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Synthesis of Pyrrolidine *C*-Nucleosides via Heck Reaction

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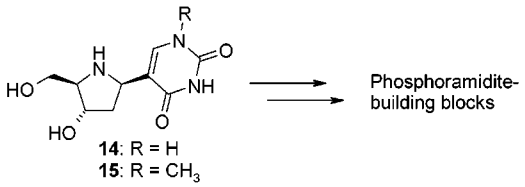
ABSTRACT



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 CH_2-unit between C-1′ and the base were incorporated into DNA by Verdine and co-workers. 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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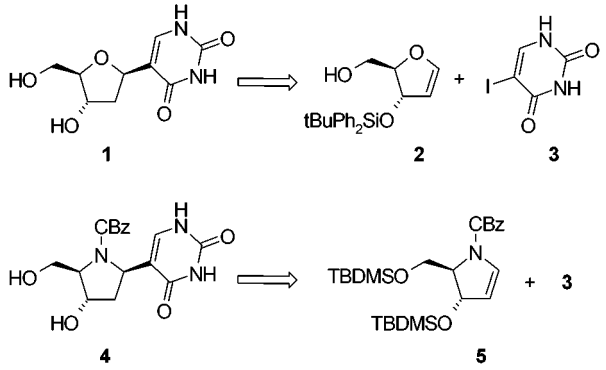
C-glycosidic bonds.[11−14] Zhang et al. used Heck chemistry for the synthesis of 2′-deoxypseudouridine[15] (Scheme 1). Less

Scheme 1. Retrosynthesis of 2′-Deoxypseudouridine (**1**) by Zhang et al.[15] and of the *C*-Aza-furanose Nucleoside **4**[a]



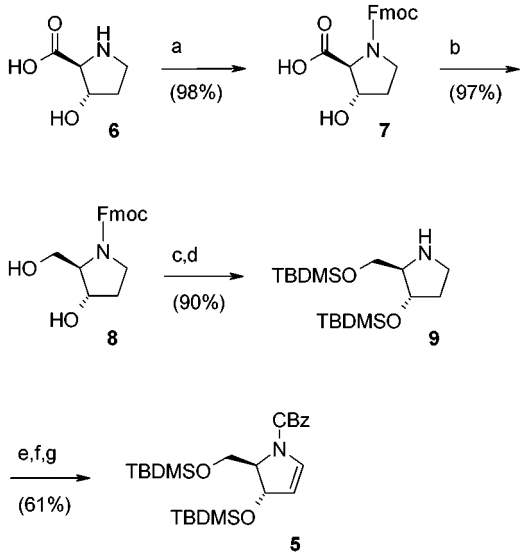
[a] CBz, benzyloxycarbonyl; TBDMS, *tert*-butyldimethylsilyl.

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 regio- and stereospecific synthesis of pyrrolidine-2′-deoxypseudouridine and of its *N*-1-methyl derivative (pyrrolidine-pseudothymidine) 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*-3-hydroxy-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 $BH_3{\cdot}S(CH_3)_2$ 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 (→ **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-2*H*-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 NEt_3 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

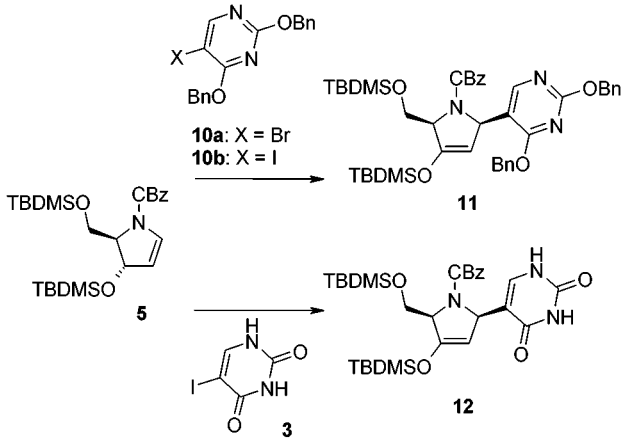
Scheme 2. Synthesis of *N*-CBz Enamine **5**[a]



[a] (a) Fmoc-Cl, dioxane, 5% aq. $NaHCO_3$ soln, 0 °C → rt, 9 h; (b) $BH_3{\cdot}(CH_3)_2S$, 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, NEt_3, THF, −78 °C → rt, 8 h.

(**10b**, synthesized from **10a** by Br−Li exchange, followed by the reaction with I_2, 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 PPh_3 or bppp as ligand and NBu_3 as base and carrying out the reaction in $CHCl_3$ 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 PPh_3, bppp, or $P(C_6F_5)_3$ as ligands led to unreacted

Scheme 3. Palladium-Mediated Heck Coupling[a]



[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]

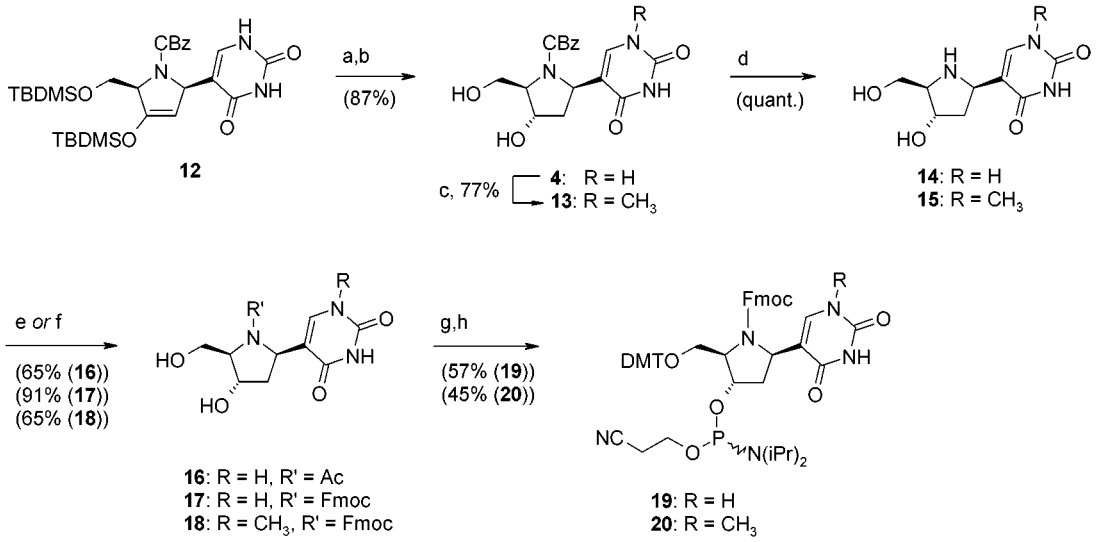
entry	aglycon	catalyst	base	ligand	additive	solvent	temp	yield
1	10a	$Pd(Ph_3)_4$	NEt_3	PPh_3		CH_3CN	80 °C	
2	10a	$Pd(OAc)_2$	K_2CO_3		Bu_4NCl	DMF	rt	
3	10b	$Pd(OAc)_2$	NBu_3	PPh_3		$CHCl_3$	60 °C	
4	10b	$Pd(OAc)_2$	NBu_3	PPh_3		CH_3CN	80 °C	
5	10b	$Pd(OAc)_2$	Ag_2CO_3	PPh_3		DMF	80 °C	
6	10b	$Pd(OAc)_2$	NBu_3		Na-acetate	DMF	90 °C	
7	10b	$Pd(OAc)_2$	$NaHCO_3$		Bu_4NCl	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 $AsPh_3$[20] 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 CH_3I for 70 h.[21] Pd-catalyzed hydrogenation of the CBz group of **4** and **13** was achieved at a H_2 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 literature[10] and proved the expected (2*R*,4*S*,5*R*)-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

Scheme 4. Synthesis of Phosphoramidites **19** and **20**[a]



[a] (a) AcOH, TBAF, THF, −15 °C → rt, 37 h; (b) $NaB(OAc)_3H$, AcOH, CH_3CN, −15 °C → rt, 20 min; (c) BSA, CH_3I, CH_2Cl_2, rt, 70 h; (d) H_2, Pd/C, MeOH, rt, 4 h; (e) Ac_2O, MeOH, H_2O, 0 °C → rt, 2.5 h; (f) Fmoc-OSu, THF, dioxane, 5% aq. $NaHCO_3$ soln, rt, 3 h; (g) DMT-Cl, pyridine, rt, 2 h; (h) (iPr_2N)($NCCH_2CH_2O$)PCl, iPr_2NEt, 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** (pyrrolidine-pseudothymidin) was developed. It was shown that Heck-type 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. $AsPh_3$ 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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