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A general synthesis of alkylpyridines

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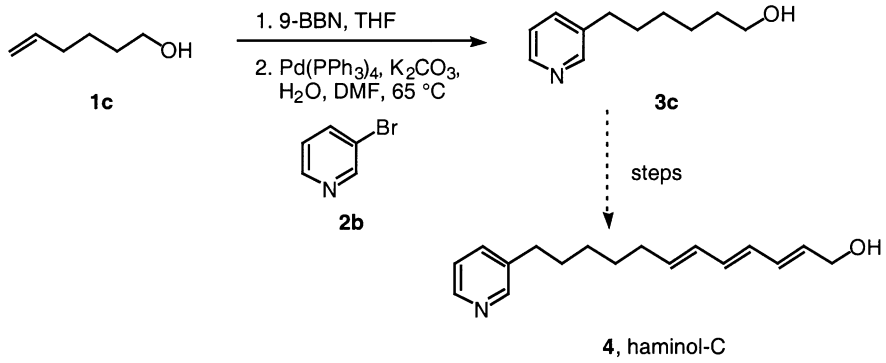
Abstract—The hydroboration of alkenes, followed by the coupling of the *B*-alkyl-9-borabicyclo[3.3.1]nonane derivatives with bromopyridines constitutes an efficient procedure for the attachment of functionalized alkyl chains to the pyridine nucleus.

1. Introduction

Besides its presence as partial structures of many pharmaceuticals, alkylpyridines constitute a structural motif commonly found in biologically active natural products.[1a] Notably among the latter are 3-alkylpyridines produced by sponges of the *Niphatidae* family[1b] which have been proposed as biosynthetic precursors of the more complex manzamine and related alkaloids.[2] Given the ready availability of halogenated pyridines, their cross-coupling to alkynylcopper species catalyzed by palladium (Sonogashira coupling reaction)[3] followed by hydrogenation of the alkynyl moiety[3a] has been the most frequently used method for attachment of the side chain to the pyridine nucleus. However, a most straightforward approach could be envisaged if direct attachment of the alkyl chain using the transmetalation to palladium of the corresponding alkyl organometallic derivative was feasible. The formation of the Csp^3–Csp^2 bond has proven to be a difficult endeavour. The discovery by Suzuki that the 9-alkyl-9-BBN derivatives efficiently transmetalate to palladium was an important breakthrough in this field. Since alkylboranes are easily prepared by hydroboration of alkenes, and the Suzuki reaction shows excellent compatibility with an array of functional groups in both reactants, being the by-products rather inocuous, the preparative scope of this coupling process is remarkable.[4,5]

In connection with a synthetic project aimed at the preparation of some metabolites with alarm pheromone activity found in Mediterranean cephalaspideans,[6] we directed our efforts to implement the Suzuki reaction for attachment of alkyl side chains to the pyridine ring found on these metabolites. Gratifyingly, the palladium-catalyzed cross-coupling reaction of the alkylborane generated in situ by hydroboration of the corresponding alkene **1c**, and 3-bromopyridine **2b** was very efficient, providing in high yield the alkanol **3c** on route to haminol-C **4** (Scheme 1). As an extension of this work, we have found that the Suzuki cross-coupling of 9-alkyl-9-BBN derivatives is equally



Scheme 1.

Keywords: pyridines; Suzuki reactions; heterocycles.

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applicable to the entire series of bromopyridines. This finding, together with the limitations encountered using other heterocyclic halides are reported.

2. Results and discussion

In order to define the scope and limitations of the alkyl Suzuki coupling reaction,[7] the positional isomers of bromopyridine (**2a–c**) were chosen as the organic electrophile partner, whereas for convenience the trialkylborane component was prepared in situ by hydroboration of commercially available alkenols **1a–c**, **5** (Fig. 1).

The coupling of 3-bromopyridine **2b** and the 9-BBN derivative of 5-hexen-1-ol **1c** (Scheme 1) was selected for optimization of the reaction conditions, and the results are listed in Table 1.

The palladium-catalyzed coupling of organic halides or pseudohalides to organoboranes (Suzuki reaction) is considered to share with other organometallic processes (e.g. the coupling of organostannanes, organozinc reagents, …) a catalytic cycle involving three basic steps: (1) the oxidative addition of the electrophilic halide to Pd (0), (2) the transmetalation of the carbon substituent from the organometal to the resulting Pd(II) complex, and (3) the rapid reductive elimination of the cross-coupling product with the regeneration of the PdL_2 catalyst. However, the Suzuki reaction differs from others in that it requires a base for the coupling reaction to have an appreciable rate. This suggests the formation of a tetravalent boron species and a halide-by-base metathesis capable of effecting boron to palladium transmetalation, as an additional step of the catalytic cycle.[4b]

For the coupling of bromopyridine **2b** to the alkylborane obtained from **1c**, we also found that an inorganic base had an essential role, since its absence precluded the reaction. The set of reaction conditions explored involve the use of bases in both aqueous and polar aprotic solvents.[8,9] Although a combination of $Pd(PPh_3)_4$ and NaOH in THF/H_2O works well in this coupling (entry 1), best yields and lower temperatures were achieved when using K_2CO_3 as base in the solvent system THF/DMF/H_2O (entry 2). With $PdCl_2$(dppf) as catalyst, best yields were obtained with less basic reagents, such as powdered K_3PO_4 or Cs_2CO_3 suspended in a THF/DMF mixture (entries 4–6), although the temperatures were in general higher than those required with $Pd(PPh_3)_4$. Previously it has been reported that treating the reaction mixture with water for 30 min after the hydroboration step resulted in improved yields of the coupling product, perhaps as a result of a more efficient hydrolysis of the residual 9-BBN.[8] However in our case this modification gave low yields of alkylpyridine **3c** (50%, entry 7).

Compared to other electrophiles, which couple at about 50°C,[9] bromopyridine **2b** generally requires higher temperatures (>65°C). Buchwald recently reported the room temperature Suzuki cross-coupling of aryl boronic acids or alkylboranes with aryl bromides and the even less-reactive aryl chlorides using mixtures of palladium acetate and 2-(di-*tert*-butylphosphino)biphenyl with low catalyst loadings in different base/solvent systems.[10] In our hands, however, the modification proved ineffective with KF in THF at 65°C (entry 8), but proceeded in moderate yield (70%) with K_3PO_4 in toluene, requiring however 100°C to go to completion (entry 9).

The combination of catalyst, base and solvent found to be optimal for the reaction (see Table 1, entry 2, $Pd(PPh_3)_4$, K_2CO_3 in THF/DMF/H_2O) was then used for coupling the

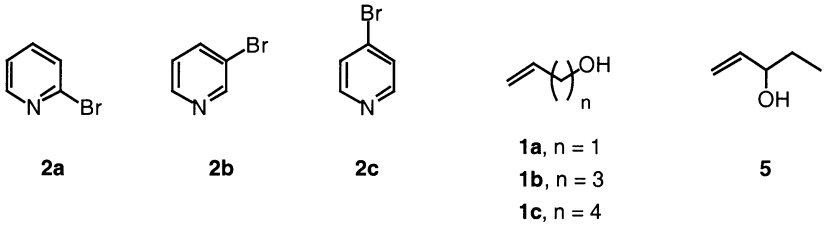


Figure 1.

Table 1. Suzuki coupling of 3-bromopyridine **2b** with the 9-BBN derivative of 5-hexen-1-ol **1c**

Entry	Catalyst	Base	Solvent	*T* (°C)	*t* (h)	Yield (%)
1	$Pd(PPh_3)_4$	NaOH	THF/H_2O	75–80	3.5	87
2	$Pd(PPh_3)_4$	K_2CO_3	THF/DMF/H_2O	65–70	1	93[a]
3	$PdCl_2$(dppf)	NaOH	THF/H_2O	65	20	60–70
4	$PdCl_2$(dppf)	K_3PO_4	THF/DMF	90	6	60–70
5	$PdCl_2$(dppf)	Cs_2CO_3	THF/DMF	80	17	89
6	$PdCl_2$(dppf)	K_2CO_3	THF/DMF	90	24	88
7	$PdCl_2$(dppf)	K_2CO_3	THF/H_2O/DMF	100	19.5	50
8	$Pd(OAc)_2$[b]	KF	THF	65	15	–
9	$Pd(OAc)_2$[b]	K_3PO_4	THF/toluene	100	17	70

[a] Ref. 6.
[b] 8 mol% 2-(di-*tert*-butylphosphino)biphenyl was added as ligand.

Table 2. Generalized synthesis of alkylpyridines by Suzuki reaction

Entry	R–Br	Alkene	Reaction conditions[a]	Product	Yield (%)
1	**2a**	**1a**	NaOH, 70°C, 14.5 h	**6a**	75
2	**2a**	**1b**	K_2CO_3, 70°C, 4 h	**6b**	86
3	**2a**	**1c**	K_2CO_3, 70°C, 3 h	**6c**	78
4	**2a**	**5**	K_2CO_3, 70°C, 4 h	**7**	78
5	**2b**	**1a**	Cs_2CO_3, 57°C, 2 h	**3a**	93
6	**2b**	**1b**	K_2CO_3, 70°C, 4 h	**3b**	69
7	**2b**	**1c**	K_2CO_3, 65°C, 1 h	**3c**	93
8	**2b**	**5**	K_2CO_3, 70°C, 2 h	**8**	69
9	**2c**	**1a**	K_2CO_3, 75°C, 3 h	**9a**	60
10	**2c**	**1b**	K_2CO_3, 70°C, 4 h	**9b**	94
11	**2c**	**1c**	K_2CO_3, 70°C, 2 h	**9c**	78
12	**2c**	**5**	K_2CO_3, 70°C, 2 h	**10**	63

[a] (1) Alkene, 9-BBN, THF, 25°C; (2) R–Br, $Pd(PPh_3)_4$, base in H_2O, DMF, 57–70°C.

isomeric bromopyridines **2a–c** to the alkylboranes derived from alkenols **1a–c**, **5** depicted in Fig. 1. The results are collected in Table 2. Alkylpyridines with different substitution pattern and side chain length could be efficiently obtained (alkylpyridines **6a**, **3a** and **9a** are commercially available) regardless of the position of the halogen atom and the length of the side chain. Only in two cases (see Table 2, entries 1 and 5) did a change in the base (NaOH or Cs_2CO_3 instead of K_2CO_3) afford better yields than the generalized reaction conditions.

Given the success in the use of heteroaromatic halides as electrophilic partners, we attempted to broaden the application of the hydroboration-alkyl Suzuki tandem reaction to the preparation of additional heterocyclic derivatives of biological interest. Appealing candidates are pyrimidine nucleosides, since the ones modified at the C5-position have been used as antiviral agents, to stabilize DNA-triple helices and for the incorporation of reporter groups into oligonucleotides.[11] Attachment of alkyl side chains to the 5-position of the pyrimidine nucleoside frequently relies on the Sonogashira coupling, followed by the hydrogenation of the alkyne.[11] However, all our attempts directed at the coupling of nucleoside **11**[12] (Fig. 2) with alkylboranes proved unsuccessful, despite the fact that iodides are in general more reactive than bromides. In addition, even simpler heterocycles such as 2-iodothiophene **12** or 4-iodopyrazole **13** (Fig. 2) proved less reactive under the same reaction conditions that worked efficiently for the bromopyridine series, including application of the improved Buchwald protocol.[10] Nevertheless, the latter gave a moderate yield (55%) for the coupling of **1c** to 5-bromopyrimidine **14**, a substrate found to be scarcely reactive under the more classical Suzuki coupling conditions, for the generation of the coupling product **15** (Scheme 2).

In summary, the palladium-catalyzed Suzuki cross-coupling reaction of *B*-alkyl-9-borabicyclo[3.3.1]nonane derivatives and bromopyridines has proved fruitful for the preparation of functionalized alkylpyridines. The method has the added benefit of compatibility with additional functional groups in both reaction components, thus providing a convenient alternative for the preparation of biologically and pharmaceutically relevant alkylpyridines.[13,14]

3. Experimental

3.1. General

Solvents were dried according to published methods and were distilled before use. All other reagents were commercial compounds of the highest purity available. Analytical thin-layer chromatography (TLC) was performed using Merck silica gel (60 F-254) plates (0.25 mm) precoated with a fluorescent indicator. Column chromatography was performed using Merck silica gel 60 (particle size 0.040–0.063 μm). Proton (^1H) and carbon (^{13}C) magnetic resonance spectra (NMR) were recorded on a Bruker AMX-400

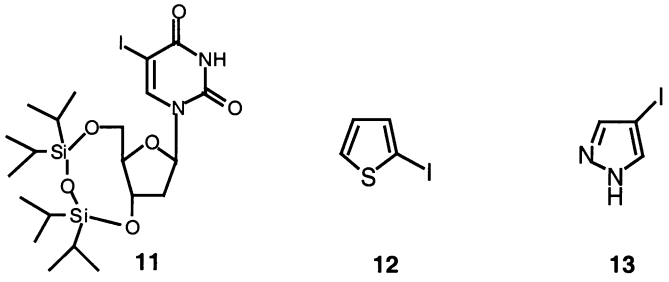
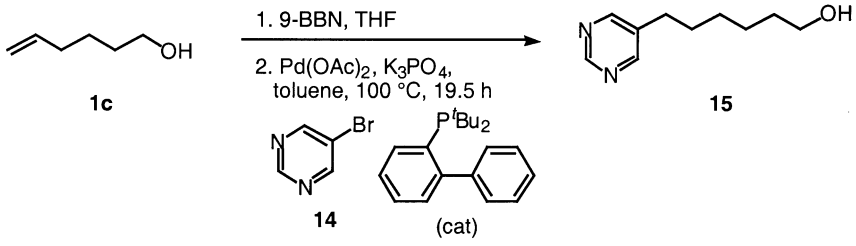


Figure 2.



Scheme 2.

[400 MHz (100 MHz for ^{13}C)] Fourier transform spectrometer, and chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane (TMS, 0 ppm) or chloroform ($CHCl_3$, 7.24 ppm for ^1H and 77.00 ppm for ^{13}C) as internal reference. ^{13}C multiplicities (s, singlet; d, doublet; t, triplet; q, quartet) were assigned with the aid of the DEPT pulse sequence. Infrared spectra (IR) were obtained on a MIDAC Prospect Model FT-IR spectrophotometer. Absorptions are recorded in wave numbers (cm^{-1}). Low-resolution mass spectra were taken on an HP59970 instrument operating at 70 eV. High-resolution mass spectra were taken on a VG Autospec M instrument.

3.2. General procedure for the hydroboration-Suzuki tandem reaction

To a cooled (0°C) solution of alkenol (1.50 mmol) in THF (3 mL) was slowly added 9-BBN (0.5 M in THF, 4.50 mmol). The mixture was slowly warmed up to 25°C and then stirred for 2–6 h to give a solution of the *B*-alkyl-9-BBN derivative. *Procedure A*. The solution of *B*-alkyl-9-BBN in THF was transferred into a separate flask containing the heterocyclic halide, the palladium catalyst [$Pd(PPh_3)_4$ or $PdCl_2$dppf] and the base (K_2CO_3, NaOH, Cs_2CO_3 or K_3PO_4) in DMF. The mixture was stirred at the appropriate temperature until TLC monitoring showed complete disappearance of the starting material. It was then diluted with AcOEt and poured into H_2O. The aqueous layer was extracted with AcOEt (3×). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated. *Procedure B* Water (3 mL) was added to the solution of *B*-alkyl-9-BBN in THF and the mixture was stirred at 25°C for 90 min. It was then transferred into a separate flask containing the heterocyclic halide, $Pd(OAc)_2$, K_3PO_4 and 2-(di-*tert*-butylphosphino)biphenyl in toluene. The final mixture was stirred at 100°C until complete disappearance of the starting material. It was then worked up as in procedure A.

3.2.1. 5-Pyridin-2-yl-pentan-1-ol (6b). Following the general procedure (procedure A, Table 2, 70°C, 4 h), the reaction of 4-penten-1-ol **1b** (0.10 g, 1.16 mmol), 2-bromopyridine **2a** (0.22 g, 1.40 mmol), $Pd(PPh_3)_4$ (0.13 g, 0.12 mmol) and K_2CO_3 (1.60 mL, 3 M in H_2O, 4.65 mmol) in DMF (8 mL) afforded, after purification by chromatography (SiO_2, AcOEt), 0.16 g (86%) of 5-pyridyn-2-yl-pentan-1-ol **6b**. ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (m, 2H, $2H_3$), 1.60 (m, 2H, $2H_4$), 1.70 (m, 2H, $2H_2$), 1.80 (br s, 1H, OH), 2.74 (t, J=7.7 Hz, 2H, $2H_5$), 3.59 (t, J=6.5 Hz, 2H, $2H_1$), 7.03 (dd, J=7.6, 4.8 Hz, 1H, $H_{5'}$), 7.08 (d, J=7.6 Hz, 1H, $H_{3'}$), 7.52 (dt, J=7.6, 1.2 Hz, 1H, $H_{4'}$), 8.44 (dd, J=4.8, 1.2 Hz, 1H, $H_{6'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3 (t), 29.4 (t), 32.4 (t), 37.9 (t, C_5), 62.0 (t, C_1), 120.8 (d, $C_{5'}$), 122.7 (d, $C_{3'}$), 136.3 (d, $C_{4'}$), 148.7 (d, $C_{6'}$), 161.9 (s, $C_{2'}$); IR (NaCl) ν 3600–3100 (br, O–H), 2929 (s, C–H), 2859 (s, C–H), 1596 (s), 1570 (w), 1477 (m), 1437 (m), 1369 (w), 1353 (w), 1055 (m), 1006 (m), 959 (w), 764 (m) cm^{-1}; MS *m/z* (%) 166 ($[M+1]^+$, 43), 120 (21), 106 (26), 93 (100), 85 (17), 83 (26); HRMS calcd for $C_{10}H_{15}NO$ 165.1154, found 165.1150.

3.2.2. 6-Pyridin-2-yl-hexan-1-ol (6c). Following the general procedure described above (procedure A, Table 2, 70°C, 3 h), starting from 5-hexen-1-ol **1c** (0.05 g, 0.50 mmol), 2-bromopyridine **2a** (0.10 g, 0.60 mmol), $Pd(PPh_3)_4$ (0.06 g, 0.05 mmol) and K_2CO_3 (0.84 mL, 3 M in H_2O, 2.5 mmol), it was obtained 0.07 g (78%) of 6-pyridin-2-yl-hexan-1-ol **6c**, after purification by chromatography (SiO_2, AcOEt). ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (m, 4H, $2H_3+2H_4$), 1.60 (m, 2H, $2H_5$), 1.70 (m, 2H, $2H_2$), 1.90 (br s, 1H, OH), 2.79 (t, J=7.7 Hz, 2H, $2H_6$), 3.63 (t, J=6.5 Hz, 2H, $2H_1$), 7.10 (dd, J=7.6, 4.6 Hz, 1H, $H_{5'}$), 7.14 (d, J=7.6 Hz, 1H, $H_{3'}$), 7.59 (dt, J=7.6, 1.8 Hz, 1H, $H_{4'}$), 8.51 (d, J=4.6 Hz, 1H, $H_{6'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4 (t), 28.8 (t), 29.8 (t), 32.5 (t, C_2), 38.1 (t, C_6), 62.7 (t, C_1), 120.9 (d, $C_{5'}$), 122.7 (d, $C_{3'}$), 136.4 (d, $C_{4'}$), 149.0 (d, $C_{6'}$), 162.3 (s, $C_{2'}$); IR (NaCl) ν 3600–3100 (br, O–H), 2931 (s, C–H), 2858 (s, C–H), 1594 (m), 1570 (m), 1476 (m), 1436 (m), 1250 (w), 1054 (m), 1001 (w), 844 (m), 759 (m) cm^{-1}; MS *m/z* (%) 180 ($[M+1]^+$, 2), 148 (5), 121 (44), 120 (19), 106 (29), 93 (100), 85 (18), 83 (29); HRMS calcd for $C_{11}H_{18}NO$ ($[M+H]^+$) 180.1388, found 180.1391.

3.2.3. *rac*-1-Pyridin-2-yl-pentan-3-ol (7). According to the general procedure described above (procedure A, Table 2, 70°C, 4 h), the reaction of *rac*-1-penten-3-ol **5** (0.10 g, 1.16 mmol), 2-bromopyridine **2a** (0.22 g, 1.39 mmol), $Pd(PPh_3)_4$ (0.13 g, 0.12 mmol) and K_2CO_3 (1.6 mL, 3 M in H_2O, 4.65 mmol), afforded, after purification by chromatography (SiO_2, AcOEt), 0.15 g (78%) of *rac*-1-pyridin-2-yl-pentan-3-ol **7**. ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J=7.4 Hz, 3H, $3H_5$), 1.40 (m, 2H, $2H_4$), 1.70 (m, 1H, H_2), 1.90 (m, 1H, H_2), 2.90 (m, 2H, $2H_1$), 3.50 (m, 1H, H_3), 7.06 (dd, J=7.5, 5.1 Hz, 1H, $H_{5'}$), 7.12 (d, J=7.5 Hz, 1H, $H_{3'}$), 7.55 (dt, J=7.5, 1.7 Hz, 1H, $H_{4'}$), 8.42 (d, J=5.1 Hz, 1H, $H_{6'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.1 (q, C_5), 30.3 (t, C_4), 34.6 (t, C_2), 35.9 (t, C_1), 72.4 (d, C_3), 121.0 (d, $C_{5'}$), 123.1 (d, $C_{3'}$), 136.7 (d, $C_{4'}$), 148.5 (d, $C_{6'}$), 161.8 (s, $C_{2'}$); IR (NaCl) ν 3600–3100 (br, O–H), 2960 (s, C–H), 2927 (s, C–H), 2875 (s, C–H), 1596 (s), 1570 (m), 1477 (m), 1436 (s), 1340 (m), 1121 (m), 992 (m), 753 (m) cm^{-1}; MS *m/z* (%) 166 ($[M+1]^+$, 1), 165 (M^+, 0.5), 164 ($[M-1]^+$, 2), 148 (10), 136 (50), 118 (14), 107 (17), 106 (49), 93 (100), 92 (11), 85 (35), 83 (54); HRMS calcd for $C_{10}H_{14}NO$ ($[M-H]^+$) 164.1075, found 164.1077.

3.2.4. 5-Pyridin-3-yl-pentan-1-ol (3b). Following the general procedure described above (procedure A, Table 2, 70°C, 4 h), starting from 4-penten-1-ol **1b** (0.10 g, 1.16 mmol), 3-bromopyridine **2b** (0.22 g, 1.39 mmol), $Pd(PPh_3)_4$ (0.13 g, 0.12 mmol) and K_2CO_3 (1.6 mL, 3 M in H_2O, 4.65 mmol), it was obtained 0.13 g (69%) of 5-pyridin-3-yl-pentan-1-ol **3b**, after purification by chromatography (SiO_2, AcOEt). ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (m, 2H, $2H_3$), 1.60 (m, 4H, $2H_2+2H_4$), 2.63 (t, J=7.7 Hz, 2H, $2H_5$), 3.65 (t, J=6.5 Hz, 2H, $2H_1$), 7.21 (dd, J=7.7, 4.8 Hz, 1H, $H_{5'}$), 7.50 (d, J=7.7 Hz, 1H, $H_{4'}$), 8.44 (d, J=4.8 Hz, 1H, $H_{6'}$), 8.44 (s, 1H, $H_{2'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3 (t), 30.9 (t), 32.5 (t), 32.9 (t, C_5), 62.6 (t, C_1), 123.3 (d, $C_{5'}$), 135.8 (d, $C_{4'}$), 137.7 (s, $C_{3'}$), 147.2 (d, $C_{6'}$), 149.8 (d, $C_{2'}$); IR (NaCl) ν 3600–3100 (br, O–H), 2928 (s, C–H), 2858 (s, C–H), 1447 (s), 1352 (m), 1217 (m), 1063 (m), 1009 (s), 958 (m), 754 (m), 714 (m) cm^{-1}; MS *m/z* (%) 166 ($[M+1]^+$, 5), 165 (M^+, 32), 164 ($[M-1]^+$, 14), 148 (5), 118 (26), 106 (100), 105 (52), 93 (43), 92 (38); HRMS calcd for $C_{10}H_{15}NO$ 165.1154, found 165.1148.

3.2.5. *rac*-1-Pyridin-3-yl-pentan-3-ol (8). According to the general procedure described above (procedure A, Table 2, 70°C, 2 h), starting from *rac*-1-penten-3-ol **5** (0.10 g, 1.16 mmol), 3-bromopyridine **2b** (0.22 g, 1.39 mmol), $Pd(PPh_3)_4$ (0.13 g, 0.12 mmol) and K_2CO_3 (1.6 mL, 3 M in H_2O, 4.65 mmol), it was obtained 0.13 g (69%) of *rac*-1-pyridin-3-yl-pentan-3-ol **8**, after purification by chromatography (SiO_2, AcOEt). ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J=7.4 Hz, 3H, $3H_5$), 1.40 (m, 2H, $2H_4$), 1.70 (m, 3H, $2H_2$+OH), 2.60 (m, 1H, H_1), 2.70 (m, 1H, H_1), 3.50 (m, 1H, H_3), 7.15 (dd, J=7.7, 4.8 Hz, 1H, $H_{5'}$), 7.46 (d, J=7.7 Hz, 1H, $H_{4'}$), 8.40 (m, 2H, $H_{2'}$+$H_{6'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.8 (q, C_5), 29.1 (t), 30.3 (t), 38.1 (t, C_1), 71.8 (d, C_3), 123.3 (d, $C_{5'}$), 136.0 (d, $C_{4'}$), 137.7 (s, $C_{3'}$), 146.9 (d, $C_{6'}$), 149.6 (d, $C_{2'}$); IR (NaCl) ν 3600–3100 (br, O–H), 2960 (s, C–H), 2926 (s, C–H), 2874 (s, C–H), 1579 (w), 1425 (m), 1342 (m), 1121 (m), 1030 (m), 713 (m) cm^{-1}; MS *m/z* (%) 166 ($[M+1]^+$, 5), 165 (M^+, 1), 164 ($[M-1]^+$, 3), 149 (9), 148 (12), 147 (97), 136 (37), 118 (54), 107 (15), 106 (62), 105 (67), 93 (37), 92 (100), 85 (20), 83 (32), 79 (15), 62 (25); HRMS calcd for $C_{10}H_{16}NO$ ($[M+H]^+$) 166.1232, found 166.1231.

3.2.6. 5-Pyridin-4-yl-pentan-1-ol (9b). According to the general procedure described above (procedure A, Table 2, 70°C, 4 h), the reaction of 4-penten-1-ol **1b** (0.10 g, 1.16 mmol), 4-bromopyridine hydrochloride **2c**·HCl (0.27 g, 1.40 mmol), $Pd(PPh_3)_4$ (0.13 g, 0.12 mmol) and K_2CO_3 (3.2 mL, 3 M in H_2O, 9.30 mmol), afforded, after purification by chromatography (SiO_2, AcOEt), 0.18 g (94%) of 5-pyridin-4-yl-pentan-1-ol **9b**. ^1H NMR (400 MHz, $CDCl_3$) δ 1.4–1.7 (m, 7H, $2H_2$+$2H_3$+$2H_4$+OH), 2.63 (t, J=7.7 Hz, 2H, $2H_5$), 3.65 (t, J=6.5 Hz, 2H, $2H_1$), 7.11 (d, J=5.8 Hz, 2H, $H_{3'}$+$H_{5'}$), 8.48 (d, J=5.8 Hz, 2H, $H_{2'}$+$H_{6'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2 (t), 29.8 (t), 32.3 (t), 34.9 (t, C_5), 61.8 (t, C_1), 123.8 (d, $C_{3'}$+$C_{5'}$), 149.0 (d, $C_{2'}$+$C_{6'}$), 151.7 (s, $C_{4'}$); IR (NaCl) ν 3600–3100 (br, O–H), 2928 (s, C–H), 2859 (s, C–H), 1608 (m), 1446 (m), 1064 (m), 1006 (s), 752 (m) cm^{-1}; MS *m/z* (%) 166 ($[M+1]^+$, 4), 165 (M^+, 20), 164 ($[M-1]^+$, 11), 147 (13), 119 (13), 118 (25), 106 (100), 105 (70), 93 (56), 92 (17), 65 (13); HRMS calcd for $C_{10}H_{15}NO$ 165.1154, found 165.1153.

3.2.7. 6-Pyridin-4-yl-hexan-1-ol (9c). Following the general procedure described above (procedure A, Table 2, 70°C, 2 h), starting from 5-hexen-1-ol **1c** (0.05 g, 0.5 mmol), 4-bromopyridine hydrochloride **2c**·HCl (0.12 g, 0.6 mmol), $Pd(PPh_3)_4$ (0.06 g, 0.05 mmol) and K_2CO_3 (0.84 mL, 3 M in H_2O, 2.5 mmol), it was obtained 0.07 g (78%) of 6-pyridin-4-yl-hexan-1-ol **9c**, after purification by chromatography (SiO_2, AcOEt). ^1H NMR (400 MHz, $CDCl_3$) δ 1.3–1.7 (m, 8H, $2H_2$+$2H_3$+$2H_4$+$2H_5$), 2.61 (t, J=7.7 Hz, 2H, $2H_6$), 3.65 (t, J=6.5 Hz, 2H, $2H_1$), 7.10 (d, J=5.5 Hz, 2H, $H_{3'}$+$H_{5'}$), 8.48 (d, J=5.5 Hz, 2H, $H_{2'}$+$H_{6'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5 (t), 28.8 (t), 30.1 (t), 32.5 (t, C_2), 35.0 (t, C_6), 62.4 (t, C_1), 123.9 (d, $C_{3'}$+$C_{5'}$), 149.3 (d, $C_{2'}$+$C_{6'}$), 151.7 (s, $C_{4'}$); IR (NaCl) ν 3600–3100 (br, O–H), 2931 (s, C–H), 2858 (s, C–H), 1606 (s), 1558 (w), 1418 (m), 1057 (m), 1003 (m), 724 (w) cm^{-1}; MS *m/z* (%) 179 (M^+, 9), 178 ($[M-1]^+$, 9), 120 (12), 118 (10), 107 (11), 106 (100), 105 (21), 93 (84), 92 (15), 85 (39), 83 (61), 65 (12); HRMS calcd for $C_{11}H_{17}NO$ 179.1310, found 179.1305.

3.2.8. *rac*-1-Pyridin-4-yl-pentan-3-ol (10). According to the general procedure described above (procedure A, Table 2, 70°C, 2 h), starting from *rac*-1-penten-3-ol **5** (0.07 g, 0.87 mmol), 4-bromopyridine hydrochloride **2c**·HCl (0.20 g, 1.05 mmol), $Pd(PPh_3)_4$ (0.10 g, 0.09 mmol) and K_2CO_3 (1.45 mL, 3 M in H_2O, 4.36 mmol), it was obtained 0.09 g (63%) of *rac*-1-pyridin-4-yl-pentan-3-ol **10**, after purification by chromatography (SiO_2, AcOEt). ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J=7.4 Hz, 3H, $3H_5$), 1.4–1.8 (m, 5H, $2H_4$+$2H_2$+OH), 2.70 (m, 1H, H_1), 2.80 (m, 1H, H_1), 3.50 (m, 1H, H_3), 7.15 (m, 2H, $H_{3'}$+$H_{5'}$), 8.49 (m, 2H, $H_{2'}$+$H_{6'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.8 (q, C_5), 30.3 (t), 31.3 (t), 37.2 (t, C_1), 71.8 (d, C_3), 124.0 (d, $C_{3'}$+$C_{5'}$), 149.1 (d, $C_{2'}$+$C_{6'}$), 151.9 (s, $C_{4'}$); IR (NaCl) ν 3600–3100 (br, O–H), 2927 (s, C–H), 2875 (s, C–H), 1606 (s), 1560 (w), 1419 (s), 1341 (m), 1220 (m), 1121 (m), 1002 (m), 755 (s) cm^{-1}; MS *m/z* (%) 166 ($[M+1]^+$, 11), 165 (M^+, 4), 147 (41), 136 (35), 118 (48), 107 (30), 106 (95), 105 (30), 93 (100), 92 (59), 80 (28), 65 (25); HRMS calcd for $C_{10}H_{15}NO$ 165.1154, found 165.1156.

3.2.9. 5-Iodo-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-2′-deoxyuridine (11). To a solution of 5-iodo-2′-deoxyuridine (0.05 g, 0.14 mmol) and imidazole (0.02 g, 0.31 mmol) in DMF (0.5 mL) was slowly added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (0.05 mL, 0.15 mmol). After 12 h stirring, excess silylating agent was decomposed by the addition of MeOH (1 mL), followed by AcOEt (1 mL). The solution was poured into a saturated aqueous NaCl solution and it was then extracted with AcOEt (3×). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated. Purification by column chromatography (SiO_2, 75:25 hexane/AcOEt) afforded 0.08 g (97%) of protected nucleoside **11** as a white solid (mp 182°C; Et_2O/hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 1.0–1.1 (m, 28H, 4×*i*-Pr), 2.2–2.3 (m, 1H, $H_{2'}$), 2.4–2.5 (m, 1H, $H_{2'}$), 3.7–3.8 (m, 1H, $H_{3'}$), 4.01 (dd, J=13.2, 2.9 Hz, 1H, $H_{5'}$), 4.13 (dd, J=13.2, 2.2 Hz, 1H, $H_{5'}$), 4.4–4.5 (m, 1H, $H_{4'}$), 6.00 (dd, J=7.2, 1.7 Hz, 1H, $H_{1'}$), 8.01 (s, 1H, H_6), 9.18 (br s, 1H, N–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4 (d), 12.8 (d), 13.0 (d), 13.5 (d), 16.8 (q), 16.9 (q), 17.0 (q), 17.1 (q), 17.2 (q), 17.4 (q), 17.6 (q), 17.7 (q), 39.9 (t, $C_{2'}$), 59.9 (t, $C_{5'}$), 67.1 (d), 68.0 (s, C_5), 84.7 (d), 85.3 (d), 144.0 (d, C_6), 149.8 (s), 160.1 (s); IR (NaCl) ν 3200–3100 (br), 3100–3000 (br), 2945 (m, C–H), 2867 (m, C–H), 2360 (m), 1698 (s, CO), 1605 (w), 1461 (m), 1270 (m), 1119 (m), 1038 (s), 887 (m), 773 (m), 698 (m), 612 (w) cm^{-1}; MS *m/z* (%) 597 ($[M+1]^+$, 7), 553 (8), 481 (11), 455 (44), 359 (15), 329 (10), 315 (22), 287 (68), 261 (100), 239 (26), 217 (13), 189 (17), 175 (32), 135 (57), 119 (71); HRMS calcd for $C_{21}H_{37}N_2IO_6Si_2$ ($[M+H]^+$) 597.1313, found 597.1306.

3.2.10. 6-Pyrimidin-5-yl-hexan-1-ol (15). According to the general procedure described above (procedure B, 100°C, 19.5 h), the reaction of 5-hexen-1-ol **1c** (0.08 g, 0.75 mmol), 5-bromopyrimidine **14** (0.08 g, 0.50 mmol), $Pd(OAc)_2$ (0.005 g, 0.02 mmol), K_3PO_4 (0.21 g, 1.00 mmol) and 2-(di-*tert*-butylphosphino)biphenyl (0.01 g, 0.04 mmol) in toluene (1.5 mL), afforded, after purification by chromatography (SiO_2, 97:3 CH_2Cl_2/MeOH), 0.05 g (55%) of 6-pyrimidin-5-yl-hexan-1-ol **15**. ^1H NMR (400 MHz, $CDCl_3$) δ 1.3–1.7 (m, 8H, $2H_2$+$2H_3$+$2H_4$+$2H_5$), 2.62 (t,

J=7.7 Hz, 2H, $2H_6$), 3.60 (br s, 2H, $2H_1$), 8.58 (s, 2H, $H_{4'}+H_{6'}$), 9.07 (s, 1H, $H_{2'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4 (t), 28.7 (t), 30.1 (t), 30.5 (t), 32.4 (t, C_6), 62.3 (t, C_1), 135.3 (s, $C_{5'}$), 156.3 (d, $C_{2'}$), 156.5 (d, $C_{4'}+C_{6'}$); IR (NaCl) ν 3600–3100 (br, O–H), 2931 (s, C–H), 2858 (s, C–H), 1562 (s), 1411 (s), 1055 (m), 728 (m), 637 (m) cm^{-1}; MS m/z (%) 181 ($[M+1]^+$, 3), 180 (M^+, 12), 179 ($[M-1]^+$, 7), 149 (11), 135 (20), 121 (12), 108 (13), 107 (100), 106 (30), 96 (17), 94 (49), 93 (18), 66 (14); HRMS calcd for $C_{10}H_{16}N_2O$ 180.1263, found 180.1269.

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