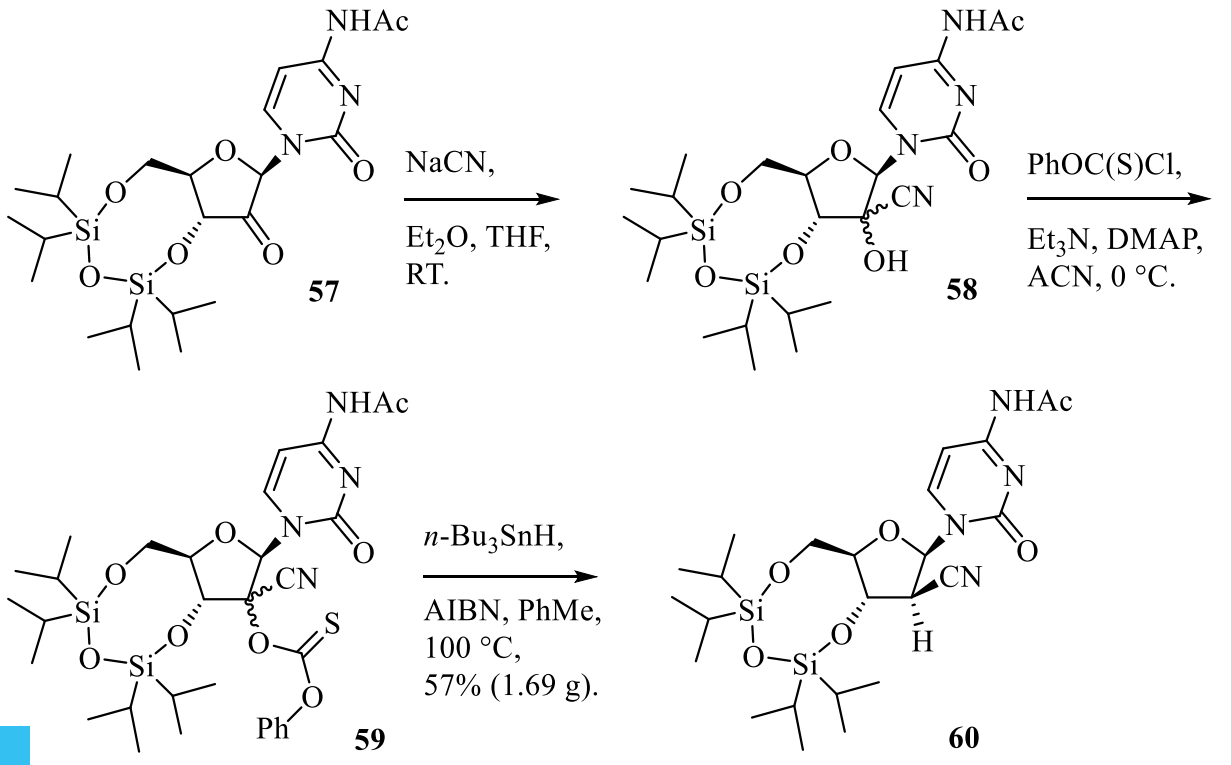
[21] A. De Mesmaeker, J. Lebreton, A. Waldner, S. M. Freier, V. Fritsch, R. M. Wolf, *Synlett*, **1993**, 733.
[22] Y. S. Sanghvi, R. Bharadwaj, F. Debart, A. D. Mesmaeker, *Synthesis* **1994**, 1163.
[23] A. De Mesmaeker J. Lebreton, P. Hoffmann, S. M. Freier, *Synlett* **1993**, 677.
[24] For recent applications, see: (a) D. Sun, H. Xu, S. R. Wijerathna, C. Dealwis, R. E. Lee, *ChemMedChem* **2009**, *4*, 1649. (b) See reference 20(b).



SCHEME 14

An interesting application of the Barton-McCombie radical deoxygenation reaction appeared in the context of the synthesis of protected 2'-*C*-Cyano-2'-deoxy-l-β-D-*arabino*furanosylcytosine **60**, as outlined in Scheme 15.[25,26]In this context, the 2'-keto nucleoside **57** was reacted with NaCN in a mixture of aqueous $NaHCO_3$ solution and ether, and the resulting isomeric mixture of cyanohydrin **58** was treated with phenyl chlorothionoformate to give the corresponding thiocarbonate **59** which was finally subjected to radical deoxygenation conditions. After purification, the protected 2'-*C*-Cyano-2'-deoxy-l-β-D-*arabino*furanosylcytosine **60** was isolated as a unique diastereoisomer in 57% overall yield from the 2'-keto nucleoside **59**. As previously discussed, the hydrogen atom came from the less hindered, α-face of the planar 2'-carbon-centered radical intermediate, opposite to the bulky protected nucleobase.

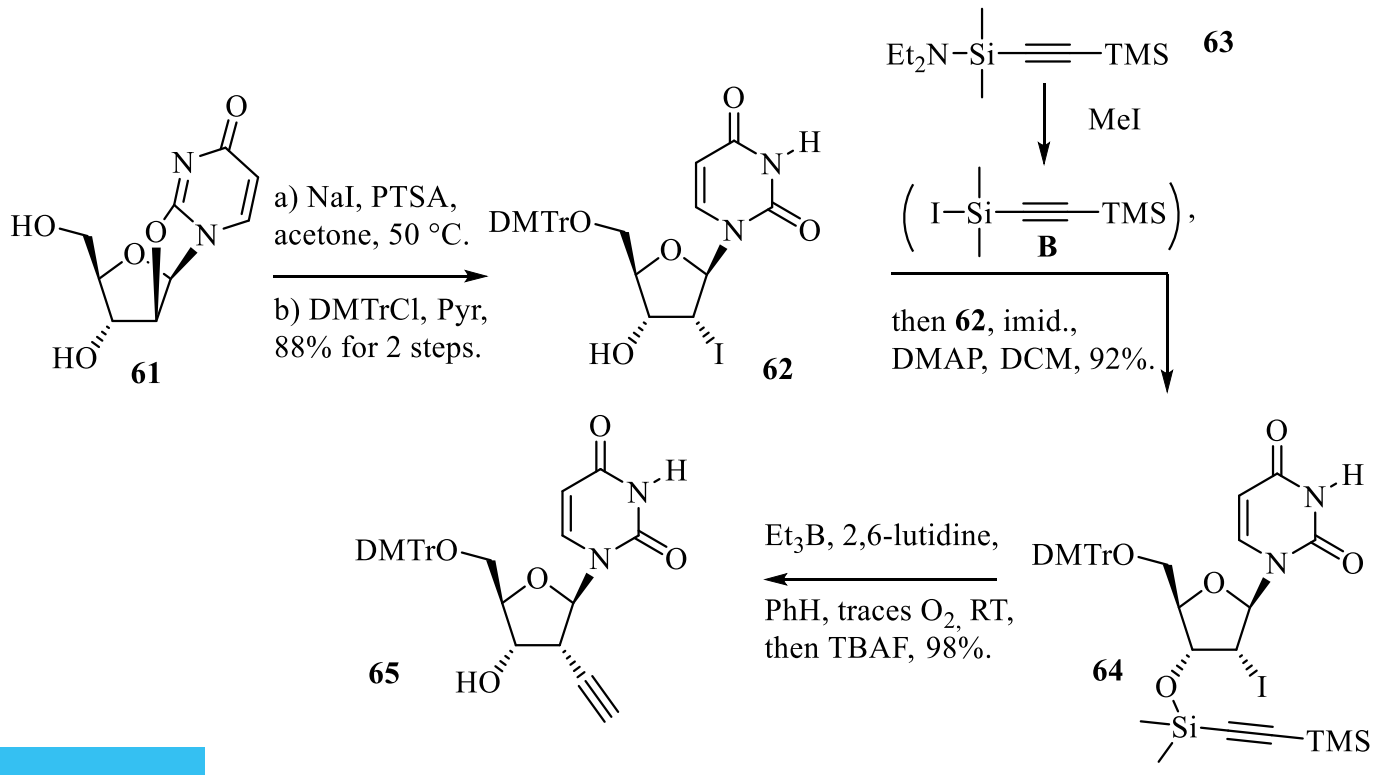
[25] A. Azuma, Y. Nakajima, N. Nishizono, N. Minakawa, M. Suzuki1 K. Hanaoka, T. Kobayashi, M. Tanaka, T. Sasaki, A. Matsuda, *J. Med. Chem*. **1993**, *36*, 4183.
[26] For a recent application, see: S. Ichikawa, M. Otawa, Y. Teishikata, K. Yamada, M. Fujimuro, H. Yokosawa, A. Matsuda, *Nucleic Acids Symposium Series* **2009**, *53*, 95.



SCHEME 15

More recently, based on an intramolecular regio- and stereoselective radical cyclisation reaction using a silicon-containing tether, as temporary link, Lovett and coll. published an efficient preparation of 2′-ethynyl-2′-deoxyuridine **65** and 2′-ethynyl-2′-deoxyadenosine (not shown) as reported in Scheme 16.[27] It should be noted that this elegant strategy was initially developed by Shuto and coll.[28] From the cyclouridine **61**, the 5'-*O*-protected 2'-iodo-2'-deoxyuridine **62** was prepared by nucleophilic ring-opening reaction at the 2'-position of 2,2'-anhydrouridine by treatment with NaI followed by selective protection of the primary alcohol. Treatment of diethylaminodimethylsilane **63** with MeI led to the formation of the unstable iododimethylsilane intermediate **B** which was then directly reacted with the 2'-iodo-2'-deoxyuridine **62** to afford the protected 2′-iodonucleoside **64** in 92% yield. This latter ethynyldimethylsilyl derivative **64** was directly engaged in the atom-transfer radical cyclization with Et_3B in the presence of traces of O_2 in benzene at RT, followed by treatment with TBAF to provide in 98% yield (1.56 g) the expected 2′-ethynyl-2′-deoxyuridine **65**.

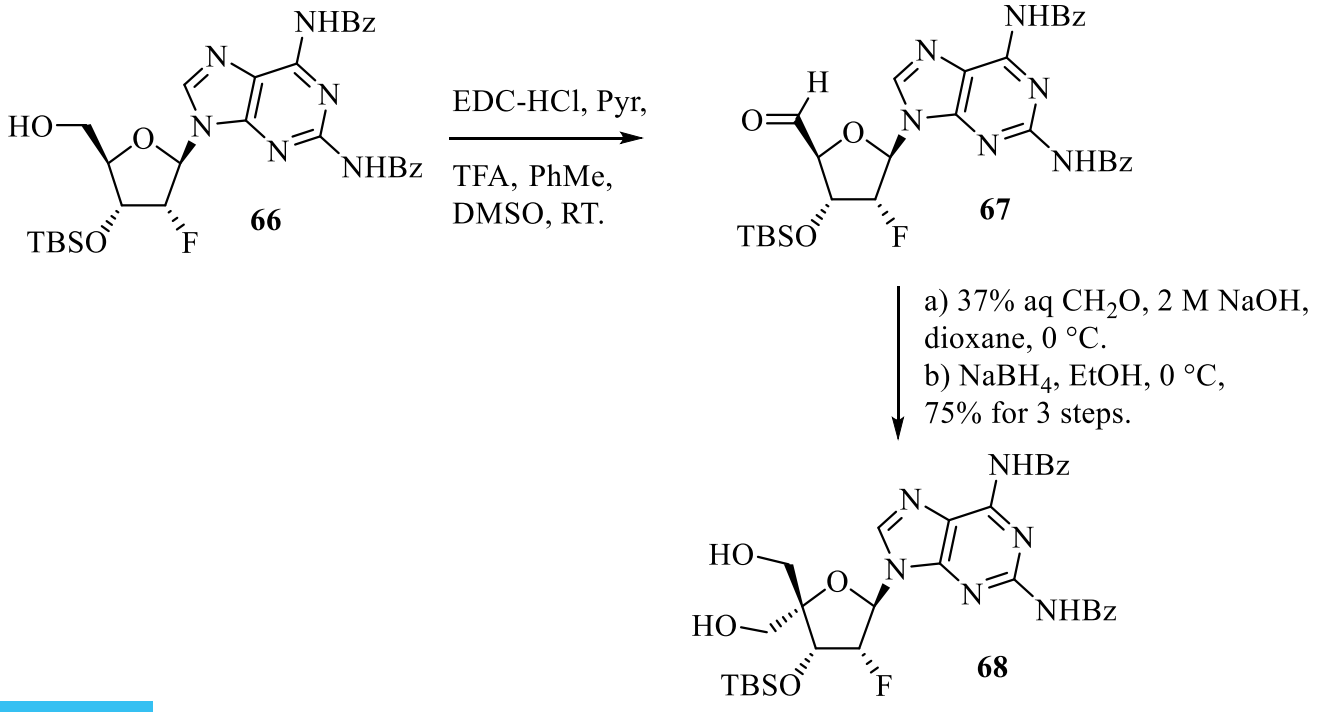
[27] M. M. Haugland, A. H. El-Sagheer, R. J. Porter, J. Peña, T. Brown, E. A. Anderson, J. E. Lovett, *J. Am. Chem. Soc.* **2016**, *138*, 9069.
[28] M. Sukeda, S. Ichikawa, A. Matsuda, S. Shuto, *Angew. Chem. Int. Ed.* **2002**, *41*, 4748.



SCHEME 16

One of the most popular method for the preparation of 4'-*C*-branched nucleoside derivatives is based on an aldolization – reduction sequence from the corresponding 5'-formyl nucleosides, as presented in the Scheme 17.[29] The fluoronucleoside **66** was oxidized to the aldehyde **67** using the Pfitzner-Moffatt protocol, and was then subjected to an aldol reaction with formaldehyde leading to the corresponding aldol which was reduced with $NaBH_4$ to provide the desired diol derivative **68** in 75% overall yield. It should be pointed out that this aldol reaction followed by reduction is more efficient on nucleosides with base-labile protecting groups than the original Cannizzaro conditions.[30]

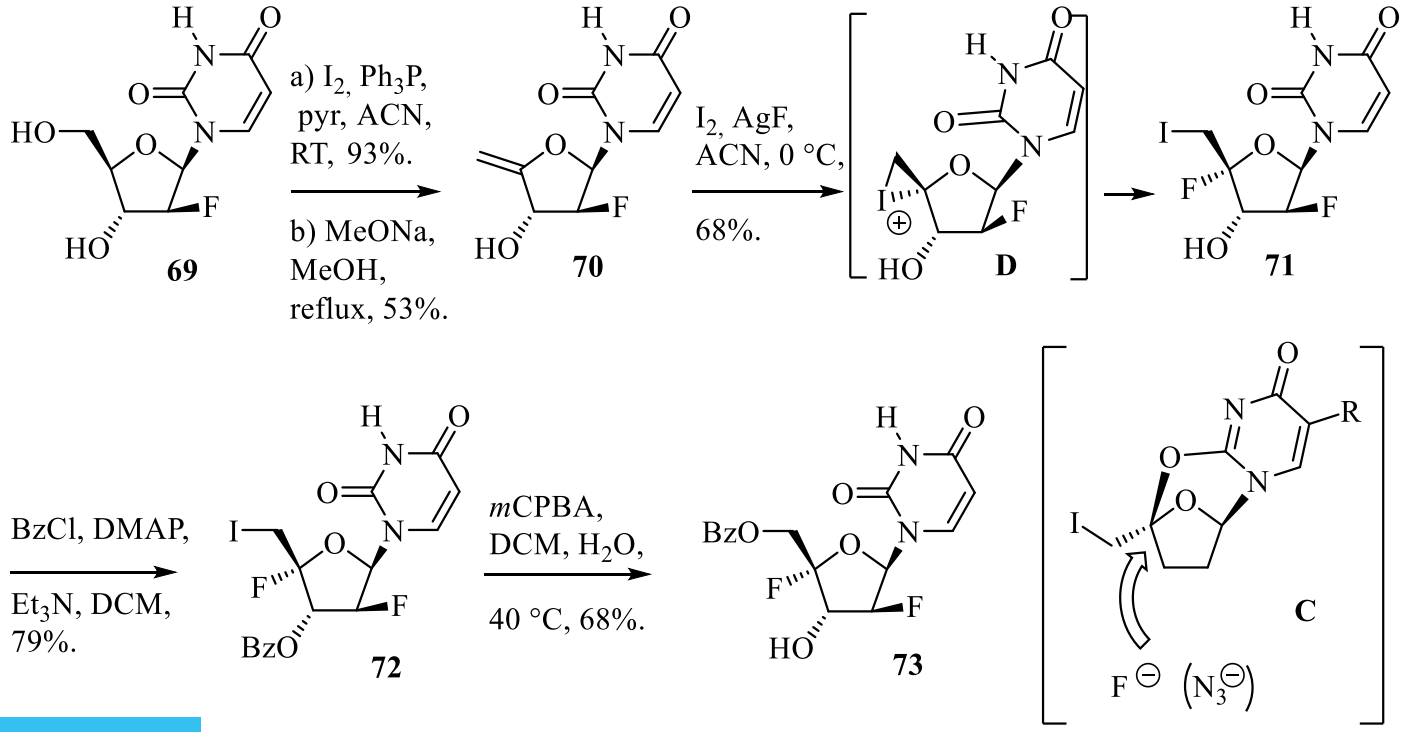
[29] R. Mackman *and al*., *Bioorg*. *Med. Chem. Lett*. **2015**, *25*, 2484.
[30] M. Nomura, S. Shuto, M. Tanaka, T. Sasaki, S. Mori, S. Shigeta, A. Matsuda, *J. Med. Chem*. **1999**, *42*, 2901.



SCHEME 17

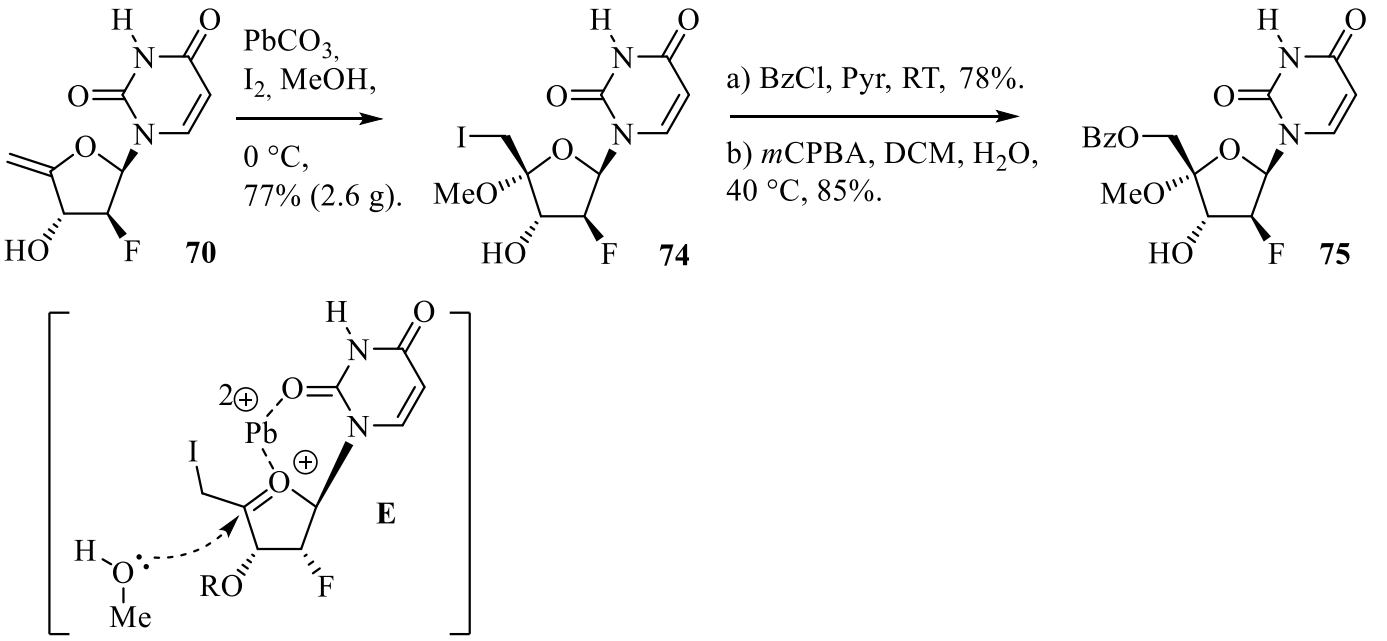
As illustrated in Scheme 18,[31] an elegant and efficient access to C4'-modified nucleosides has been developed from their corresponding 4',5'-unsaturated derivatives *via* the postulated 2,4'-anhydronucleoside **C** which was subjected to nucleophiles such as fluoride (or azide, not shown) leading in this example to 5'-iodo-4'-fluoro nucleoside **71**. Reaction of 2'-fluoro-uridine **69** with PPh_3 and iodine gave the corresponding 5'-iodo intermediate which was treated with NaOMe to provide the 4',5'-olefinic nucleoside **70** in 53% overall yield. Then, the 4'-fluoration of **70** was accomplished by mixing first AgF and iodine to generate *in situ* iodine fluoride (IF) and then addition of the substrate (**70**) resulted in the formation of the 5'-iodo-4'-fluoro nucleoside **71** as a unique diastereoisomer in 68% yield. In this latter transformation, the C2 carbonyl of the uracil opened the iodonium intermediate **D** leading to the 2,4'-anhydronucleoside such as **C** which upon attack by fluoride afforded the desired nucleoside **71**. Finally from this latter intermediate **71**, benzoylation of the remaining secondary alcohol gave **72** and treatment with mCPBA led to the displacement of iodine as hypoiodite with concomitant migration of the 3'-benzoyl ester to the 5' position affording the desired difluorouridine derivative **73** in 54% overall yield.

[31] S. Martínez-Montero, G. F. Deleavey, A. Dierker-Viik, P. Lindovska, T. Ilina, G. Portella, M. Orozco, M. A. Parniak, C. González, M. J. Damha, *J. Org. Chem*. **2015**, *80*, 3083.



SCHEME 18

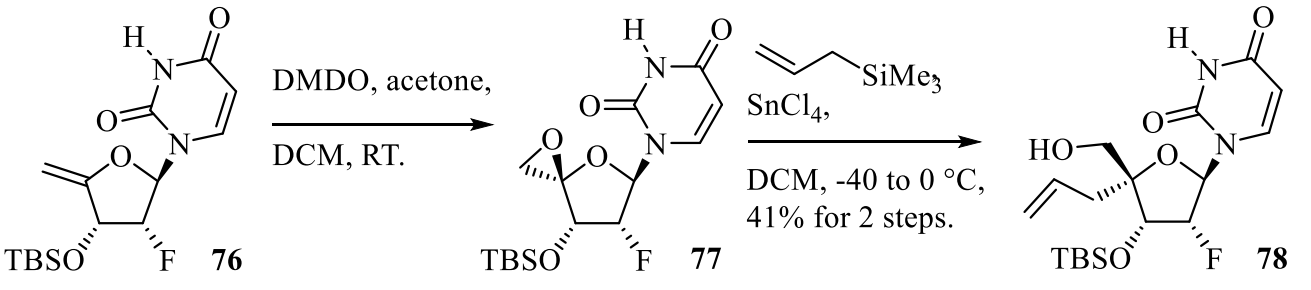
From a similar strategy, treatment of the 4',5'-unsaturated nucleoside **70** with iodine in the presence of $PbCO_3$ in methanol gave exclusively the 5'-iodo-C4'-α-MeO nucleoside **74** in 77% yield as reported in Scheme 19.[32] It has been postulated that the previous iodonium intermediate **D** (see Scheme 18) provided the oxonium intermediate **E** in which the coordination induced by Pb^{2+} blocked the β face of the nucleoside forcing the MeOH to attack from the opposite face.



SCHEME 19

[32] E. Malek-Adamian, M. B. Patrascu, S. K. Jana, S. Martínez-Montero, N. Moitessier, M. J. Damha, *J. Org. Chem.* **2018**, *83*, 9839.

A stereoselective synthesis of the 4'-α-*C*-allyl substituted fluoro uridine **78** has been recently published based on $SnCl_4$-promoted ring opening of the 4',5'-epoxy nucleoside **77** with allyltrimethylsilane as outlined in Scheme 20.[33,34] Diastereoselective epoxidation of **76** with dimethyldioxirane (DMDO) provided the epoxide **77** which was then treated with allylsilane using an excess of $SnCl_4$ to furnish the expected 4'-α-*C*-allyl substituted fluoro uridine **78** in 41% overall yield.



SCHEME 20

Conclusion

Despite decades of intense research in the field of nucleosides, there is still room for innovation!

I would like to thank Johann Leblanc (Université de Nantes) for fruitful discussions and comments. I also warmly thank my colleagues, Dr. Sylvie Archambaud, Dr. Aude Vibert, Dr. Maud Antoine and Dr. Julien Farard from AtlanChim Pharma for their valuable suggestions during the preparation of this manuscript.

[33] G. Wang, L. Beigelman *and al.*, *J. Med. Chem*. **2015**, *58*, 1862.

[34] For the seminal reference concerning this methodology, see: K. Haraguchi, S. Takeda, H. Tanaka, *Org. Lett.* **2003**, *5*, 1399.