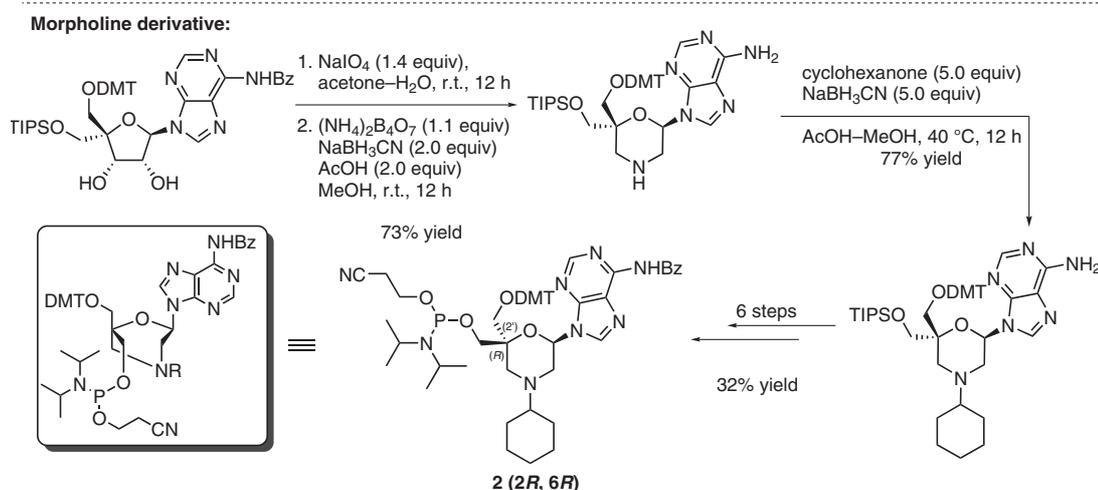
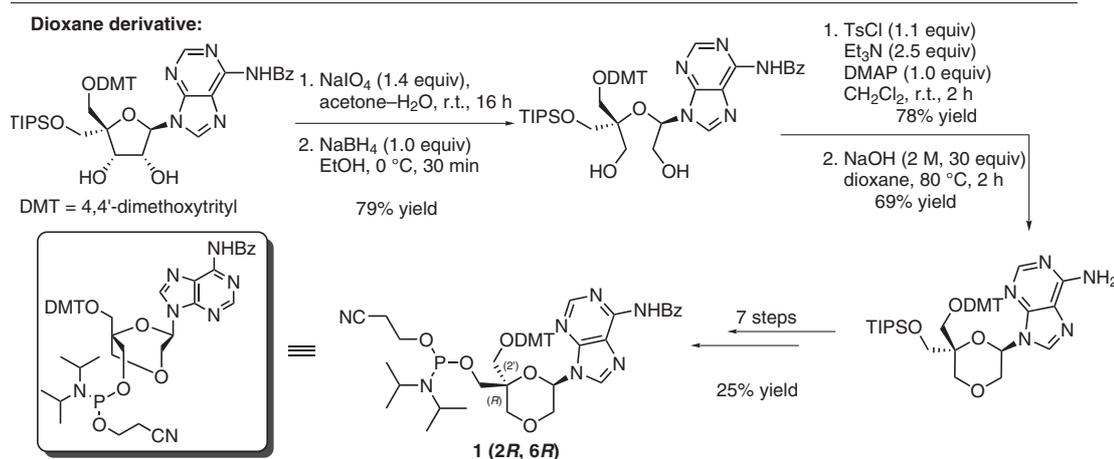
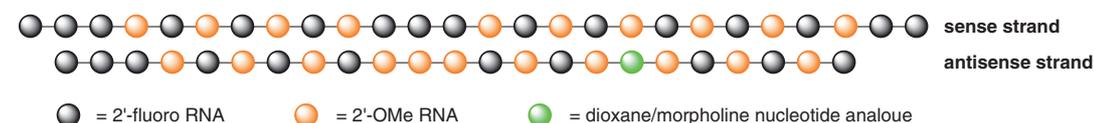


# Novel Dioxane- and Morpholino Nucleotide Analogues with Improved Off-Target Profiles in siRNAs



**Significance:** The authors describe the synthesis of novel dioxane- and morpholine-based nucleotide precursors. These nucleotides were incorporated at position 7 of an antisense strand leading to improved in vitro off-target profiles due to destabilization of the seed region.

**Comment:** Interestingly, the corresponding (2S, 2R) isomers of **1** and **2** also led to improved off-target profiles. However, significantly lower in vivo potencies were observed, potentially due to the inability of these nucleosides to undergo Watson–Crick base pairing.

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