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New and efficient synthesis of 5′-amino-5′-(*S*)-methyl-2′,5′-dideoxynucleosides

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Abstract—A short, efficient synthesis of 5′-amino-5′-(*S*)-methyl-2′,5′-dideoxynucleosides **1** has been developed through the diastereoselective addition of methylmagnesium bromide or methyllithium to an intermediate *tert*-butylsulfinimide.

Modified oligonucleotides and their analogs offer the possibility of designing compounds with potential therapeutic and diagnostic applications. Antisense or antigene technology requires modified oligonucleotides that bind strongly and specifically to defined RNA or DNA target sequences, respectively.[1] Replacement of the phosphodiester moiety in natural oligonucleotides (wild-type) with an amide moiety leads to modified oligonucleotides (amide modification) displaying higher affinity for an RNA target and greatly improved resistance toward nucleases (Fig. 1).[2] Further work demonstrated that the introduction of an *S*-methyl group within the amide backbone (*S*-methyl amide modification) further improved the binding affinity towards single stranded RNA and DNA.[3]

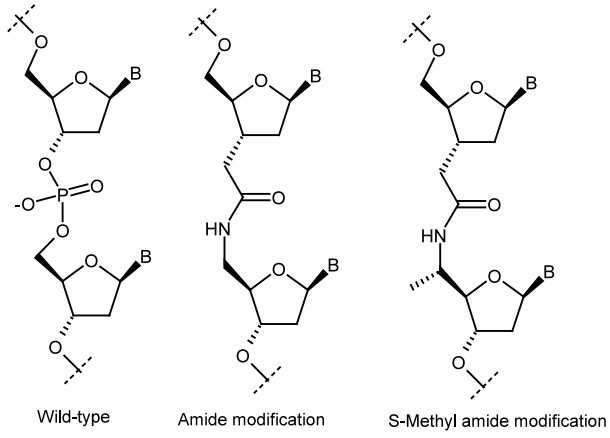

Figure 1.

Our initial approach towards the synthesis of *S*-methyl amide backbone relied on the non-selective Grignard addition to 5′-aldehydo-2′-deoxynucleoside which led to a 1:1 mixture of diastereomeric alcohols which could be transformed to the corresponding amine **1** via the nucleophilic displacement of a C5′ mesylate by an azide followed by the reduction of the latter to the amine. This synthesis provided compound **1** in eight steps and 10% overall yield starting from 2′-deoxynucleoside and is not suitable for large-scale preparation (Scheme 1).[3]

In the context of a recent program directed toward the synthesis of modified oligonucleotides with improved biophysical properties, we became interested in developing a more practical synthesis of **1** that could serve as a general route to amide-modified oligonucleotides.

Initial studies demonstrated that the nucleophilic addition of an organometallic to a 5′-oxime or a 5′-hydrazone derivatives of a protected thymine gave none or only trace amounts of the desired product along with products derived from the addition of the organometallic on C4 followed by dehydration.

For example, the reaction of hydrazone **2** in the presence of methyllithium in tetrahydrofuran at −78°C gave a mixture of **4** and **5**. The desired compound **3** could not be detected (Scheme 2). When the nucleic base was not protected by a BOM group, only the compound resulting from the nucleophilic addition of the C6 position of the nucleic base on the hydrazone bond was isolated.

Keywords: 5′-amino-5′-(*S*)-methyl-2′, 5′-dideoxynucleosides; *tert*-butylsulfinamide; nucleophilic addition.

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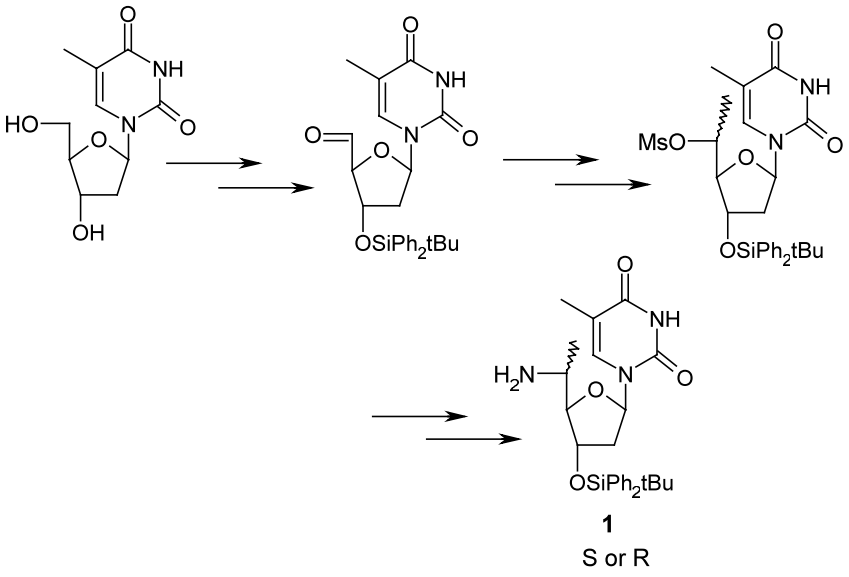
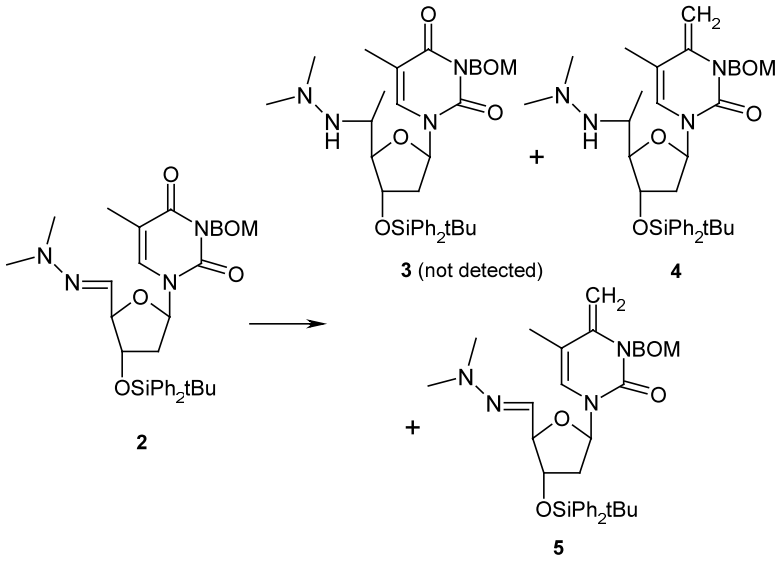


Scheme 1. Eight steps, 10% overall.



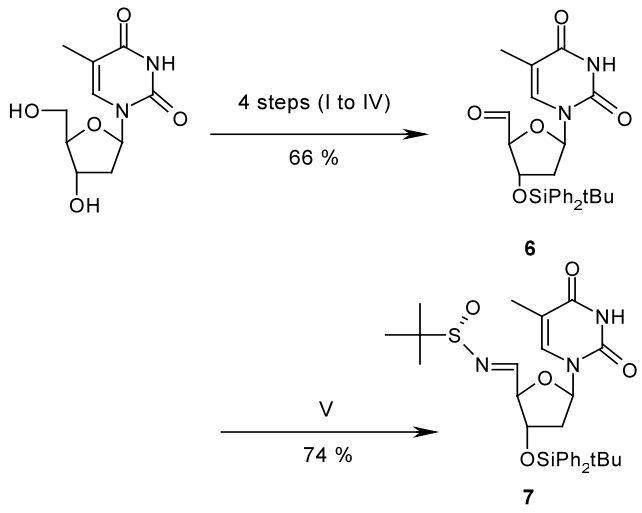
Scheme 2.

In order to avoid these side reactions, we turned our attention to the more reactive imine derived from sulfinamide.[4] The required aldehyde **6** was synthesized from thymidine in four steps in 66% overall yield,[5] and reacted with *S*-*tert*-butylsulfinamide providing **7** in 74% yield (Scheme 3).[6]

Reaction of methylmagnesium bromide or methyllithium with **7** in different solvents gave exclusively the desired addition to the imine bond. Even when an excess of organometallic was used, no side reaction was observed with the nucleic base, protected or not.

Detailed investigation (Table 1, Scheme 4) of this reaction showed that the reaction is strongly counter-ion and solvent dependent. For example, the reaction of **7** in the presence of methylmagnesium bromide in diethyl ether gave as the major product the sulfinamide which possesses the *S* configuration at C5′ (entry 1) with a selectivity of 5:1 in favor of the diastereomer **8** (combined yield 91%). Other solvents, like tetrahydrofuran or dichloromethane decreased the selectivity and the yield of the reaction. In contrast, the use of methyllithium in tetrahydrofuran gave the sulfinamide **9** with the *R* configuration at C5′, as the major product (entry 4).[7]

While the reaction is not completely diastereoselective, the separation of the two diastereoisomers, **8** and **9**, was easily accomplished chromatographically. This is in strong contrast to the separation of the diastereoisomeric mixture of **1** obtained by the nucleophilic displacement of C5′ mesylate by sodium azide followed by the reduction of the azide to the amine[3] where the separation was tedious.



Scheme 3. *Reagents and conditions*: (I) TrCl, pyridine, 81% yield; (II) $Ph_2tBuSiCl$, DMF, imidazole, 87% yield; (III) AcOH, H_2O, 98% yield; (IV) DCC, DMSO, TFA·pyr, 96% yield; (V) *S*-*tert*-butylsulfinamide, benzene.

The derivatives obtained with the corresponding *R*- or racemic *tert*-butylsulfinamide led to mixtures that were inseparable on silica gel.

In the case of methylmagnesium bromide, the predominant diastereoisomer **8** is the opposite to that predicted by the model proposed by Ellman.[7a] However, the diastereoselectivity of the reaction could be explained by the model advanced by Davis et al.[7b] where the sulfinyl oxygen is proposed to coordinate to one equivalent of the organometallic and sterically shields the Re face of the imine to give the Cram product (Scheme 5 (A)).

In contrast, the predominant diastereoisomer **9** obtained with the use of methyllithium could be predicted by Ellman's model, which involved a six-membered chair transition state (Scheme 5 (B)). Nevertheless, the results show that the ratio between **8** and **9** are a function of the nature of the solvent and of the organometallic reagent used. In addition, these results are likely strongly influenced by the heteroatoms of the nucleoside.[8]

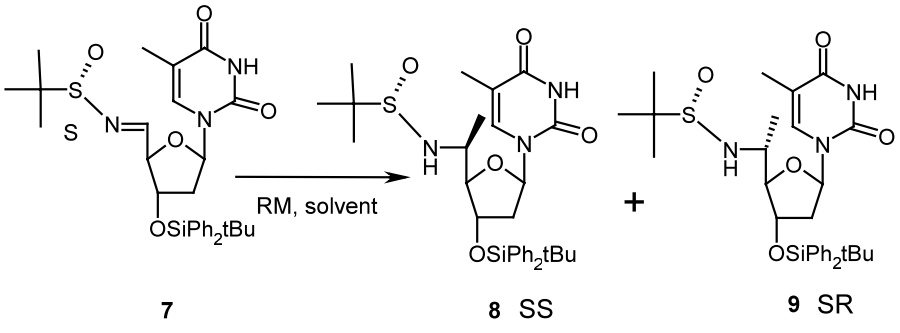
Treatment of **8** or **9** with a mixture of hydrogen chloride and methanol gave the desired amines **10** and **11** in 92% and quantitative yield, respectively (Scheme 6). The configuration at C5′ was determined by comparison of the NMR data of **10** and **11** with those of original product.[3,9]

In conclusion, we have shown that the 5′-*tert*-butylsulfinamide group could be used as activating and directing group for the preparation of 5′-amino-5′-methyl-2′,5′-dideoxynucleoside. Compounds **10** and **11** were synthesized in seven steps in 34 and 32% yield, respectively. Their incorporation into oligonucleotides for antisense and antigene applications is currently underway.

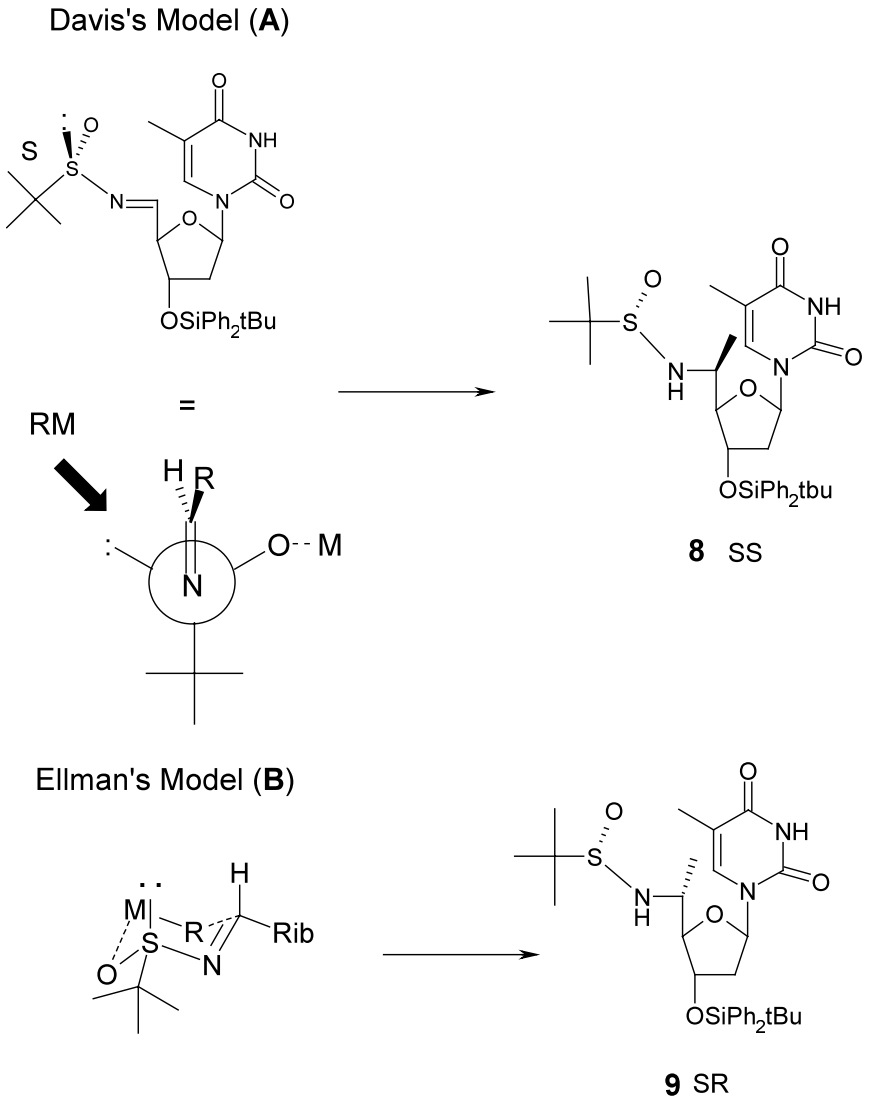
Table 1.

Entry	RM*	Solvent	Temperature	**8** (%)	**9** (%)	Yield (%)	Ratio **8**/**9****
1	MeMgBr	Et_2O	−48°C to rt	76	15	91	5/1
2	MeMgBr	THF	−48°C to rt	47	24	71	2/1
3	MeMgBr	CH_2Cl_2	−48°C to rt	43	12	55**	3.5/1
4	MeLi	THF	−48°C	30	65	95	1/2

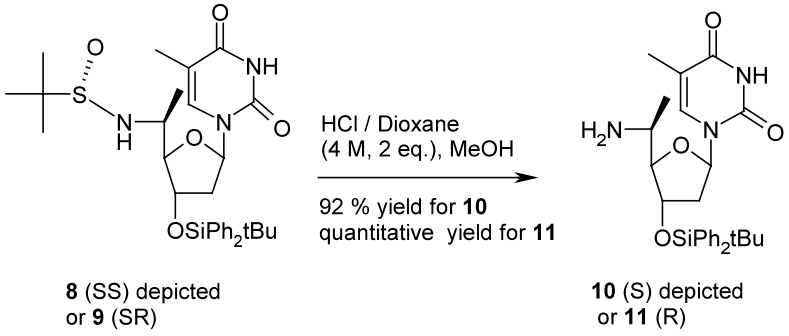
* 3 equiv.
** 36% of starting material was recovered.
*** Isolated and NMR.



Scheme 4.



Scheme 5.



Scheme 6.

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6. **7**: (*S*)-*tert*-Butylsulfinamide (0.37 g, 3.03 mM) was added to a solution of aldehyde **6** (1.45g, 3.03 mM) in benzene (250 mL). The solution was heated at reflux and the water was removed by azeotropic distillation. The solution was evaporated to dryness under vacuum. Flash silica chromatography, eluting with ethyl acetate–hexane (4:6) afforded the compound **7** as a solid (1.28 g, 74%). ^{1}H NMR ($CDCl_3$) 8.70 (1H, NH, s), 7.65 (1H, d, H-5′, 4 Hz); 7.56 (4H, m, H aro); 7.39 (7H, m, H aro, H6); 7.41 (1H, dd, H-1′, 5 Hz, 9 Hz); 4.72 (1H, m, H-4′); 4.40 (1H, m, H-3′); 2.36 (1H, m, H-2′), 1.79 (3H, s, CH_3); 1.71 (1H, m, H-2′); 1.04 (9H, s, *t*Bu).
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9. Analytic data of **10** (5′-*S*-methyl derivative): ^{1}H NMR ($CDCl_3$) 7.65 (4H, m, H aro); 7.30 (6H, m, H aro); 6.22 (1H, t, H-1′, 6 Hz); 4.32 (1H, m, H-3′); 3.69 (1H, m, H-4′), 2.64 (1H, m, H′5), 2.27 (1H, m, H-2′), 1.98 (1H, m, H-2′), 1.87 (3H, s, CH_3), 1.08 (9H, s, *t*Bu), 0.93 (3H, d, 5′-CH_3, 7 Hz). Analytic data of **11** (5′-*R*-methyl derivative) ^{1}H NMR ($CDCl_3$) 7.68 (4H, m, H aro); 7.23 (6H, m, H aro); 6.35 (1H, q, H-1′, 6 Hz, 8 Hz); 4.32 (1H, m, H-3′); 3.78 (1H, m, H-4′), 2.85 (1H, m, H-5′), 2.26 (1H, m, H-2′), 1.86 (4H, m, H-2′, CH_3), 1.08 (9H, s, *t*Bu), 0.94 (3H, d, 5′-CH_3, 7 Hz).