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Dual-Face Nucleoside Scaffold Featuring a Stereogenic All-Carbon Quaternary Center. Intramolecular Silicon Tethered Group-Transfer Reaction

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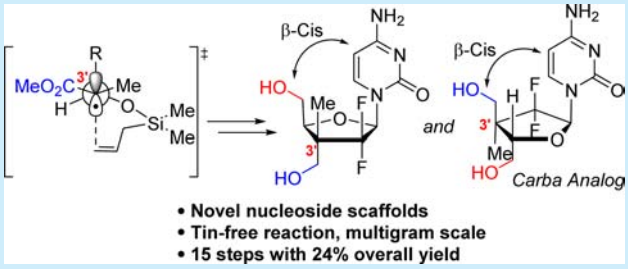
Supporting Information

ABSTRACT: The design of a novel nucleoside scaffold that exhibits an all-carbon quaternary center is reported. This allows for both α- and β-anomers of a given 2′-deoxy-2′,2′-difluoro nucleoside analog (NA) to have potential biological activity. Using an intramolecular atom-transfer reaction, an all-carbon quaternary center was obtained without the use of heavy metals and/or harsh conditions. The chemistry developed is efficient, easily scalable and leads to novel libraries of molecules.



Phosphorylated nucleosides are the building blocks of DNA and RNA. During their generation, a series of enzymes participate in the activation of the nucleosides.[1] These enzymes exhibit structurally different nucleoside or nucleotide binding domains that recognize specific ligands or substrates in a given conformation.[2] These observations have been supported by biophysical studies (X-ray) and the synthesis and biological evaluation of locked nucleosides.[3] Nucleoside analogs[4] (NAs) compete with their endogenous counterparts and alter functions of their target enzymes. For example, Gemcitabine is one of the most important chemotherapeutic agents (Figure 1).[5] The triphosphorylated 2′-deoxy-2′,2′-difluoro β-anomer, when incorporated in the DNA growing chain of a dividing cancerous cell, leads ultimately to apoptosis.[6] However, the α-anomer, as for all D-nucleoside analogs, is inactive.

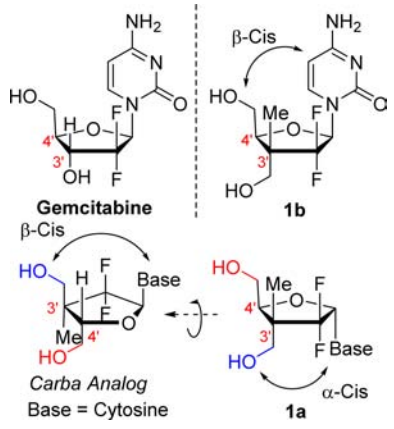


Figure 1. Gemcitabine and dual-face nucleoside scaffolds.

The present study stems from two of our research programs: the synthesis of nucleoside analogs[7] and the use of free radical chemistry for the synthesis of tertiary or quaternary stereocenters on acyclic molecules.[8] The new molecules synthesized (by varying the nucleobase and introducing various prodrugs and lipophilic carriers) bear an all-carbon quaternary center, and a hydroxymethyl at C3′ of the scaffold as illustrated in Figure 1. We hypothesized that the generated α-anomers **1a** could also be biologically relevant since the C3′ hydroxymethyl at the quaternary center has a *cis* relationship with the nucleobase at C1′. This intriguing feature is preferably visualized when the α-anomer **1a** is rotated, hence unveiling a carba-analog. Indeed, the hydroxyl group at the quaternary center of the carba-analog is now formerly at C5′. The conformations of **1a** or **1b** are also likely to be different than other nucleoside analogs due to additional steric effects at C3′. The absence of stereoelectronic effects at C3′, originating from the replacement of the hydroxyl by an all-carbon quaternary center, and the creation of a novel network of hydroxyl bonds are additional factors influencing the preferred conformations.

We have been previously studying hydrogen transfer reactions of tertiary carbon-centered radicals,[9] flanked by an ester and a stereogenic center bearing a heteroatom. These radicals originate from the homolytic cleavage of tertiary bromides obtained from a Mukaiyama aldol reaction involving an E/Z mixture of tetrasubstituted enoxysilanes. This reaction

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sequence was used successfully toward the synthesis of polypropionates as well as substituted tetrahydropyran motifs.[10] As illustrated in Figure 2, these radicals can be diastereoselectively allylated using the allyltributylstannane reagent.[11] The 2,3-*anti* relative stereochemistry is obtained when a bidentate Lewis acid (e.g., Me_3Al) is used. Embedding the carbon-centered radical in a temporary ring (endocyclic effect)[11c] leads to the low energy transition state **A**, where the allylstannane is delivered from the top face of the molecule. Importantly, we showed that group-transfer reactions could also be used to create quaternary centers.[12] Using allyltrimethylsilane in the presence of Me_3Al, the reaction gave similar yields and ratios in favor of the 2,3-*anti* product. Avoiding the use of tin was an additional benefit in this methodology.

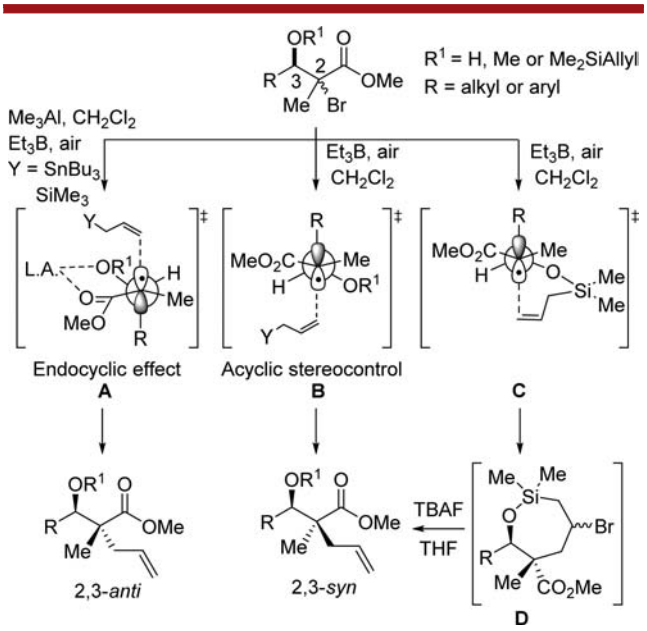


Figure 2. Proposed transition states for intramolecular and intermolecular delivery.

The 2,3-*syn* product was obtained in the absence of a Lewis acid (acyclic stereocontrol) using the allyltributylstannane reagent. Minimization of the allylic 1,3 strain, generated by the sp^2 character of the radical delocalization in the ester, and minimization of the dipole−dipole effect between the β-carbon oxygen bond and the ester leads to transition state **B**. The reagent is delivered from the bottom face of the radical leading to the 2,3-*syn* product.[10c] In this case, however, the allyltrimethylsilane proved to be less reactive and led to lower yields.[11a,12,13] An alternative approach was therefore developed, whereby the radical acceptor is tethered to the oxygen at C3. The intramolecular reaction following initiation of the radical chain led to the formation of a seven-membered silyloxy ether **D** (Figure 2) collapsing upon workup to give the 2,3-*syn* allylated product in good yield and ratio. The low energy transition state **C** minimizes both the allylic-1,3 strain and dipole−dipole interactions resulting in the radical being located on the bottom face. Using these approaches, the stereochemistry of the quaternary center on acyclic precursors could be controlled.

We envisioned a retrosynthetic analysis where the desired 2′-deoxy-2′,2′-difluoro NAs **1** would come from acyclic precursors (Figure 3). NAs **1a** and **1b** would be obtained from a Vorbrüggen coupling between the nucleobase and lactol **2a,b**.

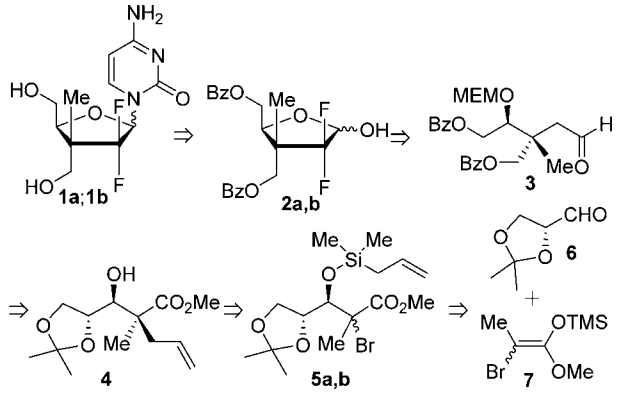
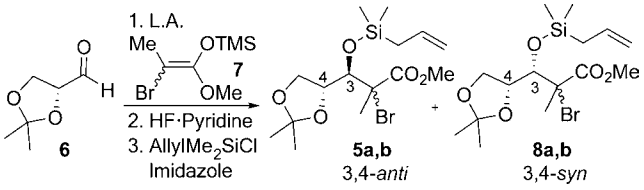


Figure 3. Retrosynthetic analysis of NAs **1a,b**.

The latter would be obtained in a one-pot synthesis from the difluorination/MEM-deprotection/cyclization of acyclic aldehyde **3**. Generation of the quaternary center would involve the silicon-tethered radical cyclization of **5a,b**. Radical precursors **5a,b** would be synthesized from the Mukaiyama coupling of 2,3-isopropylidene-D-glyceraldehyde **6** with a mixture of enoxysilanes **7**. An improved preparation of the latter is reported herein by increasing the O-silylated/C-silylated ratio and avoiding distillation.[14]

The required 3,4-*anti* relative stereochemistry suggested that the Mukaiyama aldol step should take place through a Felkin−Anh transition state. Unfortunately, the use of $BF_3{\cdot}OEt_2$ led to the degradation of aldehyde **6** most likely resulting from acetonide cleavage (Table 1; entry 1) and milder Lewis acids such as $Ti(OiPr)_3Cl$ were unsuccessful.

Table 1. Mukaiyama Aldolization Silicon-Tethered Radical Precursors



entry	L.A.[a]	ratio[b] (3,4-*anti*:3,4-*syn*)	yield[c]
1	$BF_3{\cdot}OEt_2$ (1 equiv)	degradation	N.D
2	$MgBr_2{\cdot}OEt_2$ (1 equiv)	11:1	80%
3	$MgBr_2{\cdot}OEt_2$ (0.1 equiv)	11:1	22%
4	ZnI_2 (0.75 equiv)	13:1	50%

[a]Reactions were performed with 1.5 equiv of enoxysilane **7** and a Lewis acid in CH_3CN (0.1 M) for 16 h at 0 °C. [b]Product ratios were determined by ^1H NMR analysis of a mixture of lactones after HCl workup (see Supporting Information for details). [c]Isolated yields over three steps.

Surprisingly, the 3,4-*anti* relationship was generated using bidentate Lewis acids such as $MgBr_2{\cdot}OEt_2$ or ZnI_2 (entries 2−4). Previous studies on aldehyde **6** and various enoxysilanes showed a similar reversal of selectivity.[15] It was postulated that formation of a bidentate chelate between the aldehyde and the α-oxygen is difficult due to steric hindrance of the isopropylidene moiety. As seen in entries 2 and 3, using $MgBr_2{\cdot}OEt_2$ led to the 3,4 *anti* adducts in a good ratio, with a polar Felkin−Anh transition state seemingly at play, as was also the case with ZnI_2 (entry 4, Table 1)[15a]

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A mixture of silylated and desilylated adducts were obtained from the aldol reaction, the crude mixture was treated with HF·pyridine to provide the free alcohols. These were reacted with allyldimethylchlorosilane and imidazole to yield the requisite silicon-tethered radical precursors **5a,b** in excellent yield. This sequence was easily performed on a 50 g-scale with similar efficiency.

Radical cyclization of **5a,b** was performed at 0 °C using Et_3B as the radical chain initiator under an air atmosphere. The group-transfer[12,13,16] reaction is initiated by the presence of oxygen in the reaction mixture (Figure 4). Following formation

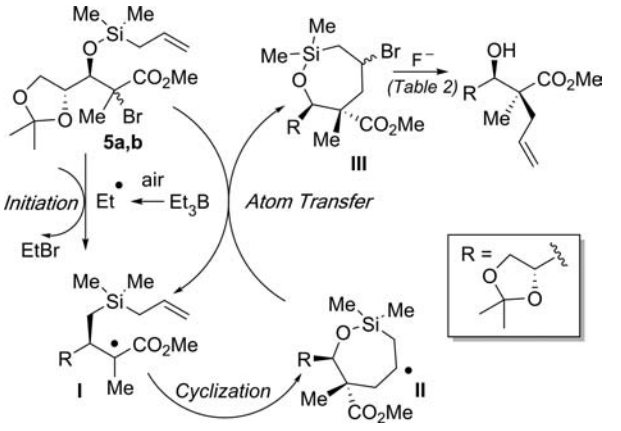
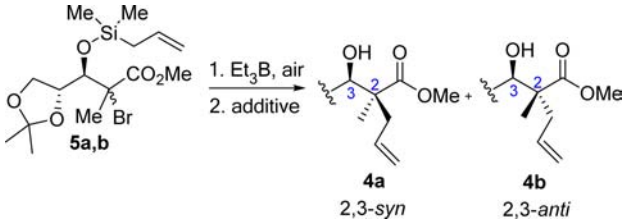


Figure 4. Group-transfer mechanism.

of radical intermediate **I**, cyclization occurs leading to cyclic silyloxy radical **II** which after atom transfer gives the cyclic intermediate **III**. Despite several attempts, the latter could not be isolated and TBAF was added at the end of the reaction, however, decomposition was observed using these conditions (Table 2, entry 1).

Adding a mild base (ethanolamine) at 0 °C prior to the addition of TBAF or $Et_3N{\cdot}3HF$ solved the problem. An excellent diastereoselectivity (>20:1) in favor of the 2,3-*syn* product **4a** was obtained, in a good yield, with toluene being the solvent of choice (entries 3−4).

Table 2. Tandem Cyclization−Elimination Reaction−Allylation

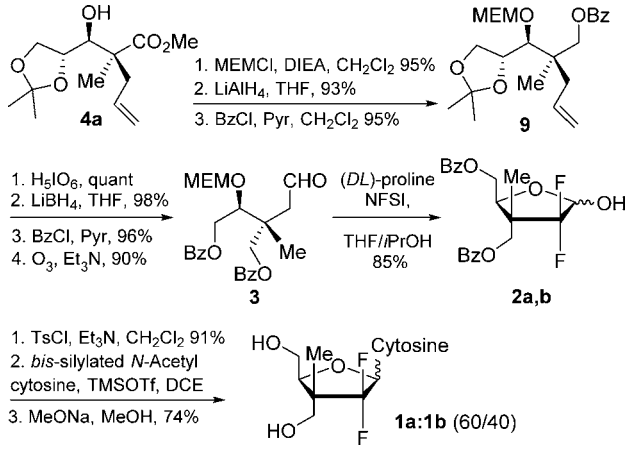


entry	additive[a]	solvent	ratio[b] (2,3-*syn*:2,3-*anti*)	yield[c]
1	TBAF	CH_2Cl_2 (0.1 M)	–	N.D.
2	TBAF[a]	CH_2Cl_2 (0.1 M)	>20:1	65%
3	$Et_3N{\cdot}3HF$[a]	CH_2Cl_2 (0.1 M)	>20:1	75%
4	$Et_3N{\cdot}3HF$[a]	toluene (1 M)	>20:1	85%

[a]Substrates were pretreated with ethanolamine (3 equiv) at 0 °C for 30 min, followed by the addition of additive (1.5 equiv) at 0 °C. [b]2,3-*syn*:2,3-*anti* product ratios were determined by ^1H NMR analysis of the crude reaction mixture. [c]Isolated yields.

This reaction is interesting in many aspects, as it does not require strong bases, toxic reagents, or heavy metals. The radical reaction was routinely performed on multigram scale (60 g) using solvent concentrations up to 1 M. The hydroxyl group at C3 of **4a** was then protected, the ester reduced with $LiAlH_4$, and the corresponding alcohol benzoylated to give **9** in 83% yield over three steps (Scheme 1). The *O*-isopropylidene

Scheme 1. Synthesis of Nucleoside Analogs 1a,b



acetal was removed with periodic acid,[17] and the intermediate diol oxidatively cleaved to give the aldehyde in quantitative yield. The latter was reduced to the primary alcohol and benzoylated, after which an ozonolyzis was performed to access the desired aldehyde **3** (84% over 3 steps). Treatment of **3** in THF/*i*PrOH with an excess of racemic proline and NFSI[18] followed by an acidic workup provided the 2-deoxy-2,2-difluoro-D-lactol **2a,b** in good yield (85%). The fluorination was easily scalable, and the crude mixtures were used without purification. The lactols **2a,b** were tosylated (Scheme 1), and the corresponding products were submitted to a Vorbrüggen coupling using the *bis*-silylated *N*-acetyl cytosine in the presence of TMSOTf to provide a mixture (60:40) of the α- and β-anomers. These were deprotected and separated by C18 reversed-phase chromatography in 60% yield over 3 steps. The hydrochloride salt of **1a** was cocrystallized with MeOH, and its structure was confirmed by X-ray crystallography. Overall this methodology allowed us to synthesize the final nucleosides in 24% yield over 15 steps.

Lipophilic conjugates of both anomers of **1** were synthesized and submitted to antiproliferative *in vitro* assays against a panel of human cancer cell lines originating from solid tumors (MCF7, A549, Capan2, HCT116). Some molecules derived from **1a** and **1b** were shown to be active in these assays and will be reported in due course. Studies are currently in progress to understand their mechanism of action.

We have demonstrated the versatility of a radical-based approach for the creation of stereogenic all-carbon quaternary centers, and its application in the synthesis of a new class of NAs. In this study, we developed a dual-face nucleoside scaffold that allows both α- and β-anomers to have potential biological activity. The radical process used to generate the quaternary center is efficient and does not require the use of tin, a benefit from a biological and environmental standpoint. The reactions allow the preparation of quaternary centers to be possible on a preparative scale. A versatile fluorination approach was used that allows efficient access to difluorinated furanolactols.

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Changing the nature of the nucleobase at C1′, the functionality at C3′, or the nature of the heteroatom at C2′ could lead to libraries of novel molecules that could be evaluated for their biological potential. Overall, we believe that this scaffold offers an avenue for chemists to identify and synthesize novel active compounds while illustrating the ease and usefulness of tin-free radical reactions.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic characterization (IR, ^{1}H, ^{13}C NMR, HRMS) of all key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Mansson, E.; Spasokoukotskaja, T.; Sallstrom, J.; Eriksson, S.; Albertioni, F. *Cancer Res.* **1999**, *59*, 5956−5963. (b) Galmarini, C. M.; Mackey, J. R.; Dumontet, C. *Leukemia* **2001**, *15*, 875−890. (c) Ferrandina, G.; Mey, V.; Nannizzi, S.; Ricciardi, S.; Petrillo, M.; Ferlini, C.; Danesi, R.; Scambia, G.; Del Tacca, M. *Cancer Chemother. Pharmacol.* **2010**, *65*, 679−686. (d) Moysan, E.; Bastiat, G.; Benoit, J. P. *Mol. Pharmaceutics* **2013**, *10*, 430−444.

(2) Marquez, V. E.; Ben-Kasus, T.; Barchi, J. J., Jr.; Green, K. M.; Nicklaus, M. C.; Agbaria, R. *J. Am. Chem. Soc.* **2004**, *126*, 543−549.

(3) (a) Sabini, E.; Ort, S.; Monnerjahn, C.; Konrad, M.; Lavie, A. *Nat. Struct. Mol. Biol.* **2003**, *10*, 513−519. (b) Zhang, Y.; Secrist, J. A., 3rd; Ealick, S. E. *Acta Crystallogr., Sect. D* **2006**, *62*, 133−139.

(4) Pradere, U.; Garnier-Amblard, E. C.; Coats, S. J.; Amblard, F.; Schinazi, R. F. *Chem. Rev.* **2014**, *114*, 9154−9218.

(5) Di Marco, M.; Di Cicilia, R.; Macchini, M.; Nobili, E.; Vecchiarelli, S.; Brandi, G.; Biasco, G. *Oncol. Rep.* **2010**, *23*, 1183−1192.

(6) Pandita, A.; Kumar, B.; Manvati, S.; Vaishnavi, S.; Singh, S. K.; Bamezai, R. N. *PloS One* **2014**, *9*, e107154.

(7) (a) Hager, M. W.; Liotta, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5117−5119. (b) Guindon, Y.; Gagnon, M.; Thumin, I.; Chapdelaine, D.; Jung, G.; Guerin, B. *Org. Lett.* **2002**, *4*, 241−244. (c) Dostie, S.; Prevost, M.; Guindon, Y. *J. Org. Chem.* **2012**, *77*, 7176−7186.

(8) Guindon, Y.; Houde, K.; Prevost, M.; Cardinal-David, B.; Landry, S. R.; Daoust, B.; Bencheqroun, M.; Guerin, B. *J. Am. Chem. Soc.* **2001**, *123*, 8496−8501.

(9) Godin, F.; Prévost, M.; Gorelsky, S. I.; Mochirian, P.; Nguyen, M.; Viens, F.; Guindon, Y. *Chem.—Eur. J.* **2013**, *19*, 9308−9318.

(10) (a) Brazeau, J. F.; Mochirian, P.; Prevost, M.; Guindon, Y. *J. Org. Chem.* **2009**, *74*, 64−74. (b) Mochirian, P.; Godin, F.; Katsoulis, I.; Fontaine, I.; Brazeau, J. F.; Guindon, Y. *J. Org. Chem.* **2011**, *76*, 7654−7676. (c) Godin, F.; Prevost, M.; Viens, F.; Mochirian, P.; Brazeau, J. F.; Gorelsky, S. I.; Guindon, Y. *J. Org. Chem.* **2013**, *78*, 6075−6103.

(11) (a) Guindon, Y.; Guérin, B.; Chabot, C.; Ogilvie, W. *J. Am. Chem. Soc.* **1996**, *118*, 12528−12535. (b) Guindon, Y.; Rancourt, J. *J. Org. Chem.* **1998**, *63*, 6554−6565. (c) Cardinal-David, B.; Guerin, B.; Guindon, Y. *J. Org. Chem.* **2005**, *70*, 776−784.

(12) Duplessis, M.; Waltz, M. E.; Bencheqroun, M.; Cardinal-David, B.; Guindon, Y. *Org. Lett.* **2009**, *11*, 3148−3151.

(13) Curran, D. P.; Ramamoorthy, P. S. *Tetrahedron* **1993**, *49*, 4841−4858.

(14) See Supporting Information for details.

(15) (a) Kita, Y.; Yasuda, H.; Tamura, O.; Itoh, F.; Ya, Y. K.; Tamura, Y. *Tetrahedron Lett.* **1985**, *26*, 5777−5780. (b) Dong, S.; Parker, G. D.; Tei, T.; Paquette, L. A. *Org. Lett.* **2006**, *8*, 2429−2431. (c) Paquette, L. A.; Parker, G. D.; Tei, T.; Dong, S. *J. Org. Chem.* **2007**, *72*, 7125−7134.

(16) Blaszykowski, C.; Dhimane, A. L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2003**, *5*, 1341−1344.

(17) Curti, C.; Zanardi, F.; Battistini, L.; Sartori, A.; Rassu, G.; Auzzas, L.; Roggio, A.; Pinna, L.; Casiraghi, G. *J. Org. Chem.* **2006**, *71*, 225−230.

(18) Our protocol was based and modified from: Fadeyi, O. O.; Lindsley, C. W. *Org. Lett.* **2009**, *11*, 943−946.