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Synthesis of a Nucleoside Analog Bearing a Branched Difunctional Sidechain Using the Palladium-Mediated Cyclization of a γ-Oxoallene

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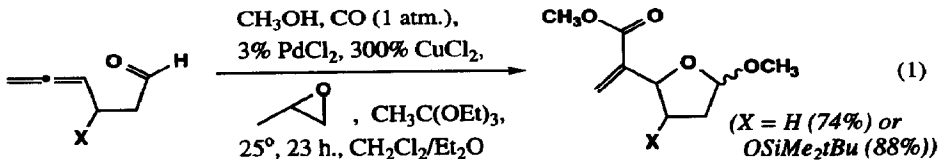
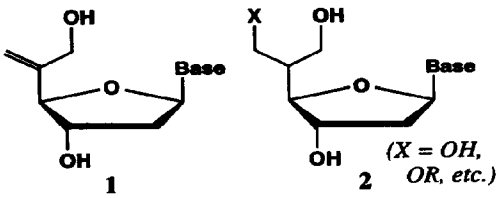
Abstract: *The aldehyde **8** was synthesized in high yield and with excellent stereoselectivity by treating a protected 3-hydroxypropanal with Corey's chiral B-propargyl boradiazoline reagent. Cyclization of this γ-oxoallene with palladium(II) in the presence of methanol and carbon monoxide produced the furanoside **9** with excellent stereoselectivity for the D-deoxyribose geometry. The furanoside **9** was converted to the branched extended sidechain deoxythymidine analog **11** by reduction, protection, and β-stereoselective Vorbruggen coupling. The hydroboration/oxidation of **10** to yield the deoxyribofuranoside analog **13**, bearing two sidechain hydroxyl groups, was also demonstrated.*

A large number of nucleoside analogs have been prepared and studied for their biological activities, particularly antiviral activity, and for incorporation into oligonucleotides for the study of their capabilities for forming "antisense" duplex and triplex complexes with DNA and RNA.[1] Our recent discovery[2] that the γ-oxoallenes 4,5-hexadienal and 3-tert-butyldimethylsilyloxy-4,5-hexadienal will undergo palladium(II)-mediated acetalization-cyclization-methoxycarbonylation in the presence of acid and water scavengers (equation 1) opens up the prospect that this transformation could be used as the means for synthesizing nucleoside analogs having a



(1)

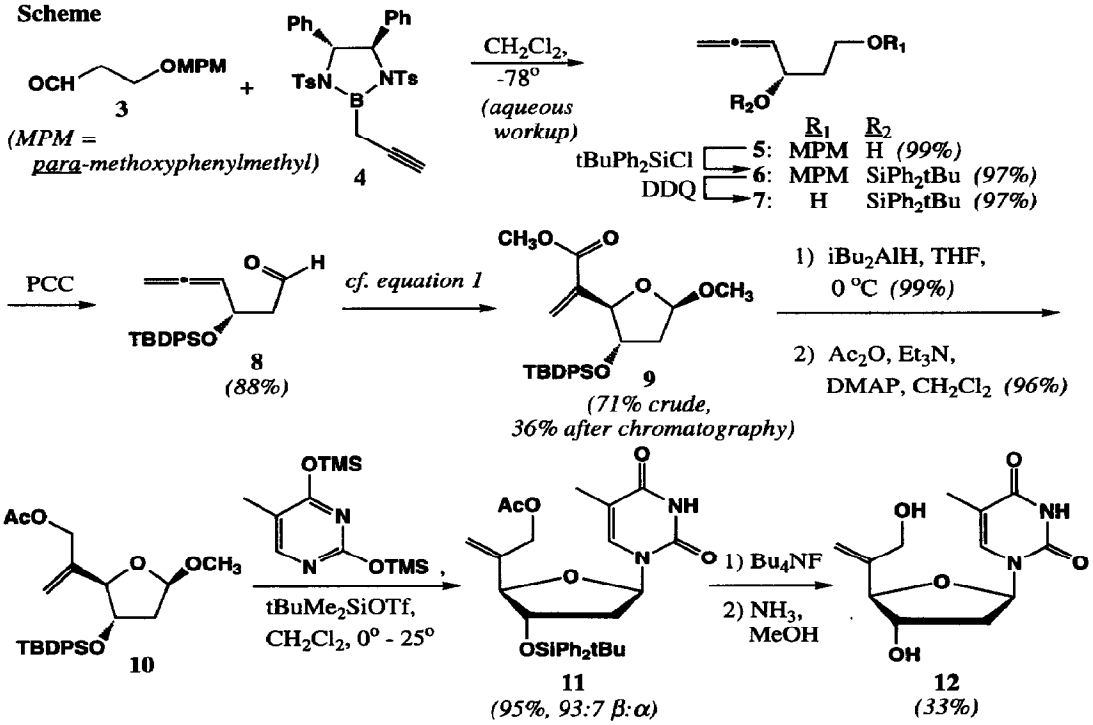
branched, extended and difunctionalized 5' sidechain. Such nucleoside analogs (generalized structures **1** and **2**) might be useful for the preparation of oligonucleotide analogs bearing "reporter" groups (for probing the structure and dynamics of DNA interactions) at selected locations via attachment of such groups to the branching group on the sidechain.[3] In addition, the extended nature of the sidechains in **1** and **2** may allow oligonucleotides bearing them to form more effective triple helix complexes.[4] In this communication, we report the asymmetric synthesis, shown



in the Scheme, of a deoxythymidine analog **12** bearing a branched, extended, alkene-bearing 5' sidechain. The synthesis of an intermediate like **9** (see Scheme), differing from **9** by bearing the tert-butyldimethylsilyl ether group instead of the tert-butyldiphenylsilyl ether group and by being in racemic form, by a different route was reported previously.[2] The present synthesis is notable for involving Corey's chiral B-propargyl boradiazoline reagent in a key step, and for featuring remarkable stereoselectivity at the cyclization step (as reported earlier[2]) and at the step involving the coupling of a methyl furanoside with thymine to form the nucleoside.

As indicated in the Scheme, treatment of the aldehyde **3** (prepared in 42% yield in two steps from 1,3-propanediol[2]) with the (R,R)-boradiazoline **4**[5] (prepared in situ) yielded, upon workup, the allenol **5** in quantitative yield and (according to ^{19}F-NMR analysis of the Mosher ester derivative of **5**, relative to a racemic control)[6] >98% enantiomeric excess.[7] Protection of the secondary hydroxyl group, removal of the MPM protecting group,[8] and oxidation yielded the aldehyde **8**.[7] The one-pot acetalization-cyclization-methoxycarbonylation procedure[2] cleanly converted **8** to the furanoside **9** as a single diastereomer (according to NMR analysis) in 71% yield; chromatography of the crude product resulted in substantial losses of material without any appreciable gain in purity.[7]

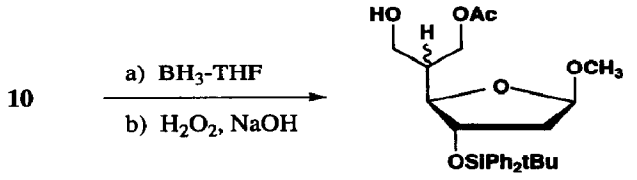
Scheme



The stereoselectivity of the cyclization of **8** to **9** has been discussed before,[2] and is attributed to a combination of steric effects exerted by the bulky trialkylsilyl group and stereoelectronic constraints in the cyclization step's transition state.[9] The assignment of the configuration was based on observed NMR coupling constants and nuclear Overhauser effects, as reported earlier for the racemic product.[2]

Reduction of the sidechain ester group of **9** followed by acetylation yielded the extended sidechain deoxyribofuranoside **10**, which was then subjected to a Vorbruggen coupling using persilylated thymine[10] to yield the protected thymidine analog **11** in excellent yield as a mixture of anomers.[7] Deprotection to the diol **12** followed by chromatography revealed that a 93:7 ratio of β to α anomers had been produced.[7,11] This diastereoselectivity, which is remarkable for Vorbruggen coupling reactions with 2'-deoxyribofuranose substrates, is attributed to a steric effect exerted by the tert-butyldiphenylsilyl group in the substrate **10**.[12]

The branched, extended difunctional sidechain analog to deoxythymidine, **12**, was thus produced as a single enantiomer in 12 steps and 6% overall yield from 1,3-propanediol, with the lowest yielding steps being the initial 1,3-propanediol monoprotection (54%) and the final deprotections (33%), both of which should be improvable. As a testimonial to the potential of this synthetic route to produce nucleoside analogs bearing difunctional sidechains for the attachment of reporter groups or other groups to a synthetic oligonucleotide strand, the intermediate **10** was hydroborated to the diprotected triol **13** in high yield, albeit with only moderate diastereoselectivity (equation 2; the configurations for the two inseparable diastereomers, whose ratio was measured by ^{1}H-NMR and by ^{19}F-NMR analysis of the Mosher ester derivative have not yet been determined).[7] Research is currently underway to improve sidechain functionalizations of this nature and to demonstrate the capability of the resulting branched, extended difunctional sidechain-containing deoxyribofuranoside analogs to be converted into the corresponding nucleosides for incorporation into synthetic oligonucleotides.



13

(95%, 2:1 ratio of diastereomers)) (2)

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6. ^{19}F-NMR ($CDCl_3$): δ 6.841 relative to trifluoroacetic acid standard (δ 0.000). Mosher ester derivative from racemic **5**: δ 6.864, 6.841.

7. All compounds were purified using silica gel chromatography with hexane/ethyl acetate elution, and gave high resolution mass spectra consistent with the assigned structures. Spectroscopic data are available from the authors upon request.

8. The p-anisaldehyde byproduct from this deprotection step coeluted with the desired product during chromatography on silica gel, so the crude reaction mixture was customarily treated with semicarbazide hydrochloride (excess, sodium acetate, 80:20 ethanol:water, overnight) to produce the semicarbazone of the aldehyde, which could be easily separated from the desired alcohol by silica gel chromatography.

9. For similar stereoselectivity in Pd(II)-mediated cyclizations of substituted alkenols, see Semmelhack, M.F., Kim, C., Zhang, N., Bodurow, C., Sanner, M., Dobler, W., Meier, M. *Pure Appl. Chem.* **1990**, *62*, 2035-2040.

10. a) Vorbruggen, H., Krolikiewicz, H., Bennua, B. *Chem. Ber.* **1981**, *114*, 1234-1255; b) Vorbruggen, H., Holfe, G., *Chem. Ber.* **1981**, *114*, 1256-1268. By using preformed, vacuum-distilled persilylated thymine, we observed that the yields for this coupling were dramatically improved.

11. The assignment of the β configuration to the major isomer of **12** was based upon the NMR signals observed for the two isomers: in the major (β) isomer, the chemical shifts for the signals corresponding to the sidechain atoms and the thymine base atoms were, in general, higher (downfield) than the corresponding signals in the minor (α) isomer, while the chemical shift for the signal for the protons at $C_{4'}$ was lower (upfield) in the major isomer than in the minor isomer. This is consistent with through-space deshielding effects exerted by the sidechain and the thymine base moieties.

12. Most Vorbruggen couplings to 2'-deoxyribofuranose substrates result in ~50:50 mixtures of α and β anomers. Strategies which have been developed to circumvent this poor stereoselectivity have included the use of removable 2'-α directing groups, e.g. 2'-phenylseleno substrates (Beach, J.W., Kim, H.O., Jeong, L.S., Nampalli, S., Islam, Q., Ahn, S.K., Babu, J.R., Chu, C.K. *J. Org. Chem.* **1992**, *57*, 3887-3894) and 2'-iodo substrates (Kim, C.U., Misco, P.F. *Tetrahedron Lett.* **1992**, *33*, 5733-5736), or the covalent involvement of neighboring groups to direct the coupling reaction, e.g. 3'-α-thioester substituents (Lavallee, J.-F., Just G. *Tetrahedron Lett.* **1991**, *32*, 3469-3472) and 5'-oxygen-linked pyrimidine substrates (Jung, M.E., Castro, C. *J. Org. Chem.* **1993**, *58*, 807-808). See the latter for a leading reference on this stereochemical issue.

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