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A Facile and Efficient Synthesis of (Purin-6-yl)alanines

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(Purin-6-yl)alanines, a new class of amino acid−nucleobase conjugates, were synthesized by palladium-catalyzed cross-coupling reactions of protected iodozincalanines with 6-iodopurines (9-Bn-6-iodopurine and 9-THP-6-iodopurine as well as acyl-protected 6-iodopurine ribonucleoside and 2-deoxyribonucleoside). Free purine base and nucleosides bearing alanine in position 6 were obtained after complete deprotection of the products of cross-coupling reactions.

Purines bearing carbon substituents attached to carbon atoms of the purine ring (at positions 2, 6, or 8) are of great interest because of their potential applications in medicinal chemistry and chemical biology. Several examples of this class of compounds were reported to possess cytostatic,[1] antimicrobial,[2] and A_2-receptor agonist activity,[3] and some of them were used as artificial nucleobases in the extension of the genetic alphabet.[4] Cross-coupling reactions are a powerful tool[5] for the synthesis of these compounds but, in most cases, have only been used for an introduction of simple unfunctionalized alkyl, alkenyl, alkynyl, aryl, and hetaryl substituents. Therefore, an extension of this methodology to functionalized carbon substituents is a very challenging target. One of the prominent functionalized substituents of high biological relevance is undoubtedly an amino acid residue. Our goal is to develop approaches toward the synthesis of a novel class of compounds: carbon−carbon-linked conjugates of amino acids and purines. Such compounds may display biological activity and may be used as building blocks in the synthesis of chemically and enzymatically stable nucleic acids−peptide/protein conjugates. Very recently, protected (purin-6-yl)glycines were prepared in our laboratory by Pd-catalyzed α arylation of ethyl *N*-(diphenylmethylidene)glycinate, but because of very limited stability, they could not be deprotected.[6] This paper reports on the synthesis of (purin-6-yl)-alanines, another important example of this type of compound.

Racemic (9*H*-purin-6-yl)alanine,[7] (9-methylpurin-6-yl)-alanines,[8] and (purin-2-yl)alanines[9] were claimed to have been prepared 4 decades ago by multistep approaches using successive construction of the amino acid moiety in position 6 or 2 of a purine base, but no spectral characterization of the products was given and neither biological activity nor any other use of these compounds was ever reported. Moreover, these laborious multistep syntheses gave low total yields and are not suitable for the synthesis of enantiomerically pure amino acids.

Results and Discussion

Our synthesis of (purin-6-yl)alanines is based on Pd(0)-catalyzed cross-coupling reactions of protected iodozincalanines **3** and **4** with 6-iodopurines. This approach should enable a simple, single-step introduction of the entire alanine moiety to the target molecule and should be applicable for both racemic and enantiopure amino acids. Suitable protecting groups for the amino acid should be easily introduced, survive under the metalation and cross-coupling conditions, and should be readily cleaved under mild conditions without racemization. Therefore, the groups of choice were benzyl ester for carboxyl functions and Boc or Cbz groups for amino functions.

A preparation of iodozincalanines was recently developed by Jackson involving metalation of protected β-iodoalanines (e.g., **1**),[10] available in three steps from serine, with a zinc/copper[10] couple or activated zinc dust.[11] The zincation proceeds smoothly in several minutes, and use

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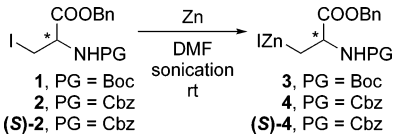
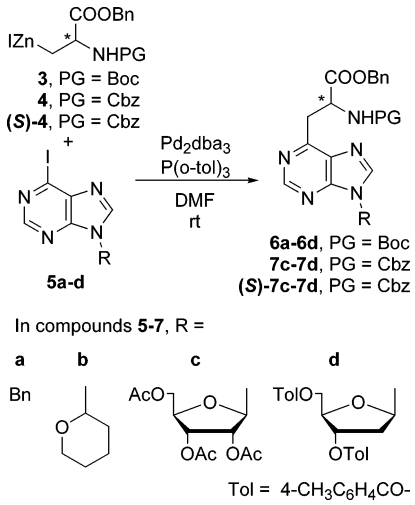
SCHEME 1. Synthesis of Alanylzinc Iodides



SCHEME 2. Synthesis of (Purin-6-yl)alanines



of obtained iodozincalanines in Pd-catalyzed cross-coupling reactions with aryl[10−13] or hetaryl[10,14] halides led to numerous aryl- or hetarylalanine derivatives. It was also established that DMF[11] is an excellent solvent for zincation as well as for subsequent cross-coupling and that the use of ultrasound[10] could increase the rate of the zincation.

We prepared racemic and enantiopure (*S*)-iodozincalanines **3** and **4** and (*S*)-**4** (Scheme 1) by sonication of the solution of iodoalanines **1** and **2** and (*S*)-**2** in DMF at room temperature with zinc dust activated only[13] by trimethylsilyl chloride (instead of the classical sequence[11] of 1,2-dibromoethane and trimethylsilyl chloride). These organozinc reagents were used in Pd-catalyzed cross-coupling reactions with 6-iodopurines **5a**−**5d** (9-Bn-6-iodopurine **5a** was used as an example of 9-alkylated purines, 9-THP-6-iodopurine **5b** is a 9-protected purine base, and derivatives **5c** and **5d** are examples of acyl-protected ribonucleosides or 2-deoxyribonucleosides; Scheme 2). The reactions were carried out in DMF at ambient temperature with a Pd(0) catalyst prepared from tris(dibenzylideneacetone)dipalladium and tri-*o*-tolylphosphine (4 equiv to Pd_2dba_3) to give the (purin-6-yl)alanines **6a**−**6d**, **7c**, **7d**, (*S*)-**7c**, and (*S*)-**7d** in excellent yields (Table 1). The slightly lower preparative yields (Table 1: entries 3, 5, and 7) of triacetylated derivatives **6c**, **7c**, and (*S*)-**7c** were caused by limited stability of the acetate protective groups during the final workup of the reaction mixtures.

TABLE 1. Synthesis of (Purine-6-yl)alanines

entry	purine	organozinc	config	product	yield (%)
1	**5a**	**3**	*R*,*S*	**6a**	95
2	**5b**	**3**	*R*,*S*	**6b**	88
3	**5c**	**3**	*R*,*S*	**6c**	75
4	**5d**	**3**	*R*,*S*	**6d**	94
5	**5c**	**4**	*R*,*S*	**7c**	80
6	**5d**	**4**	*R*,*S*	**7d**	96
7	**5c**	(*S*)-**4**	*S*	(*S*)-**7c**	72
8	**5d**	(*S*)-**4**	*S*	(*S*)-**7d**	95

The reaction was applied to both racemic and enantiopure amino acids. The enantiopure amino acids are the ones that will be used as building blocks for the conjugates, and therefore their racemization-free synthesis was crucial. However, the racemic amino acids could also be of some advantage, particularly for biological activity prescreening (parallel testing of both enantiomers). The use of racemic zincated amino acids in the synthesis of nucleosides leads to diastereomeric mixtures. This phenomenon can be used as proof that no racemization occurs during cross-coupling and deprotection using the enantiopure (*S*)-**4** by simply comparing the NMR spectra of the diastereomeric mixtures to those of the pure diastereoisomers. In the case of the diastereomeric mixtures of nucleosides **6c**, **6d**, **7c**, and **7d**, two sets of signals were clearly seen in the NMR spectra (see the Supporting Information), while the pure diastereoisomers (*S*)-**6** and (*S*)-**7** gave a single set of signals. However, these diastereomeric mixtures were not separable on achiral C-18 HPLC. On the other hand, the THP-protected derivatives **6b** and **7b**, though also diastereomeric mixtures because of an additional chiral center at the THP, gave only one set of signals in the NMR spectra and were chromatographically homogeneous. This is probably caused by a very high conformational flexibility of the THP group together with a relatively long distance between the two chiral centers.

Unlike with the (purin-6-yl)glycines,[6] we have managed to deprotect all (purin-6-yl)alanines to give free amino acids (Table 2). (9-Benzyl-purin-6-yl)alanine **9a** and (9*H*-purin-6-yl)alanine **9b** were obtained from Boc-protected intermediates **6a** and **6b**, respectively, by Pd/C-catalyzed hydrogenolysis of benzyl ester (surprisingly with simultaneous cleavage of THP in **6b**) followed by treatment of the products with HCl in ethyl acetate or trifluoracetic acid in DCM (Scheme 3 and Table 2, entries 1−6). All products of these deprotecting sequences were isolated simply by crystallization from the reaction solvents.

Similarly, we have tried to deprotect Boc derivatives **6c** and **6d** and succeeded with cleavage of the Boc group from ribonucleoside derivative **6c** under acidic conditions (TFA in DCM). Nevertheless, when the same conditions were applied to 2-deoxyribonucleoside derivative **6d**,

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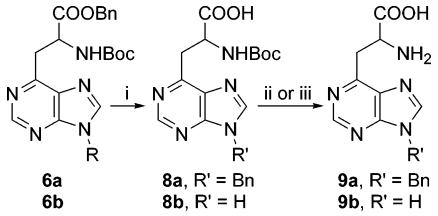
TABLE 2. Deprotection of (Purine-6-yl)alanines

entry	reagent	method[a]	product	yield (%)
1	**6a**	A	**8a**	89
2	**6b**	A	**8b**	84
3	**8a**	B	**9a**·TFA	72
4	**8b**	B	**9b**·TFA	86
5	**8a**	C	**9a**·HCl	84
6	**8b**	C	**9b**·2HCl	96
7	**7c**	D	**10c**	97
8	**7d**	D	**10d**	85
9	(*S*)-**7c**	D	(*S*)-**10c**	96
10	(*S*)-**7d**	D	(*S*)-**10d**	95
11	**10c**	E	**11c**	80
12	**10d**	E	**11d**	73
13	(*S*)-**10c**	E	(*S*)-**11c**	81
14	(*S*)-**10d**	E	(*S*)-**11d**	70

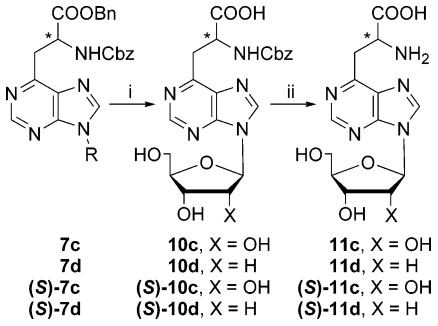
[a] Methods: (A) H_2, Pd/C, EtOH; (B) TFA in DCM; (C) HCl in EtOAc; (D) aqueous NaOH (2−3 equiv) in THF/MeOH; (E) H_2, Pd/C, Dioxane/H_2O.

SCHEME 3. Deprotection of (Purin-6-yl)alanines[a]



[a] (i) H_2, Pd/C, EtOH. (ii) TFA in DCM. (iii) HCl in EtOAc.

SCHEME 4. Deprotection of (Purin-6-yl)alanines[a]



[a] (i) Aqueous NaOH (2−3 equiv) in THF/MeOH. (ii) H_2, Pd/C, Dioxane/H_2O.

decomposition of the starting compound occurred because of the lability of its nucleosidic bond under acidic conditions. Because our goal was to find a universal combination of protective groups for both ribonucleosides and 2-deoxyribonucleosides, we focused on the intermediates **7c** and **7d**, where the amino group is protected by hydrogenolytically cleavable benzyl carbamate. Basic hydrolysis of compounds **7c** and **7d** (epimeric mixtures) by aqueous sodium hydroxide (2−3 equiv), which cleaved all of the ester groups, was followed by Pd/C-catalyzed hydrogenolysis of benzyl carbamate to afford free nucleosides **11c** and **11d** (Scheme 4 and Table 2, entries 7 and 8 and entries 11 and 12). This sequence was also applied for enantiomerically pure compounds (*S*)-**7c** and (*S*)-**7d** to give (*S*)-**11c** and (*S*)-**11d** (Table 2, entries 9 and 10 and entries 13 and 14) with no racemization of the amino acid moiety. A suitable isolation technique had to be found for the highly hydrophilic amino acids. Neither crystallization of compounds **10c**, **10d**, (*S*)-**10c**, (*S*)-**10d**, **11c**, **11d**, (*S*)-**11c**, and (*S*)-**11d** from reaction mixtures nor their separation on ion-exchange resins was successful. Finally, we used preparative reversed-phase HPLC on C-18 with water/methanol as an eluent for the final isolation and purification of these products. All compounds were fully characterized including complete assignment of all NMR signals using a combination of H,H-COSY, H,C-HSQC, and H,C-HMBC methods. Again, the diastereomeric mixtures **10c**, **10d**, **11c**, and **11d** gave two sets of signals in the NMR spectra, and in the case of the fully deprotected nucleosides **11c** and **11d**, a reasonable analytical separation was achieved in HPLC on an L-proline-based chiral column. The diastereomerically pure compounds (*S*)-**10c**, (*S*)-**10d**, (*S*)-**11c**, and (*S*)-**11d** gave one set of signals, giving proof that no racemization occurred during the cross-coupling and deprotection sequence.

Conclusions

We have developed a simple and efficient approach for the synthesis of (purin-6-yl)alanines, a new class of artificial amino acids or modified purines applicable for the synthesis of both racemic and enantiopure compounds. Though analogous reactions were used before[10−14] for the synthesis of some simple aryl- or hetarylalanines, this was the first successful use in the functionalization of protected nucleobases and nucleosides. Furthermore, we have found suitable combinations of protecting groups and mild racemization-free conditions for the deprotection of nucleosides−amino acids conjugates containing acidolabile nucleosidic bonds. Title (purinyl)alanines **9** and **11** were subjected to biological activity screening. No considerable antiviral (HCV) or antiproliferative (L1210, HL-60, HeLa S3, and CCRF−CEM cell lines) activity was observed. Further efforts will focus on the application of this methodology in other positions of the purine moiety and on the synthesis of purine−peptide (or nucleic acid−peptide) conjugates.

Experimental Section

Preparation of Organozinc Reagents from Iodoalanines and Their Cross-Coupling Reactions with 6-Iodopurines, − General Procedure. Trimethylsilyl chloride (60 μL, 0.5 mmol) was added through a septum to an argon-purged flask containing a suspension of zinc dust (1.95 g, 30 mmol) in DMF (3 mL). The mixture was sonicated at ambient temperature for 15 min. Then a solution of protected 2-amino-3-iodopropanoate (6.0 mmol) in DMF (20 mL), prepared under argon, was added through a septum to the suspension of activated zinc, sonication continued for another 40 min at ambient temperature, and then the zinc was allowed to settle. The supernatant was transferred through a septum to a mixture of appropriate 6-iodopurine (4.5 mmol), Pd_2dba_3 (95 mg, 0.1 mmol), and tri-*o*-tolylphosphine (122 mg, 0.4 mmol) in DMF (15 mL) prepared under argon. The reaction mixture was stirred at ambient temperature for 8 h and allowed to stand overnight, and then the solvent was evaporated in vacuo. The residue was diluted by ethyl acetate (90 mL) and washed with water (2 × 80 mL) and brine (80 mL). The organic phase was evaporated and the residue chromatographed on a silica gel column (ethyl acetate/hexane) to give (purine-6-yl)alanines.

Benzyl (*S*)-3-[9-(2,3,5-Tri-*O*-acetyl-*β*-D-ribofuranosyl)purin-6-yl]-2-[(benzyloxycarbonyl)amino]propanoate, (*S*)-7c. (*S*)-**7c** was prepared from (*S*)-**2** (1.15 g, 2.6 mmol) and **5c** (1.00 g, 2.0 mmol). Yield: 990 mg (72%) of (*S*)-**7c** as a colorless, amorphous solid. MS (FAB, *m/z*): 690 (45, M + 1); 432 (24, M − AcRf + 2); 259 (33); 139 (100). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 2.08 (s, 3H, CH_3); 2.11 (s, 3H, CH_3); 2.16 (s, 3H, CH_3); 3.66 (dd, 1H, J = 4.2 and 16.0 Hz, PuCH_AH_B); 3.92 (dd, 1H, J = 5.4 and 16.0 Hz, PuCH_AH_B); 4.38−4.47 (m, 3H, H-4′ + H-5′); 5.04 (m, 1H, CH from alanine); 5.10 (s, 2H, CH_2Ph); 5.12 (s, 2H, CH_2Ph); 5.67 (t, 1H, J = 4.9 Hz, H-3′); 5.96 (t, 1H, J = 5.4 Hz, H-2′); 6.20 (d, 1H, J = 5.1 Hz, H-1′); 6.45 (d, 1H, J = 8.7 Hz, NH); 7.21−7.34 (m, 10H, arom.); 8.15 (s, 1H, H-8); 8.74 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, $CDCl_3$, δ): 20.35, 20.49, and 20.70 (3 × CH_3CO); 34.39 (PuCH_2); 52.08 (CH from alanine); 62.98 (CH_2-5′); 66.93 and 67.15 (2 × CH_2Ph); 70.52 (CH-3′); 72.95 (CH-2′); 80.38 (CH-4′); 86.42 (CH-1′); 128.04, 128.14, 128.18, 128.35, and 128.43 (CH-arom.); 133.42 (C-5); 135.29 and 136.25 (2 × C-arom.); 142.59 (CH-8); 150.27 (C-4); 152.23 (CH-2); 156.08 (NCO); 158.04 (C-6); 169.28, 169.50, and 170.24 (3 × COCH$_3$); 171.08 (COOBn). $[\alpha]^{20}_D$: −26.3 (*c* 6.27, $CHCl_3$). Anal. Calcd for $C_{34}H_{35}N_5O_{11}$: C, 59.21; H, 5.12; N, 10.15. Found: C, 58.95; H, 5.25; N, 9.80.

(*S*)-3-[9-(*β*-D-Ribofuranosyl)purin-6-yl]-2-[(benzyloxycarbonyl)amino]propanoic Acid, (*S*)-10c. An aqueous solution of NaOH (0.59 M, 6.5 mL) was slowly added at 0 °C to the solution of (*S*)-**7c** (799 mg, 1.16 mmol) in THF (13 mL)/methanol (10 mL), and the reaction mixture was stirred at ambient temperature for 25 min. The pH was adjusted to 7 by aqueous HCl (3%), and the solvents were evaporated in vacuo. The crude product was purified by preparative HPLC on a C-18 column with water/methanol as the mobile phase to give 525 mg (96%) of (*S*)-**10c** as a white solid. MS (FAB, *m/z*): 474 (100, M + 1); 342 (77, M − Rf + 2). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 3.47 (dd, 1H, J_{gem} = 15.0 Hz, J_{CH2bCH} = 8.2 Hz, CH_2-b); 3.58 (dd, 1H, J_{gem} = 12.0 Hz, $J_{5'b4'}$ = 4.1 Hz, H-5′b); 3.62 (dd, 1H, J_{gem} = 15.0 Hz, J_{CH2aCH} = 6.1 Hz, CH_2-a); 3.70 (dd, 1H, J_{gem} = 12.0 Hz, $J_{5'a4'}$ = 4.2 Hz, H-5′a); 3.99 (q, 1H, $J_{4'5'a}$ = 4.2 Hz, $J_{4'5'b}$ = 4.1 Hz, $J_{4'3'}$ = 3.5 Hz, H-4′); 4.20 (dd, 1H, $J_{3'2'}$ = 5.0 Hz, $J_{3'4'}$ = 3.5 Hz, H-3′); 4.66 (t, 1H, $J_{2'1'}$ = 5.8 Hz, $J_{2'3'}$ = 5.0 Hz, H-2′); 4.87 (dt, 1H, J_{CHNH} = 8.5 Hz, J_{CHCH2b} = 8.2 Hz, J_{CHCH2a} = 6.1 Hz, CH); 4.99 (s, 2H, CH_2−Ph); 6.04 (d, 1H, $J_{1'2'}$ = 5.8 Hz, H-1′); 7.26−7.38 (m, 5H, Ph); 7.70 (bd, 1H, J_{NHCH} = 8.5 Hz, NH); 8.80 (s, 1H, H-8); 8.85 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, DMSO-d_6, δ): 34.57 (CH_2); 52.42 (CH); 61.55 (CH_2-5′); 65.55 (CH_2−Ph); 70.60 (CH-3′); 73.83 (CH-2′); 85.97 (CH-4′); 87.79 (CH-1′); 127.79 (*m*-CH−Ph); 127.97 (*p*-CH−Ph); 128.53 (*o*-CH−Ph); 133.13 (C-5); 137.17 (*i*-C−Ph); 144.54 (CH-8); 150.56 (C-4); 151.84 (CH-2); 156.08 (CO−Cbz); 158.22 (C-6); 173.11 (CO). $[\alpha]^{20}_D$: −33.5 (*c* 8.56, MeOH).

(*S*)-3-[9-(*β*-D-Ribofuranosyl)purin-6-yl]-2-aminopropanoic Acid Monohydrate, (*S*)-11c. Hydrogen was bubbled through a solution of (*S*)-**10c** (379 mg, 0.80 mmol) in water (20 mL), dioxane (20 mL), and acetic acid (0.2 mL) in the presence of Pd/C catalyst (10 wt %, 40 mg) for 4 h. The catalyst was filtered off on a Celite pad and the filtrate evaporated in vacuo. The crude product was purified by preparative HPLC on a C18 column with water/methanol as the mobile phase. The product was lyophilized from water to give 230 mg (81%) of (*S*)-**11c** (monohydrate) as a white solid. MS (FAB, *m/z*): 340 (81, M + 1); 307 (72); 215 (100). ^{1}H NMR (500 MHz, D_2O, δ): 3.73 (dd, 1H, J_{gem} = 15.5 Hz, J_{CH2bCH} = 7.3 Hz, CH_2-b); 3.78 (dd, 1H, J_{gem} = 15.5 Hz, J_{CH2aCH} = 5.3 Hz, CH_2-a); 3.83 (dd, 1H, J_{gem} = 12.8 Hz, $J_{5'b4'}$ = 4.0 Hz, H-5′b); 3.90 (dd, 1H, J_{gem} = 12.8 Hz, $J_{5'a4'}$ = 2.9 Hz, H-5′a); 4.27 (q, 1H, $J_{4'3'}$ = 4.0 Hz, $J_{4'5'b}$ = 4.0 Hz, $J_{4'5'a}$ = 2.9 Hz, H-4′); 4.35 (dd, 1H, J_{CHCH2b} = 7.3 Hz, J_{CHCH2a} = 5.3 Hz, CH); 4.44 (t, 1H, $J_{3'2'}$ = 5.3 Hz, $J_{3'4'}$ = 4.0 Hz, H-3′); 4.81 (t, 1H, $J_{2'1'}$ = 5.6 Hz, $J_{2'3'}$ = 5.3 Hz, H-2′); 6.17 (d, 1H, $J_{1'2'}$ = 5.6 Hz, H-1′); 8.66 (s, 1H, H-8); 8.85 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, D_2O, ref(dioxane) = 67.19 ppm): 33.02 (CH_2); 53.42 (CH); 61.89 (CH_2-5′); 70.99 (CH-3′); 74.39 (CH-2′); 86.20 (CH-4′); 89.06 (CH-1′); 133.24 (C-5); 145.60 (CH-8); 150.74 (C-4); 152.42 (CH-2); 157.71 (C-6); 173.64 (CO). $[\alpha]^{20}_D$: −22.2 (*c* 2.70, H_2O). Anal. Calcd for $C_{13}H_{19}N_5O_7$: C, 43.70; H, 5.36; N, 19.60. Found: C, 43.35; H, 5.28; N, 19.48.

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Supporting Information Available: General methods; synthesis of starting compounds; synthetic procedures; characterization data for compounds **6a**−**6d**, **7c**, **7d**, (*S*)-**7d**, **8a**, **8b**, **9a**, **9b**, **10c**, **10d**, (*S*)-**10d**, **11c**, **11d**, and (*S*)-**11d**; and deprotection of **6c** under acidic conditions are available free of charge via the Internet at http://pubs.acs.org.

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