Synthesis of Pyrrolidine *C*-Nucleosides via Heck Reaction

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ABSTRACT

A novel method for the synthesis of pyrrolidine *C*-nucleosides has been developed. The key step of the synthesis is the palladium(0)-mediated coupling of a disubstituted *N*-protected 2-pyrroline and 5-iodouracil. *C*-Nucleoside 14 and its *N*-methyl derivative 15 can easily be converted to the corresponding phosphoramidite building blocks for DNA synthesis.

In the context of our ongoing research on the synthesis and properties of oligonucleotide analogues, we became interested in an efficient access to pyrrolidine *C*-nucleoside building blocks for DNA synthesis.

Several pyrrolidine *C*-nucleosides with aromatic (hetero)cycles, such as substituted phenyls, imidazoles, or 9-deazaguanine, as aglycons were synthesized as transition state inhibitors for nucleoside hydrolases or nucleoside phosphatases by Schramm and co-workers. The aglycon was introduced via addition of the corresponding aryl-lithium or aryl-Grignard reagents to the imine function of substituted 3,4-dihydro-2*H*-pyrroles.^{1–3} Yokoyama and co-workers synthesized different stereoisomers of pyrrolidine *C*-nucleosides, pyrrolidine 2'-deoxy-*C*-nucleosides, and pyrrolidine 2',3'dideoxy-*C*-nucleosides as glycosidase inhibitors. The C–C bond formation was performed by the addition of the lithium or Grignard reagents of the heterocycles to the corresponding substituted γ -lactams or related compounds.^{4–7} Abasic pyrrolidine 2'-deoxy-*C*-nucleoside and pyrrolidine 2'-deoxyadenosine with an additional CH₂-unit between C-1' and the base were incorporated into DNA by Verdine and coworkers. These oligomers were tested as inhibitors for glycosidase II and base-excision DNA repair enzymes.^{8,9} Starting from 2-deoxy-D-ribose, Kim et al. synthesized *N*-acetyl-pyrrolidine-2'-deoxy- β -D-pseudouridine in 19 steps in an overall yield of 3.4% via Staudinger—aza-Wittig cyclization of a 2,4-di-*O*-benzylpyrimidin-5-yl-substituted γ -azido ketone.¹⁰

Palladium-mediated coupling reactions of furanoid glycals with appropriate aglycon derivatives were successfully employed for the regio- and stereospecific formation of

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C-glycosidic bonds.^{11–14} Zhang et al. used Heck chemistry for the synthesis of 2'-deoxypseudouridine¹⁵ (Scheme 1). Less



^a CBz, benzyloxycarbonyl; TBDMS, *tert*-butyldimethylsilyl.

is known about the palladium-catalyzed reactions to form a C–C bond between *N*-protected enamines and heterocycles.^{16,17} In this communication we report on the regioand stereospecific synthesis of pyrrolidine-2'-deoxypseudouridine and of its *N*-1-methyl derivative (pyrrolidinepseudothymidine) using Heck chemistry, as well as their elaboration into phosphoramidite building blocks for DNA synthesis. As a key step the palladium-mediated coupling of CBz-protected enamine **5** and 5-iodouracil (**3**) was chosen (Scheme 1).

As starting material the commercially available trans-3hydroxy-L-proline (6) was chosen, which already possesses the correct stereochemistry at C(2) and C(3). The amino group was protected as Fmoc carbamate, followed by the selective reduction of the carboxylic acid of 7 with the BH₃•S(CH₃)₂ complex in almost quantitative yield to give diol 8^{18} In a one-pot reaction, both hydroxy groups were protected as TBDMS ethers, followed by the cleavage of the Fmoc group with piperidine $(\rightarrow 9)$. To introduce the enamine functionality, 9 was N-chlorinated with NCS followed by the LTMP-mediated elimination of HCl at -78°C, after a procedure by Schramm and co-workers.² NMR data of the intermediate 3,4-dihydro-2H-pyrrole derivative, which can be isolated by FC, proved that the deprotonation occurred exclusively at the C(5) position. CBz-protected enamine 5 was obtained after the addition of benzyl chloroformate and NEt₃ to the in situ formed imine at low temperature. Overall yield of 5 from 6 was 52% (Scheme 2).

Our initial experiments on the palladium(0)-catalyzed coupling of enamine **5** with 5-bromo- (**10a**,¹⁹ Scheme 3, Table 1 entries 1 and 2) or 5-iodo-2,4-di-*O*-benzylpyrimidine

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^{*a*} (a) Fmoc-Cl, dioxane, 5% aq. NaHCO₃ soln, 0 °C → rt, 9 h; (b) BH₃•(CH₃)₂S, THF, reflux, 2 h; (c) TBDMS-Cl, imidazole, THF, rt, 2 h; (d) piperidine, THF, rt, 12 h; (e) NCS (*N*-chlorosuccinimide), hexane, rt, 1 h; (f) LTMP (lithium 2,2,6,6-tetramethylpiperidide), THF, -78 °C, 2 h; (g) benzyl chloroformate, NEt₃, THF, -78 °C → rt, 8 h.

(10b, synthesized from 10a by Br–Li exchange, followed by the reaction with I₂, entries 3–7) were unsuccessful. The coupled product 11 was only obtained in the reaction of 5 and 10b in low yields of less than 5% using Pd(OAc)₂ as catalyst with PPh₃ or bppp as ligand and NBu₃ as base and carrying out the reaction in CHCl₃ at 60 °C for several days (entries 8 and 9).¹¹ Higher temperatures and longer reaction times led to the decomposition of the starting materials. Iodide 10b was then replaced by the commercially available, unprotected 5-iodouracil (3). The Heck reaction of 5 and 3 using PPh₃, bppp, or P(C₆F₅)₃ as ligands led to unreacted



^{*a*} Experimental conditions, see Table 1. TBDMS, *tert*-butyldimethylsilyl.

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Table 1. Reaction Conditions and Yields of the Heck Coupling of 5 with 3 or 10 to 11 or 12^a								
entry	aglycon	catalyst	base	ligand	additive	solvent	temp	yield
1	10a	Pd(Ph ₃) ₄	NEt ₃	PPh ₃		CH ₃ CN	80 °C	
2	10a	Pd(OAc) ₂	K ₂ CO ₃		Bu ₄ NCl	DMF	rt	
3	10b	Pd(OAc) ₂	NBu ₃	PPh_3		$CHCl_3$	60 °C	
4	10b	Pd(OAc) ₂	NBu ₃	PPh ₃		CH ₃ CN	80 °C	
5	10b	Pd(OAc) ₂	Ag ₂ CO ₃	PPh ₃		DMF	80 °C	
6	10b	Pd(OAc) ₂	NBu ₃		Na-acetate	DMF	90 °C	
7	10b	Pd(OAc) ₂	NaHCO ₃		Bu₄NCl	DMF	60 °C	
8	10b	Pd(OAc) ₂	NEt ₃	PPh ₃	-	CHCl ₃	60 °C	< 5%
9	10b	Pd(OAc) ₂	NBu ₃	bppp		CHCl ₃	60 °C	< 5%
10	3	Pd(OAc) ₂	NBu ₃	PPh ₃		CHCl ₃	60 °C	
11	3	Pd(OAc) ₂	NBu ₃	bppp		CHCl ₃	60 °C	
12	3	Pd(OAc) ₂	NBu ₃	PPh ₃		DMF	65 °C	
13	3	Pd(OAc) ₂	NBu ₃	$P(C_6F_5)_3$		DMF	65 °C	
14	3	Pd(OAc) ₂	NBu ₃	AsPh ₃		DMF	65 °C	50 - 58 %

^{*a*} Scheme 3, catalyst concentration 10-33 mol %. If no coupling product was observed, the reactions were stopped after 2 days. bppp, 1,3-bis(diphenylphosphino)propane.

starting material or to decomposition at higher temperatures. No product arising from Heck coupling could be isolated (entries 10–13). Finally, **12** was obtained in a yield of 58% after replacement of the phosphine ligands by the "soft" ligand AsPh₃²⁰ and by using DMF as the solvent (entry 14). As expected,^{11–15} the double bond flipped to the 3,4-position of the pyrrolidine ring. The *R*-configuration of the new stereocenter was proven at a later stage.

Both silyl ethers of **12** were cleaved with TBAF under mild acidic deprotection conditions. At -15 °C the obtained keto group was stereoselectively reduced with NaB-(OAc)₃H.¹⁵ Diol **4** was separated by FC from a minor stereoisomer (<5%), which was not further analyzed. The corresponding *N*-1-Me compound **13** was obtained in 77% yield after reaction of the tetrasilyl derivative of **4**, which was prepared in situ, with CH₃I for 70 h.²¹ Pd-catalyzed hydrogenation of the CBz group of **4** and **13** was achieved at a H₂ pressure of 1 bar. For determination of the relative configuration, amine **14** was converted into the *N*-acetyl compound **16**. The NMR data of **16** were identical with those reported for the same compound in the literature¹⁰ and proved the expected (2R,4S,5R)-configuration (independent confirmation by NOE experiments). For the remaining part of the synthesis, **14** and **15** were *N*-protected with the Fmoc group that was shown earlier to be compatible with standard oligonucleotide synthesis.⁸ The phosphoramidite building blocks **19** and **20** were obtained by dimethoxy-tritylation of the primary alcohol of **17** and **18**, respectively, followed by



^{*a*} (a) AcOH, TBAF, THF, $-15 \text{ °C} \rightarrow \text{rt}$, 37 h; (b) NaB(OAc)₃H, AcOH, CH₃CN, $-15 \text{ °C} \rightarrow \text{rt}$, 20 min; (c) BSA, CH₃I, CH₂Cl₂, rt, 70 h; (d) H₂, Pd/C, MeOH, rt, 4 h; (e) Ac₂O, MeOH, H₂O, 0 °C \rightarrow rt, 2.5 h; (f) Fmoc-OSu, THF, dioxane, 5% aq. NaHCO₃ soln, rt, 3 h; (g) DMT-Cl, pyridine, rt, 2 h; (h) (*i*Pr₂N)(NCCH₂CH₂O)PCl, *i*Pr₂NEt, THF, rt, 2 h.

reaction with 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite. The amidites **19** and **20** can be directly used for standard cyanoethyl phosphoramidite oligonucleotide synthesis. The total yields of **19** and **20** from **6** were 14% and 6%, respectively (Scheme 4).

In conclusion, an efficient method for the syntheses of the pyrrolidine-2'-deoxypseudouridine phosphoramidite building block **19** and its *N*-1-methyl derivative **20** (pyrrolidinepseudothymidin) was developed. It was shown that Hecktype reactions can be employed to build up pyrrolidine *C*-nucleosides from the corresponding *N*-protected enamines and functionalized heterocycles. However, the reaction conditions, especially the tuning of the electronic properties of the ligand, are critical for the success of the Pd-catalyzed coupling. AsPh₃ as a "soft" ligand of monodentate donicity proved to be appropriate.

The incorporation of the new phosphoramidites into oligonucleotides and the evaluation of their biophysical and biological properties are in progress.

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Supporting Information Available: Experimental procedure for the synthesis of all compounds and their spectroscopic characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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